Molecular Ferment:
The Rise and Proliferation of Yeast Model Organism Research

by

Erika Michelle Langer, M.S.

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Abstract

Molecular Ferment: The Rise and Proliferation of Yeast Model Organism Research

Erika Langer

This study examines the history of yeast hereditary research out of the fermentation industries and into the genetics laboratory, where a single-celled fungus underwent material, technical, and conceptual transformations to become an experimental system, an ideal eukaryotic cell, a model organism, and a genetically-engineered cell factory with which to advance the molecularization of human health and disease. The work draws from new and existing oral histories and archives across academic and commercial institutions to follow the development, circulation, and use of *Saccharomyces cerevisiae* wild-type yeast strain S288C and its mutants along with their accompanying experimental practices and politics in a range of international settings. The rise of the yeast model organism in U.S. biomedical research is shown to have been a political application of eukaryotic molecular biology with particular utility, for example, in accessing basic science funding for cancer research at the level of the cell. A final case study of yeast-made recombinant Hepatitis B vaccine reveals how the biotech industry manufactured therapeutics out of human molecules on the rise of eukaryotic molecular biology.

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Introduction

Yeast in the postgenomic era has been called an "ideal model genome" for systematic analysis of gene function thought to be predictive of human disease processes.[1] Following completion of the yeast genome sequence in 1996, it was suspected that nearly a third of all human disease-associated genes have functional homologs in yeast.[2] Other human disease genes lacking homology have been introduced into "humanized" yeast models as a way of enabling their functional analyses, to conduct high-throughput screening of therapeutic targets, and to test drug candidates for possible toxicity in humans. Yeast models have been developed for human diseases including breast cancer, Parkinson's disease, Huntington's disease, Alzheimer's disease and several other tauopathies, amyotrophic lateral sclerosis (ALS), proteopathies like cystic fibrosis (CF), as well as processes thought to be associated with the phenomenon of human aging.[3]

This study of the yeast model organism asks the simple historical question: how is it that a single-celled fungus with no nervous system, tissues or organs came to be representative of these complex human disease processes? Over the course of the next five chapters, I will argue that the development and rise of yeast model organism research turns on a key shift beginning in

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[1] A. Kumar and M. Snyder, "Emerging Technologies in Yeast Genomics," *Nature Reviews Genetics* 2, no. 4 (2001): 302.

[2] Françoise Foury, "Human Genetic Diseases: A Cross-Talk between Man and Yeast," *Gene* 195, no. 1 (1997): 7. See also A. Goffeau et al., "Life with 6000 Genes," *Science* 274, no. 5287 (1996): 546-567.

[3] See, for example, X. C. Li, J. C. Schimenti, and B. K. Tye, "Aneuploidy and Improved Growth Are Coincident but Not Causal in a Yeast Cancer Model," *PLoS Biology* 7, no. 7 (2009): e1000161. Accessed June 6, 2016, doi:10.1371/journal.pbio.1000161; Mathias Verduyckt et al., "Yeast as a Model for Alzheimer's Disease: Latest Studies and Advanced Strategies," in *Systems Biology of Alzheimer's Disease*, ed. I. Juan Castrillo and G. Stephen Oliver (New York: Springer, 2016), 201; M. Breitenbach, S.M. Jazwinski, and P. Laun, *Aging Research in Yeast* (New York: Springer, 2012), 2.

the 1970s from the experimental study of heredity to the hereditary study of human disease processes. To understand it, we have to explore why common baker's yeast was brought into the genetics laboratory in the first place and how those motivations were transformed from the earliest breeding experiments of the mid-1930s to the "eukaryotic turn" toward higher organism biology at the end of the 1960s. The political advantages of biomedically-oriented research that emerged after that time worked to transform an earlier anthropomorphization of molecules to a new project of "molecularizing humans" which continues in our own time.

Yeast is not a taxonomic classification, but a common name for many fungal species that make up a small portion of the eukaryotic (meaning they have a nucleus) fungi (meaning their cell walls contain both glucans and chitin - and not, for example, cellulose). Yeasts are so varied that they hang together by more of what they do not share with plants, animals, protists, and bacteria, than what they have in common with each other. They are predominantly unicellular, although some are multicellular. They reproduce asexually by budding or by fission, but also sexually by fusion. Some yeasts, like *Saccharomyces cerevisiae* (*S. cerevisiae*), are central to the human diet in the production of foods like bread, wine, beer, saki, and soy sauce, while others, such as *Candida albicans*, are common infectious pathogens. *Pichia pastoris* and *Schizosaccharomyces pombe* are two species that have been especially useful in the laboratory, but none has had such an extensive scientific life as *S. cerevisiae*. Most scientific and popular culture references to "yeast" occur as shorthand for this species, and this study adopts this common usage unless otherwise specified.

The very plurality of yeast - as a specific species, as strain, or genome - provides the lens for analysis in this study, for it was the study of yeast variety, variation, and variability that moved the organism from the industrial context into the research laboratory. There, prolific

reproduction of the experimental organism under various national interests, disciplinary paradigms, and institutional practices has produced a heritable material never precisely replicated but always interactive with its environment.

There were two inspirations which shaped this choice of topic and guided my path through the archives. The first was the idea that yeast science traversed the many entangled relationships between academia and industry to show not just the pursuit of knowledge at the frontiers of science but its exploitation in many different kinds of applications in society. In the course of this work, I found that practical knowledge of yeast heredity entered, existed, and returned to the laboratory in a cycle shaping pertinent research questions and future opportunities for extramural support. Rather than maintaining a false boundary between the laboratory and an "external" sociological world, I entered the archives with a plan to read across the basic-applied research dichotomy to look at how both academic and industrial scientists have contributed to modern laboratory science with yeast and the contemporary notion of "research translation." Unlike Darwin's forays into the "extra-scientific" culture of English pigeon fanciers, yeast workers worked continuously, from the mid-nineteenth century, within or alongside the yeast-based industries.[4] Within this long view, the exceptionalism of the 1950s and 1960s becomes apparent for American yeast researchers in terms of the federal laboratories, contracts, and consultation roles oriented to the interests of national defense, yet even then the boundaries with yeast-based industries remained fluid.[5] When federal involvement continued in the yeast

[4] See James A. Secord, "Nature's Fancy: Charles Darwin and the Breeding of Pigeons," *Isis* 72, no. 2 (1981): 163-186.

[5] At mid-century, for example, yeast researcher Seymour Pomper completed his doctoral training in microbiology at Yale University on a fellowship from Standard Brands (the parent company of Fleischmann's Yeast). He went on to perform yeast radiation studies for the American Energy Commission at Oak Ridge National Laboratory, leaving to do postdoctoral research at the University of California in Berkeley, and next going on to direct Fleischmann Laboratories. At

laboratories of the 1970s and 1980s, I found, the shift in national environmental and biomedical interests fermented into new opportunities for industry.

The second inspiration stemmed from science studies scholarship on hybridity and drew from both Bruno Latour's sense of networked nature-culture and the collapsed duality and contracted term of Donna Haraway's naturecultures.[6] Here I hoped to explore the possibilities for "multispecies history" on the model of anthropologists who are radically rethinking categories of nonhuman otherness through new modes of multispecies ethnography.[7] A recent defense of Actor Network Theory (ANT) as a coherent *methodology* for incorporating nonhumans into social scientific accounts invited the question of how historians of the life sciences might

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Fleischmann's, reportedly, Pomper mixed all of the experimental yeast strains he had collected over the years to develop Fleischmann's brand of common baker's yeast. See Seymour Pomper, "The Biochemical Genetics of Yeast" (PhD diss., Yale University, 1949); Seymour Pomper, "Recent Developments in Yeast Genetics," ed. U.S. Atomic Energy Commission Technical Information Division (Oak Ridge, Tenn.: Oak Ridge National Laboratory, 1950), 17, 20; Ora Marshino, *Research Fellows of the National Cancer Institute*, vol. 658, U.S. Department of Health and Human Services Public Health Service Publication (Washington, DC: U.S. Government Printing Office, 1959), 82; R. C. von Borstel, "Taming the Oldest Domesticated Organism," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 189.

[6] For example, Bruno Latour, *We Have Never Been Modern*, trans. Catherine Porter (Cambridge, MA: Harvard University Press, 1993); Donna Jeanne Haraway, *Simians, Cyborgs, and Women: The Reinvention of Nature* (New York: Routledge, 1991). See also Paul Rabinow on "biosociality" and the concept of nature modeled on culture. In Paul Rabinow, "Artificiality and Enlightenment: From Sociobiology to Biosociality," in *Anthropologies of Modernity: Foucault, Governmentality, and Life Politics*, ed. J.X. India (Oxford, UK: Blackwell Publishing Ltd., 2005), 179-193.

[7] The "species turn" in anthropology treats biological difference as a permeable boundary and instead describes novel entanglements and relational emergence of creatures through their encounters. See, for example, Stefan Kirksey and Stefan Helmreich, "The Emergence of Multispecies Ethnography," *Cultural Anthropology* 25, no. 4 (2010): 545-576; Eduardo Kohn, *How Forests Think: Toward an Anthropology Beyond the Human* (Berkeley: University of California Press, 2013). Posthumanist "species discourse" seeks to demonstrate entanglements rather than parse who counts and how much in the humanist project of "animal rights." The latter is thought to reinstate differences. See Cary Wolfe, *What Is Posthumanism?* (Minneapolis: University of Minnesota Press, 2010), 118.

interrogate model organisms within relational networks of the past.[8] It has been argued that without any "stable prime mover, social or individual, to construct anything, no builder, no puppeteer," explanation in ANT must undergo a shift from "construction" to "relational enactment."[9] This allows historians to investigate the material circumstances, social ties, established practices, and bodies of knowledge that make up the networks in which model organisms have functioned as research tools, but it also permits a historical "thinking with" model organisms as companion species.[10] By taking account of the ways in which "matter comes to matter," model organism history can examine how both yeast and scientists have emerged from their "intra-action."[11] This type of analysis, feminist scholar Karen Barad has said, requires reading diffractively for "patterns of difference that make a difference." [12] This she borrows from

[8] Edwin Sayes, "Actor–Network Theory and Methodology: Just What Does It Mean to Say That Nonhumans Have Agency?," *Social Studies of Science* 44, no. 1 (2014): 134-149.
[9] John Law, "Actor Network Theory and Material Semiotics," in *The New Blackwell Companion to Social Theory*, ed. B.S. Turner (Oxford, UK: Wiley-Blackwell, 2008), 151.
[10] See Donna Jeanne Haraway, "Encounters with Companion Species: Entangling Dogs, Baboons, Philosophers, and Biologists," *Configurations* 14, no. 1 (2006): 97-114. Anna Tsing has touched upon yeast as one of many fungal companion species, arguing that the ability of yeast to ferment rum from sugar cane also served to produce slave trade as a masculine adventure because "fermentation… detracted attention from the cruelty of shore-bound domestication, both human and nonhuman" through the production of alcohol. In Anna Tsing, "Unruly Edges: Mushrooms as Companion Species," *Environmental Humanities* 1 (2012): 149. See also *Thinking with Animals: New Perspectives on Anthropomorphism* (New York: Columbia University Press, 2005).
[11] Karen Barad has described "intra-action" as a relational emergence involving boundary drawing practices. She has proposed the use of this "agential realism" as a new materialism that goes beyond the reproduction of causal explanations. See Karen Barad, "Getting Real: Technoscientific Practices and the Materialization of Reality," *Differences: A Journal of Feminist Cultural Studies* 10, no. 2 (1998): 89; Malou Juelskjær and Nete Schwennesen, "Intra-Active Entanglements–an Interview with Karen Barad," *Kvinder, Køn & Forskning*, no. 12 (2013): 21; Karen Barad, "'Matter Feels, Converses, Suffers, Desires, Yearns and Remembers': Interview with Karen Barad," in *New Materialism: Interviews & Cartographies*, ed. Rick Dolphijn and Iris van der Tuin, Utrecht University (Ann Arbor, MI: Open Humanities Press, 2012), 48-70.
[12] Karen Barad, *Meeting the Universe Halfway: Quantum Physics and the Entanglement of Matter and Meaning* (Durham: Duke University Press, 2007), 72.

Haraway, who has explained that "Diffraction is about heterogeneous history, not about originals."[13] While this project has not relinquished the aim of making an original historical contribution, a "diffractive reading" of the archives has allowed me to revisit some classic evidence in the historiography of biochemistry, microbiology, biophysics, and genetics with fresh eyes for yeast as historical actor.[14] Yeast is in many ways inseparable from the development of human civilization. As the world's oldest biotechnology, yeast does more than prescribe back to us our own human relations. The contested origins of lager yeast are illustrative.

The Case of Lager Beer

Lager beer is produced from barley grain and a strain of yeast which is named *Saccharomyces pastorianus* to honor the nineteenth-century microbiologist Louis Pasteur – unless, of course, the strain is called *Saccharomyces carlsbergensis*, in which case Emil Christian Hansen is the intended honoree for his contributions to Carlsberg brewery. Today, depending on their allegiances, textbook publishers, brewers, and yeast culture stock centers choose one name over another to describe the same lager strain.[15] Scientific legacies hang in the balance.

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[13] Donna Jeanne Haraway, *Modest_Witness@Second_Millennium. Femaleman©_Meets_Oncomouse™: Feminism and Technoscience* (New York: Routledge, 1997), 273.

[14] Perhaps "fingeryeyes" is a more accurate description. Eva Hayward, "Fingeryeyes: Impressions of Cup Corals," *Cultural Anthropology* 25, no. 4 (2010): 577–599.

[15] Currently, Pasteur is leading in popularity, although Carlsberg Brewery prefers the latter. Carlsberg yeast geneticist Jürgen Wendland recently proposed that lager yeasts be differentiated into two "groups", known by these traditional names, but corresponding to total gene pools rather than species. In Jürgen Wendland, "Lager Yeast Comes of Age," *Eukaryotic Cell* 13, no. 10 (2014): 1256-1265.

The production of lager beer is believed to have begun in fifteenth century Bavaria with the accidental introduction of a new yeast strain which formed in a cross between the Northern European ale yeast, *Saccharomyces cerevisiae*, and another strain capable of producing fermentation at cooler temperatures. In 2011, a candidate for the mystery progenitor strain was found among the beech tree forests of Patagonia. This strain, *Saccharomyces eubayanus*, was 99.56% match for the genome of the missing wild genetic stock.[16] The findings immediately introduced questions about the origins of lager yeast and the connections of a cold-fermenting strain to its human users. Did lager yeast arrive in Northern Europe as a transatlantic stowaway from the New World?[17] As geneticists set out to reconstruct the yeast's evolutionary genealogy, they began simultaneously to negotiate the shared cultural heritage of the yeasts and humans.

The task was further complicated in 2014, when a strain of *Saccharomyces eubayanus* isolated from the Tibetan Plateau was found to be an even greater genetic match (99.82%) for the proposed lager parental strain. Microbiologists of the Chinese Academy of Sciences who performed the analysis proposed that their "Far East Asian origin hypothesis" better accounted for lager yeast ancestry.[18] Appearing in an entirely different hemisphere, nearly 1,500 years

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[16] Diego Libkind et al., "Microbe Domestication and the Identification of the Wild Genetic Stock of Lager-Brewing Yeast," *Proceedings of the National Academy of Sciences* 108, no. 35 (2011): 14539.

[17] Libkind et. al hypothesized that, "The facile recovery of this species from Patagonia suggests that *S. eubayanus* may have been absent in Europe until it was imported from overseas after the advent of trans-Atlantic trade." Ibid., 14543.

[18] The scientists wrote that, "Europe and Asia are located in the same landmass, and it would have been much easier for Tibetan *S. eubayanus* strains to make their way to Europe through the Eurasian continental bridge." Noting that Bavarian lager brewing began almost a century before Columbus' first voyage to the new world, they suggested that trade along the Silk Road begun 2,000 years ago left "plenty of time for Tibetan *S. eubayanus* strains to colonize Europe before they were domesticated." In Jian Bing et al., "Evidence for a Far East Asian Origin of Lager Beer Yeast," *Current Biology* 24, no. 10 (2014): R380-R381.

earlier, Pasteur and Hansen's fickle namesake suddenly became a far older global traveler along the transcontinental Silk Road.

Construction of this yeast genealogy continues. Argentinian, French, Portuguese, Canadian, and American collaborators have countered the Chinese claims with evidence that greater biodiversity of strains on the South American continent supports the Patagonian origin. After the discovery of *Saccharomyces eubayanus* in Wisconsin, USA, the "out of Patagonia" evolutionary theory has been maintained by enlisting migratory birds, oak tree growth patterns, and even "ski bums" along lager yeast's path to both North America, Asia, and Europe.[19] Yeast strains and species flicker in and out of distinction along the borders of scientific frames, as evolutionary geneticists revise their interpretations to accommodate both the remoteness of Patagonia's beech forest and its popularity as an international ski destination. Yeast and human history are rewritten in the encounter.

A Model Historiographic Subject

These interests in a model organism history of yeast can be further informed by the existing literature on model organisms. Such work forms a late chapter in the historiography of molecular biology, a subject which has undergone transformation in recent years as both its

[19] See D. Peris et al., "Population Structure and Reticulate Evolution of Saccharomyces Eubayanus and Its Lager-Brewing Hybrids," *Molecular Ecology* 23, no. 8 (2014): 2031-2045; P. Almeida et al., "A Gondwanan Imprint on Global Diversity and Domestication of Wine and Cider Yeast Saccharomyces Uvarum," *Nature Communications* 5 (2014): 4044. Accessed June 6, 2016, doi:10.1038/ncomms5044. These studies exploring the ability of organisms to locally adapt have been justified on the basis that this knowledge will be critical for "determining the outcome of rapid climate changes." In J. B. Leducq et al., "Local Climatic Adaptation in a Widespread Microorganism," *Proceedings of the Royal Society B: Biological Sciences* 281, no. 1777 (2014): 1. The "ski bums" comment comes from University of Wisconsin-Madison scientist Chris Hittinger, who is quoted in Brett Smith, "Brewer's Yeast Used in European Lagers Has Its Roots in South America," accessed April 10, 2014, redOrbit.com.

disciplinary status and long-held scientific tenets have come under question. Historians have taken issue with the "biology" portion of "molecular biology" as a coherent disciplinary or institutional specialty. More recently they have preferred the broader analytical lens of "molecularization of the life sciences."[20] The "molecular" portion of "molecular biology" has equally come under fire as hereditary explanations have been subject to their own transformations in the postgenomic period. Historians concerned with Mendelian genetics and neo-Darwinian evolutionary theory during the "century of the gene," for example, must attend to the movement of current biological research away from gene-centrism.[21] The recent reemergence of alternative concepts such as epigenetics do not discount the relative significance of earlier dogma, but they do require new types of explanations to justify what that science was about in the first place.[22]

The earliest histories of molecular biology were first-person accounts written by practicing scientists who had something to win or lose by these portrayals. These men (for they were men to a person) argued for disciplinary authority and sought to popularize and raise the profile of their "advances" in an attempt to consolidate future resources. They debated the relative importance of various actors, institutions, disciplinary approaches, and "schools." While these accounts offer rich sources of detail to the historian, they are largely uncritical of the

[20] Hans-Jörg Rheinberger, "Recent Science and Its Exploration: The Case of Molecular Biology," *Studies in History and Philosophy of Biological and Biomedical Sciences* 40, no. 1 (2009): 6.
[21] The attribution of the twentieth century as the "century of the gene" is found in Evelyn Fox Keller, *The Century of the Gene* (Cambridge, MA: Harvard University Press, 2000).
[22] Staffan Müller-Wille has recommended the utility of a cultural concept of heredity since it is possible that twentieth century genetics "was about something entirely different than histories have so far told us." See Staffan Müller-Wille, "Leaving Inheritance Behind: Wilhelm Johannsen and the Politics of Mendelism," in *A Cultural History of Heredity IV: Heredity in the Century of the Gene*, ed. Max Planck Institut für Wissenschaftsgeschichte (Berlin: Max Planck Gesellschaft, 2008), 8.

contributing geopolitical, sociocultural, or economic influences characterizing the work as "progress." Beginning in the 1960s, these earliest texts included, for example, *Phage and the Origins of Molecules Biology* (1966), which located the origins of molecular biology in Max Delbrück's biophysical studies of the genetics of bacteria *E. coli* and its viruses (the bacteriophage). At New York's Cold Spring Harbor Laboratory of Quantitative Biology, Delbrück had taught a course on phage genetics, and students of "the phage group," including James Watson, Gunther Stent, and John Cairns, assembled this volume in recognition of his influence.[23] British biochemist and crystallographer John Kendrew criticized the phage group's assumption of priority in "How Molecular Biology Started" (1967). Instead, Kendrew asserted the significance of the British or "structural" school of molecular biology concerned with macromolecules.[24] In 1968, just before assuming the directorship of Cold Spring Harbor Laboratory, Watson published on his own work on the elucidation of the double helical structure of DNA as the pinnacle of biology "gone molecular."[25] Early revisionist accounts asserted the importance of neglected actors in this story, such as Rosalind Franklin, whose work served as critical evidence of the DNA model and was used without attribution.[26]

In the 1970s, the first historians to treat the emergence of molecular biology maintained close ties with its high-profile actors. The forward of Robert Olby's book, *The Path to the Double Helix* (1974), for example, was written by Francis Crick, who had shared the 1962 Nobel Prize in Physiology or Medicine with Watson for their discovery of DNA structure. Olby offered

[23] J. Cairns et al., *Phage and the Origins of Molecular Biology* (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory of Quantitative Biology, 1966).
[24] J.C. Kendrew, "How Molecular Biology Started," *Scientific American* 216 (1967): 141-144.
[25] James D. Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (New York: Atheneum, 1968).
[26] Aaron Klug, "Rosalind Franklin and the Discovery of the Structure of DNA," *Nature* 219 (1968): 808-844.

additional "founders'" interviews and reworked the account of the phage group's relative contributions while still conferring authority to their claims. As compromise, Olby recognized Kendrew's vision of the two schools: the "informational school" represented by Watson, Delbrück, and the phage group which attributed a physical order to biology in the idea of a genetic code, and a "structural school" represented by Crick, J.D. Bernal, and the application of x-ray crystallography to hereditary material.[27] These different approaches, he held, were correct but incomplete without one another until they met along "the path" to the double helix - a transformation Olby claimed to have spanned from 1900 with the rediscovery of Mendel's laws to Watson and Crick's discovery in 1953.[28] As the 1970s progressed, French practitioners defended their own discoveries of gene regulation as central to contemporary molecular practice and asserted the importance of the French microbiological tradition.[29] Horace Judson's journalistic account, *The Eighth Day of Creation*, brought these claims together – the American, British, and French contributors, and Franklin together with Watson and Crick – in a summary account which traced the emergence of molecular biology from five disciplinary sources of equal significance: physical chemistry, crystallography, biochemical genetics, microbiology, and biochemistry.[30] Well-received for its satisfactory representation of institutional interests and the

[27] Robert Olby, *The Path to the Double Helix: The Discovery of DNA* (Seattle: University of Washington Press, 1974).
[28] Pnina Abir-Am has recognized the essential teleology of Olby's title. Pnina Abir-Am, "Themes, Genres and Orders of Legitimation in the Consolidation of New Scientific Disciplines: Deconstructing the Historiography of Molecular Biology," *History of Science* 23, no. 1 (1985): 80.
[29] A. Lwoff and A. Ullmann, eds., *Origins of Molecular Biology: A Tribute to Jacques Monod* (New York: Academic Press, 1979).
[30] Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology* (New York: Simon and Schuster, 1979).

day's feminist politics, this work became a standard introduction to the discipline for new practitioners in training.[31]

The next set of historians to approach the subject tried to make up for the defects of hagiography. They reinserted contingency to explain the field's growth from a relatively small group of practitioners in the 1930s to the beginning of more widespread institutionalization after 1950. These historians looked, for example, to the unrecognized early influence of the Rockefeller Foundation in shaping the field's research agenda.[32] They explored the commercial lure of biotech as it reconfigured academic-industry relations and incentivized the use of new genetic engineering tools in their own period.[33] One of the distinctive characteristics of even this professional historiography before 1980, however, was the extent to which it reproduced the prokaryotic paradigm established by the first accounts of scientists working in bacteria and the phage. Judson, for example, argued that the fundamental transformation in biology from the 1930s to the 1950s was working out the idea of specificity. He connected this concept to several earlier research programs, including microbiology, by focusing on well-known prokaryotic geneticists André Lwoff, Jacques Monod, Max Delbrück, and Salvador Luria.[34] Molecular

[31] In an early review of the book, John Edsall called it "essential reading." See John T. Edsall, "Horace Judson and the Molecular Biologists," *Journal of the History of Biology* 13, no. 1 (1980): 158; Abir-Am, "Themes, Genres and Orders of Legitimation in the Consolidation of New Scientific Disciplines: Deconstructing the Historiography of Molecular Biology," 98; Rheinberger, "Recent Science and Its Exploration: The Case of Molecular Biology," 8.
[32] Robert E. Kohler, "The Management of Science: The Experience of Warren Weaver and the Rockefeller Foundation Programme in Molecular Biology," *Minerva* 14, no. 3 (1976): 279-306; Pnina Abir-Am, "The Discourse of Physical Power and Biological Knowledge in the 1930s: A Reappraisal of the Rockefeller Foundation's 'Policy' in Molecular Biology," *Social Studies of Science* 12, no. 3 (1982): 341-382.
[33] An early example is Edward Yoxen, "Life as a Productive Force: Capitalising the Science and Technology of Molecular Biology," *Science, Technology and the Labour Process: Marxist Studies* 1 (1981): 66-123.
[34] Horace Freeland Judson, "Reflections on the Historiography of Molecular Biology," *Minerva* 18, no. 3 (1980): 398-399.

biology was a story of the gene, DNA, and the genetic code, and it was largely a story of *E. coli*. These accounts did not turn a critical eye to practitioners' claims at the end of the 1960s that they had fulfilled the early promise of molecular biology and could move onto the next set of more complex problems over the 1970s, including gene regulation, transcription, and development in the higher organisms.[35]

Over the 1980s and 1990s, the widespread uptake of genetic engineering tools ushered in another historiographic transition - one gaining momentum across the history and sociology of science at that time: the practice turn.[36] Historians of molecular biology began to examine the world of the laboratory and opened the door to common materials of experimental practice, such as model organisms.[37] The literature on model organisms has only continued to grow since the early 1990s and today encompasses studies of the frog, the rat, the fruit fly, the worm, tobacco mosaic virus, the mouse, cell culture, and the zebrafish, among many others.[38]

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[35] One internalist account at the end of the 1960s was Gunther Stent, "That Was the Molecular Biology That Was," *Science* 160, no. 3826 (1968): 390-395.

[36] See L. Soler et al., *Science after the Practice Turn in the Philosophy, History, and Social Studies of Science* (New York: Routledge, 2014).

[37] For an early example of this genre see Soraya de Chadarevian, "Sequences, Conformation, Information: Biochemists and Molecular Biologists in the 1950s," *Journal of the History of Biology* 29, no. 3 (1996): 361-386.

[38] Frederic L. Holmes, "The Old Martyr of Science: The Frog in Experimental Physiology," *Journal of the History of Biology* 26, no. 2 (1993): 311-328; Bonnie Tocher Clause, "The Wistar Rat as a Right Choice: Establishing Mammalian Standards and the Ideal of a Standardized Mammal," *Journal of the History of Biology* 26, no. 2 (1993): 329-349; Robert E. Kohler, *Lords of the Fly: Drosophila Genetics and the Experimental Life* (Chicago: University of Chicago Press, 1994); Soraya de Chadarevian, "Of Worms and Programmes: Caenorhabditis Elegans and the Study of Development," *Studies in History and Philosophy of Science Part C* 29, no. 1 (1998): 81-105; Rachel A. Ankeny, "Fashioning Descriptive Models in Biology: Of Worms and Wiring Diagrams," *Philosophy of Science* 67, Supplement, no. 3 (2000): S260-S272; Angela N.H. Creager, *The Life of a Virus: Tobacco Mosaic Virus as an Experimental Model, 1930-1965* (Chicago: University of Chicago Press, 2002); Karen A. Rader, *Making Mice: Standardizing Animals for American Biomedical Research, 1900-1955* (Princeton, NJ: Princeton University Press, 2004); Hannah L. Landecker, *Culturing Life: How Cells Became Technologies* (Cambridge, MA: Harvard University Press, 2007); Robert Meunier, "Stages in the Development

Model organism histories have developed in sync with the most recent transformation in the historiography of molecular biology – dissolution of the disciplinary concept. These narratives have continued to maintain their material lens on scientific practice to examine the social world of scientists through the disciplinary strategies, institutional ties, and funding arrangements characterizing the production of scientific knowledge. They have more recently taken up the politics of life at stake in processes of molecularization.[39] Recent scholarship has focused in particular on the influence of the genome sequencing projects in reconfiguring the relationships, scale, and scope of molecular study. The distinctly collaborative form of science represented in model organism research has been another line of interest leading scholars to examine the development of shared community resources such as experimental stock, media, newsletters and sequence databases.[40]

Additional historical analyses have sought to append the early prokaryotic historiography and rewrite the history of heredity to not end with the gene. These reflect evolutions within the science, for example, with the recent emergence of "epigenetic" theories about the heritable

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of a Model Organism as a Platform for Mechanistic Models in Developmental Biology: Zebrafish, 1970–2000," *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 43, no. 2 (2012): 522-531.

[39] Nikolas Rose has defined molecularization as the "reorganization of the gaze of the life sciences, their institutions, procedures, instruments, spaces of operation and forms of capitalization." In Nikolas Rose, *The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century* (Princeton, NJ: Princeton University Press, 2007), 44.

[40] See, for example, Christopher M. Kelty, "This Is Not an Article: Model Organism Newsletters and the Question of 'Open Science'," *BioSocieties* 7, no. 2 (2012): 140-168; Rachel A Ankeny and Sabina Leonelli, "What's So Special About Model Organisms?," *Studies in History and Philosophy of Science Part A* 42, no. 2 (2011): 313-323; Sabina Leonelli and Rachel A. Ankeny, "Re-Thinking Organisms: The Impact of Databases on Model Organism Biology," *Studies in History and Philosophy of Biological and Biomedical Sciences* 43, no. 1 (2012): 29-36; Sabina Leonelli, "Introduction: Making Sense of Data-Driven Research in the Biological and Biomedical Sciences," *Studies in History and Philosophy of Biological and Biomedical Sciences* 43, no. 1 (2012): 1-3; Sabina Leonelli and Rachel A. Ankeny, "What Makes a Model Organism?," *Endeavour* 37, no. 4 (2013): 209-212.

transmission and developmental influence of environmental exposures. Since Jan Sapp's work on the controversy in biology over the relative importance of the cytoplasm and the nucleus in theories of heredity against the politics of the Cold War, others have shown how, by the end of the 1960s, so-called "cytoplasmic heredity" became less of a heretical idea.[41] Evelyn Fox Keller, for example, has attributed this shift to the gender politics of embryology which could recognize the importance of the cytoplasm in developmental biology.[42] Michel Morange too, citing molecular biologists' experimental difficulties and doubts upon turning to higher organism development, has described the contact of molecular biologists with embryology as causing a "displacement of the descriptive level from the molecules to the cell."[43]

In a recent defense of longue durée history, David Armitage and Joanna Guldi have argued that this once-common mode of analysis can now leverage an unprecedented availability of materials and tools to make sense of them. At a time when knowledge production is in crisis, they argue, there is an ethical need for this perspective, which can be more broadly impactful to general audiences.[44] Several historians have utilized this longer view to explore what early and late twentieth century molecular biology retain in common and what accounts for their differences. Raphael Falk, for example, has approximated an end to the "century of reductionism" in hereditary research and the start of a new "century of integration" in 1960, in

[41] Jan Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (New York: Oxford University Press, 1987), xv, xvi.
[42] Keller, *The Century of the Gene*, 41.
[43] Michel Morange, "The Transformation of Molecular Biology on Contact with Higher Organisms, 1960-1980: From a Molecular Description to a Molecular Explanation," *History and Philosophy of the Life Sciences* 19, no. 3 (1997): 369.
[44] David Armitage and Joanna Guldi, "Le Retour De La Longue Durée: Une Perspective Anglo-Américaine," *Annales. Histoire, Sciences Sociales* 70, no. 2 (2015): 291-292.

part motivated by the finding of different prokaryotic and eukaryotic gene regulation.[45] Steffan Müller-Wille, too, has used the longer view to argue that in the nineteenth and twentieth centuries the microbes, and not Darwin, appear at the center of the modern history of biology and that microbiology served as an organizing agenda for the discipline.[46]

Despite these acknowledgements of the turn to eukaryotic genetics, the central role of microbiology, and the return to cytoplasm and the cell, yeast research is largely absent from the historiography of genetics and molecular biology throughout the twentieth century. A yeast history of molecular biology appends this prokaryotic historiography with a more recent eukaryotic chapter since the 1960s, but it also challenges the prokaryotic status quo by acknowledging lesser known yeast workers working contemporaneously with the field's more familiar figures from the earliest days of biochemical (microbial) genetics. The longer view of yeast science helps to explain developments in genetics and molecular biology as these fields reworked in conceptual and technical terms their experimental material. As a simple eukaryotic cell, the rise of yeast model organism research at the start of the 1970s offers a conceptual bridge between two transformative processes of the twentieth century: molecularization of the life sciences and biomedicalization of society across the laboratory, industry, and the clinic.[47] Consider that in the twenty-first century, four Nobel Prizes have been awarded for work done in

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[45] Raphael Falk, "Heredity and the Century of the Gene," in *A Cultural History of Heredity IV: Heredity in the Century of the Gene*, ed. Max Planck Institut für Wissenschaftsgeschichte (Berlin: Max Planck Gesellschaft, 2008), 280-281.

[46] Staffan Müller-Wille, "Hybrids, Pure Cultures, and Pure Lines: From Nineteenth-Century Biology to Twentieth-Century Genetics," *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 38, no. 4 (2007): 796-806.

[47] Additional links between molecularization to biomedicalization are described in Soraya de Chadarevian and Harmke Kamminga, eds., *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s* (Amsterdam: Harwood Academic Publishers, 1998).

yeast, three of these in Physiology or Medicine.[48] Today, yeast is one of thirteen model organisms designated by the National Institutes of Health (NIH) as relevant to the study of the molecular mechanisms of human disease.[49] The story of how yeast got there begins with transformations in biology beginning in the nineteenth century.

The "Biography" of a Strain as a Path through the Archives

My research began in university and company archives of the yeast geneticists, and I soon identified yeast "S288" as the model *Saccharomyces cerevisiae* strain that was circulated between laboratories from the start of the 1960s as the genetic wild-type experimental system. I used S288C to work backwards to the archives of biophysicists, biochemists, microbiologists, food technologists, pressed yeast manufacturers, winemakers, and brewers who provided material, concepts or techniques used in its construction as well as forward to geneticists, molecular biologists, environmental health scientists, genetic engineers, and others who used the strain in their research. I explored the historical legacy that yeast geneticists formally claimed for themselves either through first person accounts or through their published citations, and I revisited primary source material (for example, from the well-known historiography of biochemistry and biochemical genetics) to examine their claims. I drew heavily upon the published literature, and particularly the "materials and methods" and "acknowledgements"

[48] Since the year 2000, Nobel laureate yeast workers are Leland Hartwell, Tim Hunt and Paul Nurse (Physiology or Medicine in 2001 for their discoveries of key regulators of the cell cycle), Roger Kornberg (Chemistry in 2006 for work on the molecular basis of eukaryotic transcription), Elizabeth Blackburn, Carol Greider and Jack Szostak (Physiology or Medicine in 2009 for their discovery of the role of telomeres and telomerase in chromosome protection), and Randy Schekman (one-third share in Physiology or Medicine in 2013 for work on the regulatory machinery of cell transport).

[49] National Institutes of Health, "Model Organisms for Biomedical Research," accessed April 14, 2016, http://www.nih.gov/science/models.

sections of scientific papers, to establish material transfers, which I could then follow up in archival correspondence, oral histories, and the laboratory notebooks of scientists. I translated scientific literature from multiple non-English languages to follow these relationships across national borders. I utilized trade journals, textbooks, patent records, and federal records, and brought in additional cultural references from newspapers, magazines, cookbooks, and contemporary literature and poetry wherever possible. A complete list of the archives I utilized is provided in the bibliography.

Yeast workers, on the model of phage researchers before them, are and were as a collective group highly conscientious of the legacy of their work. From the earliest days of yeast genetics, they too sought to preserve their contributions for posterity. Frequent review articles and many personal recollections are a boon to the historian hoping for a window into the early yeast community. I have found extremely useful these insider recollections, among them a volume of first-person accounts in *The Early Days of Yeast Genetics* and other commemorations throughout the years, such as that of the yeast course at Cold Spring Harbor Laboratory.[50] These sources are cited throughout the text as they occur. Past issues of the community newsletter, *Yeast*, dating to its start in 1950, are publically available online courtesy of Western University in Ontario.[51] Since September of 1985, there has been an entire scientific journal devoted solely to research in yeast (*Yeast*), whose pages offer frequent review articles.[52] After a half-century of

[50] Michael N. Hall and Patrick Linder, *The Early Days of Yeast Genetics* (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993); Peter W. Sherwood, "The Yeast Genetics Course at Cold Spring Harbor Laboratory: Thirty Years and Counting," *Genetics* 157, no. 4 (2001): 1399-1402.
[51] "Yeasts: A News Letter for Persons Interested in Yeasts," accessed June 6, 2016, http://www.uwo.ca/biology/YeastNewsletter. In later years the newsletter became “the Official Publication of the International Commission on Yeasts of the International Union of Microbiological Societies.”
[52] Gianni Litti (ed.), *Yeast (1985-2016)*, John Wiley & Sons Ltd., accessed June 6, 2016, http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1097-0061.

laboratory work on yeast sugar utilization and systematics, James Barnett produced a remarkable fourteen-part series in this journal on the scientific history of yeast research. I made ready use of his comprehensive bibliography in the tenth article, "Foundations of Yeast Genetics."[53] The enormous compilation of experimental evidence recounted from the perspective of the present state of knowledge in these fields was a useful reference which allowed me to better follow the exceptions, failures, and deviations arising from in my own sources. Finally, there is a short chapter on the scientific history of the yeast model organism given by *Neurospora* geneticist Rowland Davis in his comparative study of microbial models, and another describing the ambitions for its use as genomic "super model."[54] This text served as a helpful introduction to some of the main centers producing yeast research, but was limited in historical explanation. In

[53] J.A. Barnett, "A History of Research on Yeasts 1: Work by Chemists and Biologists 1789-1850," *Yeast* 14, no. 16 (1998): 1439-1451; J.A. Barnett, "A History of Research on Yeasts 2: Louis Pasteur and His Contemporaries, 1850-1880," *Yeast* 16, no. 8 (2000): 755-771; J.A. and Lichtenthaler Barnett, F.W., "A History of Research on Yeasts 3: Emil Fischer, Eduard Buchner and Their Contemporaries, 1880-1900," *Yeast* 18, no. 4 (2001): 363-388; J.A. Barnett and C.F. Robinow, "A History of Research on Yeasts 4: Cytology Part I, 1890-1950," *Yeast* 19, no. 2 (2002): 151-182; J.A. Barnett and C.F. Robinow, "A History of Research on Yeasts 4: Cytology Part II, 1950-1990," *Yeast* 19, no. 9 (2002): 745-772; J.A. Barnett, "A History of Research on Yeasts 5: The Fermentation Pathway," *Yeast* 20, no. 6 (2003): 509-543; J.A. Barnett, "A History of Research on Yeasts 6: The Main Respiratory Pathway," *Yeast* 20, no. 12 (2003): 1015-1044; J.A. Barnett, "A History of Research on Yeasts 7: Enzymic Adaptation and Regulation," *Yeast* 21, no. 9 (2004): 703-746; J.A. Barnett, "A History of Research on Yeasts 8: Taxonomy," *Yeast* 21, no. 14 (2004): 1141-1193; J.A. Barnett and K.D. Entian, "A History of Research on Yeasts 9: Regulation of Sugar Metabolism," *Yeast* 22, no. 11 (2005): 835-894; J.A. Barnett, "A History of Research on Yeasts 10: Foundations of Yeast Genetics," *Yeast* 24, no. 10 (2007): 799-845; A.A. Eddy and J.A. Barnett, "A History of Research on Yeasts 11. The Study of Solute Transport: The First 90 Years, Simple and Facilitated Diffusion(1)," *Yeast* 24, no. 12 (2007): 1023-1059; J.A. Barnett, "A History of Research on Yeasts 12: Medical Yeasts Part 1, Candida Albicans," *Yeast* 25, no. 6 (2008): 385-417; J.A. Barnett, "A History of Research on Yeasts 13. Active Transport and the Uptake of Various Metabolites," *Yeast* 25, no. 10 (2008): 689-731; J.A. Barnett, "A History of Research on Yeasts 14: Medical Yeasts Part 2, Cryptococcus Neoformans," *Yeast* 27, no. 11 (2010): 875-904. This series was compiled in James A. Barnett and Linda Barnett, *Yeast Research: A Historical Overview* (Washington, DC: ASM Press, 2011).

[54] Rowland H. Davis, *The Microbial Models of Molecular Biology: From Genes to Genomes* (New York: Oxford University Press, 2003), 61-72, 199-215.

response to the question posed as to why “the glory days” of yeast model organism research were delayed until the early 1970s, Davis offers the unsatisfactory conclusion that the research first had to be perceived as the foundation of major advances in biology. This dissertation work aims to identify and contextualize the reasons for those perceptions.

Chapter Organization

The first two chapters cover broad transformations in the study of yeast heredity over the approximate period 1860 to 1960. The gradual return of the complexity of the cell is the subject of the next three chapters, during the 1960s, 1970s, and 1980s, respectively. These are followed by a brief epilogue. Chapter 1 is divided into three sections offering a “pre-history” of yeast heredity along different lines of biochemical and statistical, microbiological, and genetic research. The first section describes the recognition of yeast variation and variety as a practical problem emerging out of the yeast-based industries from the mid-nineteenth century and the formation of a model describing yeast heredity as a matter of chemical difference. The second section follows the adoption of this chemical model of heredity by general microbiologists in universities in Delft, Netherlands, and Berkeley and Davis, California. The third section follows further adaptation and application of the chemical model of heredity in industrial and academic laboratories of the first biochemical geneticists.

Chapter 2 describes conflicting observations among the early laboratories of yeast genetic researchers. It follows the extensive negotiations required to develop yeast into a shared “experimental system” by 1956, and it traces the breeding of a particular yeast strain - as the conveyor of particular practices and possibilities – as the manifestation of this agreement in

"wild-type" *S. cerevisiae*. This analysis benefits from prior work on standards' setting in science.[55]

The third chapter investigates how the yeast experimental system was made representative of higher organism biology through the analogy of the eukaryotic cell. The chapter highlights the central role played by molecular geneticists at the University of Washington in Seattle and the benefits that began to accrue to favor the study of a single-celled eukaryote. Since the 1970s, yeast has served as a model organism in the sense that it provided simple representations of molecular structures and processes thought to be generalizable to higher eukaryotes, including humans. Yeast in these contexts has been used as a surrogate, or a descriptive model *of*. But there is another normative sense in which yeast has served as an exemplar or ideal. This is yeast as a model *for*.[56] In both senses, yeast models have served "as research tools and means of communicating scientific visions," to borrow from Nick Hopwood on representational devices in the sciences.[57] Model organisms themselves are meant to serve as

[55] The literature on standardization is extensive. Select examples include Adele E. Clarke, "Research Materials and Reproductive Science in the United States, 1910–1940," in *Physiology in the American Context, 1850–1940*, ed. Gerald L. Geison (New York: Springer, 1987), 323-350; Joan H. Fujimura, "Crafting Science: Standardized Packages, Boundary Objects, and "Translation"," *Science as Practice and Culture* (1992): 168-211; Adele Clarke and Joan H. Fujimura, *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences* (Princeton, NJ: Princeton University Press, 1992); Joan H. Fujimura, "Standardizing Practices: A Socio-History of Experimental Systems in Classical Genetic and Virological Cancer Research, Ca. 1920-1978," *History and Philosophy of the Life Sciences* 18, no. 1 (1996): 3-54; Geoffrey C. Bowker and Susan Leigh Star, *Sorting Things Out: Classification and Its Consequences* (Cambridge, MA: MIT Press, 1999).

[56] See Evelyn Fox Keller, "Models of and Models For: Theory and Practice in Contemporary Biology," *Philosophy of Science* 67, Supplement, no. 3 (2000): S72-S86; James Griesemer, "Three-Dimensional Models in Philosophical Perspective," in *Models: The Third Dimension of Science*, ed. Soraya de Chadarevian and Nick Hopwood (Stanford, CA: Stanford University Press, 2004), 433-442.

[57] Nick Hopwood, ""Giving Body" to Embryos: Modeling, Mechanism, and the Microtome in Late Nineteenth-Century Anatomy," *Isis* 90, no. 3 (1999): 496.

disciplinary tools. As stabilized material, they are expected to transfer technical and conceptual standards from local, specific sites of production to wider research communities.[58]

The fourth and fifth chapters examine this expectation, which I hold to have been shaped by the political advantages of research oriented to environmental health and biomedicine. Chapter 4 follows the development of new research and training opportunities at places like Cold Spring Harbor Laboratory, which emerged as yeast became a way to study the molecular mechanisms of human diseases, and cancer in particular. Chapter 5 extends the applications of yeast modeling to the biotech industry, where the genetically-engineered "cell factory" adopted the eukaryotic vision of "molecularized human" to specify the manufacture of human molecules. This chapter offers a case study of the first yeast-made human vaccine for Hepatitis B virus by researchers at the University of Washington in Seattle, the University of California, San Francisco, Chiron Corporation, and Merck, Sharp and Dohme Research Laboratories. The dissertation ends with a brief epilogue describing the ongoing role of yeast models to molecularize human health and disease. We are left to consider: have the humans or the yeasts been the engineers?

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[58] Rachel A. Ankeny, "Historiographic Reflections on Model Organisms: Or How the Mureaucracy May Be Limiting Our Understanding of Contemporary Genetics and Genomics," *History and Philosophy of the Life Sciences* 32, no. 1 (2010): 95. Some have argued that the scientific value of models derives from their inherent flexibility and hybridity, which makes them useful as experimental systems to multiple users. Successful laboratory organisms have "embodied a standard that could be reconfigured to suit local research agendas, while also remaining highly defined and capable of representing natural forms of life." Robert G.W. Kirk, ""Standardization through Mechanization": Germ-Free Life and the Engineering of the Ideal Laboratory Animal," *Technology and Culture* 53, no. 1 (2012): 61. On the concept of "interpretive flexibility" see Trevor J. Pinch and Wiebe E. Bijker, "The Social Construction of Facts and Artefacts: Or How the Sociology of Science and the Sociology of Technology Might Benefit Each Other," *Social Studies of Science* 14, no. 3 (1984): 399-441. See also Hans-Jörg Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube* (Stanford, CA: Stanford University Press, 1997).

Chapter 1

The Laboratory Organism: Heredity as Chemical Variation

As heredity emerged in the mid-nineteenth century as one of the central problems of biology, it was made a measurable and tractable research topic by the diagnosis and control of variety and variation in the yeasts.[1] Decades before yeast genetics was established as a breeding practice in the late 1930s and 1940s, these organisms helped to construct a set of statistical and chemical practices designed to investigate and make use of biological specificity. These methods became a source of hereditary speculation at the turn of the twentieth century. A new genetic science at that time was developed in other organisms and was adapted in yeasts and other microbes more than three decades later. This chapter will argue that the success of microbial genetics in the late 1930s and 1940s was a consequence of the reapplication of statistical and chemical practices developed in the yeasts in an earlier period.

The first section of this chapter covers that long transformation – the chemical, physiological, medical and statistical investigations of yeast fermentation and practices which emerged in and outside of the brewing industry. As industrially-useful yeasts became grouped taxonomically under just a few species varieties, microbial culture collections outside of the breweries served as a resource to identify what differentiated them from the wild infectious yeasts responsible for food spoilage and medical pathologies. The second section of this chapter

[1] The word "yeast" has had various meanings in different settings over time. I use the plural form at the start of the chapter since this group of organisms was undifferentiated for much of the nineteenth century. Throughout the chapter, when the singular form is used, it should retain this plural meaning unless reference is made to a single "type", "race", "species", "strain" or "population", such as "baker's" yeast, which today would be synonymous with the species *Saccharomyces cerevisiae*. Such categories are, as this chapter explains, widely variable over time.

explores how early twentieth century winemakers, food technologists and yeast manufacturers utilized an increasingly chemically-oriented microbiological classificatory system to achieve greater specificity among the yeasts for a number of purposes. The chapter's final section links these developments to the emergence of microbial genetics – first in *Neurospora*, *E. coli* and the phage – and later in a particular industrially-useful species of yeast. The next chapter will examine how growing collections of yeast stock, media, and research devotees over the 1940s and 1950s helped yeast geneticists make a bid for recognition by the larger discipline of genetics, and how yeast geneticists referenced the yeasts' legacy of contributions in science and industry as evidence of their likely continued relevance to genetics. This chapter examines those claims, finding them more accurate than probably realized, by tracing a number of scientific and industrial practices with the yeasts beginning in the nineteenth century.

SECTION I.

Pasteur's Culture Medium

Louis Pasteur was not the first to recognize the ferments – yeasts – as living organisms, but his experiments established the biological basis of fermentation and began to chemically define the conditions under which living yeasts could act. Where others saw chemical degradation of the fermenting broth, Pasteur anticipated causative microorganisms living in the air and growing in the broth's nutrients. Fermentation was produced by different microorganisms because the alkalinity, acidity, and chemical composition of the broth enabled differential growth and fostered biological competition. Organisms could be isolated, therefore, by sowing them

directly onto the broth to see which would take hold since "the life of each does not adapt itself to the same degree to different states of the environment."[2]

Pasteur's work on fermentation is perhaps best known for its refutation of the theory of spontaneous generation and for its substantiation of the germ theory of disease. Scholars before and since sociologist Bruno Latour have noted the significant transformation through which brewer's yeast became - in the mid-nineteenth century - "one instance of a whole class of phenomena," that is to say, microbial life. Few, however, have taken up what Latour briefly referred to as the transformation of Pasteur's "organic broth, which… is now made the food of organisms and becomes a medium of culture."[3] The chemical composition of the broth – the controlled environment of the yeasts – had attained organic significance because it had become determinant of the living yeast's survival. As Pasteur saw it in 1857:

> [I]f brewer's yeast instead of the lactic ferment is sown in limpid, sugared, albuminous liquid, brewer's yeast will develop, and with it, alcoholic fermentation [will again occur]... One should not conclude from this that the chemical composition of the two yeasts is identical, any more than that the chemical composition of two plants is the same because they grew in the same soil… One of the essential conditions for good fermentations is the purity of the ferment, its homogeneity, its free development without any hindrance and with the help of a nutrient well suited to its individual nature.[4]

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[2] Originally, "parce que leur vie ne s'accommode pas au même degré des divers états des milieux" in Louis Pasteur, "Mémoire Sur La Fermentation Appelée Lactique [1857]," in *Mémoires De La Société Impériale Des Sciences, De L'agriculture Et Des Arts De Lille* (Lille: impr. L. Danel, 1858), 23.

[3] Bruno Latour, "Pasteur on Lactic Acid Yeast: A Partial Semiotic Analysis," *Configurations* 1, no. 1 (1993): 135.

[4] Originally, "Si l'on sème dans le liquide sucré albumineux limpide de la levûre de bière et non de la levûre lactique, c'est de la levûre de bière qui se développera, et avec elle la fermentation alcoolique… Il ne faudrait pas en concure qu'il y aura identité de composition chimique entre les deux levûres, pas plus que la composition chimique de deux végétaux n'est la même parce qu'ils ont vécu dans le même sol…La pureté d'un ferment, son homogénéité, son développement libre, sans aucune gêne, à l'aide d'une nourriture très bien appropriée à sa nature individuelle, voilà l'une des conditions essentielles des bonnes fermentations," In Pasteur, "Mémoire Sur La Fermentation Appelée Lactique [1857]," 21-23.

Biological specificity in this case was thus a matter of preferential interaction – a "fitness" or correspondence – of the organism to its environment. Two yeasts fermenting in the same broth were not identical and may have had different nutritional needs. The brewer's ingredient, "yeast," could contain contaminants, but its individual "nature" could be nurtured by the conditions of the organic broth. Because yeast varieties emerged from the broths they created, conditions of the brewing broth were closely bound up in the organisms' identity.[5] The broth as culture medium was a central diagnostic tool in studies of yeast variety for nineteenth century brewers and taxonomists, and it would remain so for twentieth century geneticists in the application to yeast variation too.[6]

Fermentation Science

Early chemical interest in the yeasts arose from observation of the phenomena of fermentation. While a thorough history of fermentation research is beyond the scope of this chapter, it is significant to note that the plainly visible activity of the rising dough or fermenting broth was long a subject of curiosity before yeast was ever observed to exist. It was from the various products of fermentation that the first yeasts gained their identity and value.

The widespread natural occurrence of yeast in the air and soil - and on fruits and grains - suggests that spontaneous uses of yeast are likely as old as their human users, making yeast

[5] In 1883, "Erratic Enrique" quipped in the weekly farm periodical *Colman's Rural World* that, "Yeast was invented in the year leaven." The wordplay was sure to generate a few laughs from the local Anheuser-Busch Brewing Association for St. Louis' favorite fungus, and few people would have challenged the ancient (11 CE) and environmentally-prescribed (leavened dough) origins for yeast implicated in the pun. "This and That," *Colman's Rural World*, April 19, 1883. See also George F. Lemmer, "The Agricultural Program of a Leading Farm Periodical, Colman's Rural World," *Agricultural History* 23, no. 4 (1949): 245-254.

[6] Media is medial. The word literally means the intervening substance through which impressions are conveyed.

perhaps the world's oldest biotechnology. As the fermented properties of food and drink became desirable, preferred yeast species were selected empirically, and yeast was likely among the first organisms to be domesticated. While it is not known when yeast was first used intentionally for its fermenting and leavening properties, evidence continues to amass for yeast winemaking, bread-making, brewing, and distilling by ancient peoples in regions around the globe: beer in Mesopotamia from 6000 BCE, viticulture in Southwest Asia before 5000 BCE, bread-making in ancient Egypt from 2000 BCE, distilled spirits in ancient China from 25 CE.[7] Early biblical references to leavened and unleavened bread have given a basis to centuries of religious practices. Wine jugs too seem to abound across human history, most significantly because wine was free from the many disease-causing bacteria and viruses found in local water supplies.[8] Yeast's history is in a very real sense inseparable from the development of human civilization.

Many languages share a common root word for "yeast" and these cognates give a sense of the concept's age and significance. Shared derivations frequently serve as both nouns and verbs, as is the case with the English "ferment," and suggest that the yeasts' frothing or leavening actions and products had meaning before these were attributed to any specific agent. Select translations for yeast have been given as: "French levure; Italian lievito; Spanish levadura; German Hefe [or] yes (to ferment) and gäscht (ferment or boil); Dutch gist; Greek zéein (to boil), zestos (fervent, boil, hot), zethos (beer)... Medieval English… zeest or yest, Danish… gjœr,

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[7] See, for example, Delwen Samuel, "Ancient Egyptian Cereal Processing: Beyond the Artistic Record," *Cambridge Archaeological Journal* 3, no. 2 (1993): 276-283; Delwen Samuel, "Investigation of Ancient Egyptian Baking and Brewing Methods by Correlative Microscopy," *Science* 273, no. 5274 (1996): 488-490; H.T. Huang, *Fermentations and Food Science* (Cambridge: Cambridge University Press, 2000), 203-231; J.B. Lambert, *Traces of the Past: Unraveling the Secrets of Archaeology through Chemistry* (Cambridge, MA: Perseus Publishing, 1997), 137.

[8] Given the contemporary need for water sanitation improvements and infrastructure around the globe, today's ubiquitous plastic bottle may give some parallel to ancient amphorae.

Medieval Islandic jast, and medieval Scandanavian… jast."[9] Prose from the eleventh century gives the Old English "bearmteäge," meaning yeast-box, a word that has alternatively been translated to mean a box carried by its owner for safekeeping.[10] The term "goddisgood" was an alternate to "berme" in the fifteenth and sixteenth centuries and is a phrase indicating yeast's valuable action granted by "the grete grace of God," knowledge of which indeed required safekeeping.[11]

Early chemical research on alcohol fermentation is marked by a conspicuous absence of the yeasts. As chemistry emerged from its alchemic roots in the first half of the seventeenth century, fermentation attracted the Flemish physician Jan Baptista Van Helmont to characterize "gas sylvestre" as a byproduct of the process that could also be found in caves, mines, and wells.[12] It was only later that the Dutch microscopist Antoni van Leeuwenhoek produced what is believed to be the first recorded observation of germinating yeast, although he never supposed it

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[9] Robert K. Mortimer, Technical Documents, 1950-1999, (November 13, 1997), Box 5, Folder 16, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[10] The medieval English manor officer (the reeve) must have many objects, including yeast-boxes. In M.J. Swanton, *Anglo-Saxon Prose* (London: J.M. Dent, 1993). Original source: "Be Gescéadwísan Geréfan (Concerning Sagacious Reeves)," (Cambridge: Corpous Christi College, 11-12th century). The Dictionary of Old English (DOE) gives "bearmteag" as "yeast-box" or alternatively "lap-box" (a money box or a jewelry box that was carried about by the owner for safe-keeping). The addition of this alternative translation to the DOE is reported in *Old English Newsletter*, ed. R.M. Liuzza, 2 ed., vol. 37 (Kalamazoo, MI: The Board of the Medieval Institute, 2004), 19.

[11] As reported in Frederick James Furnivall, *Early English Meals and Manners with Some Forewords on Education in Early England* (London: Oxford University Press, 1868), xcviii.

[12] The sylvestre gas was released in making wine from the juice of grapes. Originally, "Nam ut farina differt à pasta fermentata, & massa farinacea à pane: ita vinum à succo uvarum. Atque ut farina, si coquatur, non parit flatus, fermentata autem, sponte flatus erućtat: ita cibi flatum natura sui non continent, quem fermenta eliciunt... Porrò de Gas musti, ac spiritus sylvestris proprietatibus, alibi, satis." In the posthumously-published work J.B. van Helmont, *Joannis Baptistae Van Helmont ... Opera Omnia: Additis His De Novo Tractatibus Aliquot Posthumis Eiusdem Authoris,Maximecuriosis Pariter Ac Perutilissimis, Antehac Non in Lucem Editis ; Una Cum Indicibus Rerum Ac Verborum Ut Locupletissimis, Ita Et Accuratissimis. Opuscula Medica Inaudita* (Francofurti: Erythropilus, 1682), 408.

to be a living organism. Leeuwenhoek described the dregs he saw clouding his glass of beer for philosophers of the still-fledgling Royal Society of London in June of 1680.[13] It was another hundred years before Italian naturalist Giovanni Valentino Fabbroni was theorizing that a "vegeto-animal" acted upon sugar to produce fermentation.[14] This phenomenon was taken up in the chemical investigations of Antoine-Laurent de Lavoisier, who believed that in wine fermentation the resulting products of carbonic acid gas and alcohol had to be equal in "quality and quantity" to the starting elements.[15] These early chemical studies were concerned with the composition of the fermented broth in which yeast was an important ingredient. Lavoisier had compared the proportions of sugar, water and yeast present in a mixture before and after fermentation and found a balanced chemical composition.[16]

By the beginning of the nineteenth century, the action of the ferment had come to interest "every class of society from the artisan to the philosopher, on account of its produce," according to the French chemist Louis Jacques Thénard. The fermented broth was an end unto itself but it was also the means of learning something about yeast's chemical reactions. Study of the phenomenon of fermentation might become a "fertile source of new reflections and truths,"

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[13] Antoni van Leeuwenhoek, ed. *The Collected Letters of Antoni Van Leeuwenhoek, Vol. III: 1679-1682* (Amsterdam: Swets & Zeitlinger, Ltd, 1948).

[14] Adamo Fabbroni, ed. *Dell'arte Di Fare Il Vino*, Edicion seconda ed. (Firenze: Presso Jacopo Grazioli, 1790), 166.

[15] Lavoisier wrote, "Upon this principle the whole art of performing chemical experiments depends: We must always suppose an exact equality between the elements of the body examined and those of the products of its analysis." In Antoine Lavoisier, *Elements of Chemistry*, trans. Robert Kerr (Edinburgh: William Creech, 1790), 130.

[16] French chemist Joseph Gay-Lussac revised Lavoisier's figures early in the nineteenth century and found slight differences in the mass of starting elements and the mass of the final products. See J.L. Gay-Lussac, "Extrait D'une Memoire Sur La Fermentation," *Annales de Chimie* 76 (1810): 245-259; J.L. Gay-Lussac, "Sur L'analyse De L'alcohol Et De L'ether Sulfurique, Et Sur Les Produits De La Fermentation," *Annales de Chimie* 95 (1815): 311-318.

Thénard argued.[17] Such reflections run through the writing of English poet John Keats, who in 1818, argued that the best of men were "propelled to act, and strive, and buffet with Circumstance" by "a kind of spiritual yeast" which created "the ferment of existence."[18]

A Living Ingredient

Alongside chemical studies of the yeasts, the organisms became objects of biological investigation for the first time in the 1830s, after the German physiologist Theodor Schwann, German botanist Friedrich Traugott Kützing, and French engineer Charles Cagniard-Latour independently asserted the yeasts' living nature.[19] In 1838, German botanist Franz J.F. Meyen derived the name *Saccharomyces cerevisiae* from the Latin for "sugar fungus of beer" for the common brewer's or baker's yeast.[20] Even as it became a botanical subject, then, this yeast was named for chemical and environmental associations (sugar and beer).[21]

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[17] Louis Jacques Thénard, "Memoir on Vinous Fermentation (1803)," in *The Repertory of Arts, Manufactures, and Agriculture* (London: J. Wyatt, 1806), 134.

[18] John Keats, "X.X.X.I. - to Benjamin Bailey (January 23, 1818)," in *Letters of John Keats to His Family and Friends*, ed. Sidney Colvin (London: MacMillan and Co., 1891), 61.

[19] See Theodor Schwann, "Vorläufige Mittheilung, Betreffend Versuche Über Die Weingährung Und Fäulniss," *Annalen der Physik* 117, no. 5 (1837): 184-193; Friedrich Kützing, "Microscopische Untersuchungen Über Die Hefe Und Essigmutter, Nebst Mehreren Andern Dazu Gehörigen Vegetabilischen Gebilden," *Journal für Praktische Chemie* 11, no. 1 (1837): 385-409; Charles Cagniard-Latour, "Mémoire Sur La Fermentation Vineuse," *Annales de chimie et de physique* 68 (1838): 206-223.

[20] J. Meyen, "Jahresbericht Über Die Resultate Der Arbelten Im Felde Der Physiologischen Botanik V. D. Jahre 1837," *Archiv fur Naturgeschichte* 4, no. 2 (1838): 100.

[21] Although the taxonomic boundaries of the yeasts have frequently been revised, the cultural familiarity of the industrial yeasts has warranted their collective reference under the singular term "yeast." This was originally the term for a biological ingredient which could contain many different desirable and undesirable organisms. For much of its history, "yeast" in singular form has also been used interchangeably to mean the species *Saccharomyces cerevisiae*, a taxonomic category into which many of industrial species once known by other names have been consolidated.

The living nature of yeast was taken to be an absurd concept by some in 1839, as evidenced by the anonymous publication of "The riddle of alcoholic fermentation solved." The article mocked the supposition that industrial yeast could be a tiny animal, and that fermentation was just the sum total of an organism's physiological processes. A personified yeast cell was described eating and digesting sugar, excreting alcohol, and draining carbonic acid from its bladder, which, when full, resembled a champagne bottle.[22]

With such quips circulating among scientists, yeast's biological nature became a subject of some interest to the general public. In 1840, after receiving multiple inquires, *Godey's Magazine* advised that the economy-minded housekeeper might "make" her own yeast by extracting yeast from the "settlings" of common family beer, or by mixing water, hops, wheat bran and flour, waiting, and then adding a good smart yeast.[23] But how does one "*originate* what is so indispensable," asked the fictional "Country Lady Housekeeper" in *The Horticulturist and Journal of Rural Art and Rural Taste*. The answer by 1856 was that yeast was a microscopic vegetable which developed spontaneously in the organs of putrefying plants and nitrogenous substances.[24] Readers of women's and agricultural magazines considered this explanation of spontaneous generation at the same time Pasteur was preparing his "Mémoire sur la fermentation appelée lactique" published in the following year – the first in a series of studies that would refute the theory.

[22] Originally, "Mit einem Worte diese Infusorien fressen Zucker, entleeren aus dem Darmkanal Weingeist, und aus den Harnorganen, Kohlensäure. Die Urinblase besitzt im gefüllten Zustande die Form einer Champagnerbouteille." In "Das Enträthselte Geheimnis Der Geistigen Gährung," *Annalen der Pharmacie* 29, no. 1 (1839): 101.
[23] L.A. Godey and S.J.B. Hale, *Godey's Magazine* (New York: Godey Company, 1840), 42-43.
[24] C. J. Wister, "The Yeast Plant," *Horticulturist and Journal of Rural Art and Rural Taste* 6 (1856): 271.

The shaping of yeast's chemical and biological identity was closely linked to its widespread power of metaphor. Literature of the nineteenth century shows us that yeast's fermenting and leavening activities were images with popular appeal. From the American poet Henry Wadsworth Longfellow in 1839, we have the Hesperus about to wreck in a storm at sea while "the billows frothed like yeast," and in 1854, the "rules" for using yeast were so closely entwined with daily living that they came to represent part of the sanctimony that the American author Henry David Thoreau sought to escape at Walden Pond:

> Leaven, which some deem the soul of bread, the spiritus which fills its cellular tissue, which is religiously preserved like the vestal fire — some precious bottleful, I suppose, first brought over in the Mayflower, did the business for America, and its influence is still rising, swelling, spreading, in cerealian billows over the land — this seed I regularly and faithfully procured from the village, till at length one morning I forgot the rules, and scalded my yeast; by accident I discovered that even this was not indispensable.[25]

By the middle of the nineteenth century, biologists and chemists began to debate this very point. Either yeast was an indispensable vital cause of the physiological process of fermentation, or else it had the chemical properties to trigger the decomposition of organic matter just like any other agent of putrefaction.[26] For observers of Pasteur, yeast provided an analogy for the existence and role of microbial life in disease processes, due to "speculations on germs, their nature, propagation, and functions, and their connexion [*sic*] with certain processes of disease."[27] The German chemist Justus von Liebig was a major proponent of the chemical alternative, arguing that the "ferment, or yeast, is nothing but [vegetable matter] in a state of decomposition… The putrefaction of… animal matters is a process identical with the

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[25] Henry Wadsworth Longfellow, *The Wreck of the Hesperus* (New York: E.P. Dutton and Company, 1886), 22; H.D. Thoreau, *Walden, or, Life in the Woods [1854]* (New York: Dover Publications, 1995), 40-41.
[26] A detailed account of this debate is given in Barnett, "A History of Research on Yeasts 2: Louis Pasteur and His Contemporaries, 1850-1880."
[27] C. T. Kingzett, "Germ Theory, 'Paper'," *Journal of the Society of Arts* 26 (1877): 312.

metamorphosis of the vegetable matters."[28] All processes resulted from the same instability of decomposing matter. Ferments were not alive, they were just carriers of that activity.

The Yeast-Based Industries

These biological and chemical investigations of the yeasts had cultural consequences for the yeast-based industries and a public that consumed yeasts' products. There had been many variations to the organization of brewing practices though the centuries. In Northern Europe, brewing had been a tradition of the monasteries until the first secular breweries were established there in the thirteenth and fourteenth centuries.[29] While there is some evidence that leavening agents were sold by bakeries and breweries for individual use at least from the fifteenth century, it would not have been any form we recognize as yeast today.[30] More likely it would have been a portion of dough starter or fermenting wort.[31] The Dutch began selling pressed cakes of yeast for

[28] J. von Liebig, *Animal Chemistry or Organic Chemistry in Its Application to Physiology and Pathologie by Justus Liebig: Edited from the Authors Manuscript, by William Gregory. With Additions, Notes and Corrections by Gregory, and Other by John Webster* (Cambridge: John Owen, 1842), 115.

[29] R.W. Unger, *Beer in the Middle Ages and the Renaissance* (Philadelphia: University of Pennsylvania Press, 2007), 38.

[30] In 1468, the Corporate Assembly of Norwich declared a maximum price that "certeyn… common brewers… for their singler lucre and avayle" could charge for yeast, which up until that point had "frely be yoven [given] or delyvered for brede whete malte egges or othir honest rewarde to the value only of a farthyng at the uttermost." Quoted in L.F. Salzman, *English Industries of the Middle Ages: Being an Introduction to the Industrial History of Medieval England* (Boston: Houghton Mifflin Company, 1913), 192.

[31] There was a late twentieth century revival of this practice among American home bakers who passed along yeast starters like chain letters. In one case in the late 1970s and early 1980s, a starter dough named "Herman" by a mother-daughter duo was particularly popular. Charlene Nevada, "Herman Is the Latest Starter for a Sourdough Bread with a Sweet Touch," *Chicago Tribune*, January 28, 1982, 1-N_A13; Betsy Balsley, "Sweet Herman's Fans Growing and Growing," *Los Angeles Times*, July 8, 1982, 4-K1; "Anne's Readers Exchange," *The Washington Post*, November 28, 1984; Phyllis Magida, "Friendship Cake Takes Time, but It Pays Delicious Dividends," *Chicago Tribune*, June 4, 1987; Dorothy Pohl, "A Diet of Bread and Commitment," *Chicago Tribune*, April 12, 1989, 17; Pat Dailey, "Cooks' Dialogue," *Chicago Tribune*, February

use in bread making from the 1780s. These were leftover remnants from the gin distilleries. At the turn of the nineteenth century, the Germans sold yeast in cream form and replaced this with dehydrated blocks produced from leftover brewer's yeast in 1825.[32]

Between 1857 and 1863, Pasteur's experiments with yeast fermentation in the presence and absence of oxygen had practical utility not just for brewers but also for these commercial preparations of yeast. He had shown that under conditions of limited oxygen, yeast would not readily reproduce and would instead produce large quantities of alcohol and carbon dioxide. These conditions held for rising dough, and when yeast was trapped in unaerated beer, wine or spirit mashes. However, when yeast fermented sugar in the presence of oxygen, the outcome of fermentation changed. Yeast no longer produced much in the way of carbon dioxide or alcohol end products; instead it used sugar to bud, divide, and make more yeast. Even as it began to connect biological processes of the organism to its chemical environment then, this newfound method of control over yeast reproduction implied tradeoffs for brewers and distillers between the production of alcohol and the yield of excess yeast to be sold for baking.[33]

21, 1991; Carol Lekel, "I Just Can't Get Started," *The Washington Post*, July 13, 1994; "Let's Get Started," *The Washington Post*, August 24, 1994; Nancy Wride, "The Blob of Guilt - Friends Don't Give Friends Amish Friendship Bread," *Los Angeles Times*, April 21, 1999.

[32] A.H. Rose and J.S. Harrison, *The Yeasts: Yeast Technology* (San Diego, CA: Academic Press, 2012), 402. The Germans dominated in this production until their technological advantage began to wane. For a history of distillery-made yeast in Britain after 1860, see Ron Weir, "Science, Marketing and Foreign Competition in the Yeast Trade,1860–1918," *Business History* 33, no. 4 (1991): 43-67.

[33] In 1901, the French civil engineer Gaston Dejonghe, who was professor at the Institut Industriel du Nord and former head of manufacturing at several large distilleries, wrote that he had seen how "aeration increases the production of yeast to the detriment of the yield of alcohol." Originally, "l'aération augmente la production de la levure au détriment de rendement en alcool." In G. Dejonghe, *Traité Complet Théorique Et Pratique De La Fabrication De L'alcool Et Des Levures*, vol. II (Lille: Imprimerie Typographique et Lithographique Le Bigot Freres, 1901), 729.

In Vienna, a new process for manufacturing granulated yeast set off rapid international growth of the yeast-making industry in the second half of the nineteenth century.[34] After being carried to the surface of fermenting wort by carbon dioxide bubbles, the yeast produced a foam that was then skimmed off, filtered, washed and compressed. Fleischmann & Co. adopted this process and introduced a new commercial yeast to American audiences at the 1876 World's Fair with a model Viennese bakery. Airborne yeasts had previously been used for baking and the commercial yeast was such an improvement that it met with immediate success.[35] New cafes serving Viennese baked goods and coffee began to open in the United States as leisure spots for the rich and sophisticated.[36] Although baker's yeast manufacturing patents were issued on 178 inventions worldwide before 1900, including a further "aeration process" that gave higher amounts of yeast as Pasteur had predicted, the Vienna process came to dominate because it entailed the simultaneous and profitable production both yeast and alcohol.[37] Alcohol acted as an antiseptic against the introduction of any "wild yeasts" in this process and could be sold for

[34] R.H. Thurston, *Reports of the Commissioners of the United States to the International Exhibition Held at Vienna, 1873* (U.S. Government Printing Office, 1876), 87.
[35] Fleischmann's had also established a large and efficient distribution system for its product. P.C. Klieger, *The Fleischmann Yeast Family* (Chicago: Arcadia, 2004), 15.
[36] Fleischmann & Co. (Cincinnati Gaff, Ohio), "Centennial Exhibition Vienna Model Bakery Erected by Gaff, Fleischmann & Co.," in *A Treasury of World's Fair Art & Architecture*, ed. University of Maryland Libraries Special Collections (1876); J.A. Dacus and J.W. Buel, *A Tour of St. Louis; or, the inside Life of a Great City* (St. Louis: Western Publishing Company, 1878), 293.
[37] Pierre Gélinas has disputed the common claim that Pasteur's yeast patent was the first to "patent life." Although it is true that there were earlier patents on yeast manufacture, yeast before Pasteur can fairly be said to not have been alive. Latour, "Pasteur on Lactic Acid Yeast: A Partial Semiotic Analysis," 11. Patent counts are taken from Pierre Gélinas, "Mapping Early Patents on Baker's Yeast Manufacture," *Comprehensive Reviews in Food Science and Food Safety* 9, no. 5 (2010): 484.

additional profit.[38] Such practices adopted scientific knowledge as much as they adapted and contributed to it.

Cellular Chemistry

In the second half of the nineteenth century, chemical investigations of yeast physiology had begun to focus attention on the internal composition of the living cell as a source of biological continuity.[39] The modern idea of cell as protoplasm surrounding a nucleus had been proposed by German histologist Max Schultze in 1861.[40] While later in the decade German zoologist Ernst Haeckel would propose that factors in the cell nucleus transmitted heredity, and the Swiss biologist Friedrich Miescher would discover nuclein, the chemical differentiation of protein from nucleic acids was still years away.[41] The "proteinaceous" protoplasm was believed

[38] By one approximation use of the Vienna process rather than the aeration process resulted in 3 to 10 fewer pounds of yeast, but 1.5 to 2 gallons more of spirits. In R.N. Hart, *Leavening Agents: Yeast, Leaven, Salt-Rising Fermentation, Baking Powder, Aerated Bread, Milk Powder* (Easton, PA: Chemical Publishing Company, 1914), 22. For more on the "méthode viennoise" and "Fabrication de l'aéro-levure pressée" see chapters 26 and 27 in Dejonghe, *Traité Complet Théorique Et Pratique De La Fabrication De L'alcool Et Des Levures*, II.

[39] Neil Morgan has described how organisms' "inwards" were believed to be increasingly significant to their physiology as they exhibited greater organizational complexity. In combination with the observations of English brewing technologists, the imported physiological conception of botany from Germany at this time placed a new emphasis on vitality rather than systematics. See Neil Morgan, "The Development of Biochemistry in England through Botany and the Brewing Industry (1870-1890)," *History and Philosophy of the Life Sciences* 2, no. 1 (1980): 141-166.

[40] Max Schultze, "Über Muskelkörperchen Und Das, Was Man Eine Zelle Zu Nennen Habe," *Arch. F. Anat. Physiol. Wissentsch. Medicin* (1861): 1-27.

[41] Haeckel suggested that the cell nucleus was responsible for reproduction and hereditary phenomena. Originally, "Indem der Zellenkern als hauptsächlicher Träger der Fortpflanzungs - und somit der Vererbungs-Erscheinungen…" In Ernst Haeckel, *Generelle Morphologie Der Organismen*, vol. 2 (Berlin: Georg Reimer, 1866), 122. Miescher discovered a phosphorus-rich substance in the nuclei of leukocytes which he named nuclein (later DNA) and which he suspected would prove equal in significance to the proteins. In Friedrich Miescher, "Ueber Die Chemische Zusammensetzung Der Eiterzellen," *Medicinisch-chemische Untersuchungen* 4 (1871): 441-460. Before allowing him to publish these results, Miescher's mentor, Felix Hoppe-

in all probability to be responsible for the vital and chemical activities of the cell. It was a term that gained popular attention after 1869, when Thomas Henry Huxley - the English biologist and staunch defender of Darwinian Theory - published a summary of the accumulated morphological, physiological, and chemical evidence for a "physical basis of life," interior to the cell.[42] Huxley argued that protoplasm was the most likely candidate for a material which could provide the essential structural character and reproductive function shared by all phenomena of life. He defended this view in the essay "Yeast."[43]

In recounting the accumulated evidence for the existence of such a material, Huxley's position generated strong criticism for threatening the "vast plan" with a chemical reductionism. If, as Huxley said, men and lobster could be made into one another through rearrangements of their substance, then nothing was left to sustain the hierarchy of the great chain of life, argued the Scottish philosopher James Hutchison Stirling.[44] In Stirling's view, the appalling "molecular

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Seyler, confirmed the findings in a study which identified nuclein also in the nuclei of yeast cells. Originally, "Es scheint sonach ein dem Nuclein der Eiterzellenkerne verwandter oder damit identischer Körper auch in den Hefezellen enthalten zu sein." In F. Hoppe-Seyler, "Ueber Die Chemische Zusammensetzung Des Eiters," *Medicinisch-chemische Untersuchungen* 4 (1871): 500.

[42] Thomas Henry Huxley, *On the Physical Basis of Life*, Fortnightly Review (New Haven, Connecticut: The College Courant, 1869). Huxley refused any novelty to his position, and noted that the word protoplasm had first been used by German botanist Hugo von Mohl in 1846. Gerald Geison has argued that "the struggle for the idea of a substance of life had already been fought and won by others; Huxley's main contribution, not untypically, was to communicate and to popularize the results of that victory… his prestige and brilliant rhetoric soon made protoplasm quite literally a household word." Gerald L. Geison, "The Protoplasmic Theory of Life and the Vitalist-Mechanist Debate," *Isis* 60, no. 3 (1969): 279.

[43] Thomas Henry Huxley, "Yeast," *The Contemporary Review*, December 1, 1871, 34.

[44] This moral objection wasn't the only argument against protoplasmic theory. Others argued against it in scientific terms. The amateur botanist Grant Allen, for example, argued in 1885 that the chlorophyll of plants might more fairly be characterized as the true "physical basis of life." In Allen's example, a yeast cell feeding directly or indirectly on the material of green plants would grow and reproduce whenever it reached a certain size, proving the chemical significance of chlorophyll for life. In Grant Allen, "Genesis," *The Eclectic Magazine of Foreign Literature*,1885, 236.

disposition" subjected "all vital and intellectual functions" to moral equivalence. Undifferentiated protoplasm also subjected biological specificity to a certain ambiguity as it did not offer a cause of life's seemingly infinite variety.[45]

The public controversy which surrounded protoplasm at the time of Huxley's speech began to dissipate in the 1870s once it appeared that complexity, morality, and specificity could be returned to the material. A new hybrid science was beginning to enable the study of physiology in chemical terms, and yeast would be its testing ground. In 1874, for example, a French physiological study seemed to confirm the position that the occurrence of animal putrefaction was chemically equivalent to the yeast fermentation of beer when the chemist Paul Schützenberger added yeast to arterial blood serum and found that yeast absorbed oxygen. The deoxygenated blood turned black, proving yeast's role as a respiring and putrefying ferment.[46]

Further resolution seemed possible in the late 1870s, with the proposal by German physiologist Wilhelm Kühne that there were in fact two different chemical and physiological ferments. In 1878, Kühne coined the word "enzyme," meaning literally, "in yeast" to clarify this difference.[47] The term was meant to designate soluble material or "unorganized" ferments, such

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[45] "We are more curious about the modification than the protoplasm. In the difference, rather than in the identity, it is, indeed that the wonder lies." In J.H. Stirling, *As Regards Protoplasm, in Relation to Professor Huxley's Essay on the Physical Basis of Life* (New Haven, CT: Charles C. Chatfield & Co., 1871), 15, 63 and 70.

[46] Paget Higgs, *Schutzenberger on Combustion in the Animal Organism*, vol. II, The London Medical Record (London: Smith, Elder & Co., 1874). See also Kingzett, "Germ Theory, 'Paper'," 311.

[47] Kühne wrote, "[O]n the one hand, it was objected that chemical bodies… could not be called ferments, since the name was already given to yeast and other organisms… while on the other hand it was said that yeast cells could not be called ferment, because then all organisms, including man, would have to be so designated… I have taken the opportunity to suggest the name enzyme for some of the better known substances, called by many unformed ferments… The name …is intended to imply that more complex organisms from which the enzymes, pepsin, trypsin, and so on, can be obtained, are not fundamentally different from the unicellular organisms." Originally, "…allgemeine Zustimmung nicht erwerben können, indem von der einen

as those chemicals "in yeast" which might be shared by other organisms.[48] Kühne defined enzyme in contrast to the "organized" ferments, such as yeast itself, which had until then, by the analogy of fermentation, been held responsible for all of life's chemical processes. In time, as the word enzyme came into use as a non-specific term for a chemical catalyst that extended beyond yeast, fermentation came to be understood as a process less generalizable than previously supposed.[49]

In France, the physiologist Claude Bernard, an older contemporary of Kühne, was at this time revisiting the question of whether life could be considered a specific, spiritual, or *vital* force or whether there could be some general, natural laws to describe it mechanistically.[50] He showed that yeast could persist in a dried desiccated form to survive unfavorable "atmospheric vicissitudes." When the yeast was later revived, Bernard thought it had been an example of life in a latent state.[51] A colleague observed that the noxious external environment had made "beer

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Seite erklärt wurde, man könne chemische Körper… nicht Fermente nennen da der Name schon an Hefezellen und andere Organismen vergeben sei … während von der andern Seite gesagt wurde, Hefe könnten kein Ferment sein und heissen, weil man dann alle Organismen, mit Einschluss des Menschen dazu mache… habe ich zunächst aus dem blossen Widerspruche Anlass genommen, einen neuen vorzuschlagen, indem ich mir erlaubte, einige besser bekannte, von Manchen als ungeformte Fermente bezeichnete Substanzen Enzyme zu nennen…. in der Zyme etwas vorkomme… gesagt, dass verwickeltere Organismen, aus denen die Enzyme: Pepsin, Trypsin u.s.w. zu gewinnen sind, nicht so grundsätzlich von den einzelligen verschieden seien." In W. Kühne, "Erfahrungen Und Bemerkungen Über Enzyme Und Fermente," in *Untersuchungen Aus Dem Physiologischen Institute Der Universität Heidelberg: 1877*, ed. C. Winter (Universität Heidelberg. Physiologisches Institut, 1878), 293.

[48] See Robert E. Kohler, "The Enzyme Theory and the Origin of Biochemistry," *Isis* 64, no. 2 (1973): 188.

[49] See Mikuláš Teich, "Ferment or Enzyme: What's in a Name?," *History and Philosophy of the Life Sciences* 3, no. 2 (1981): 215.

[50] Bernard has been cited on both sides of the vitalism/mechanism debate, and likely held a more nuanced position which allowed him to engage flexibly in these discussions. In Christiane Sinding, "Claude Bernard and Louis Pasteur: Contrasting Images through Public Commemorations," *Osiris* 14 (1999): 67.

[51] C. Bernard, *Leçons Sur Les Phénomènes De La Vie Communs Aux Animaux Et Aux Végétaux* (Paris: Baillière, 1878), 94-96.

yeast [fall] asleep like man under the influence of ethereal vapors."[52] Even in its unique responses to conditions of the environment, yeast shared a fundamental unity, a vital enchantment, with higher organisms.

Bernard sought a general description of this physiology common to animals and plants. He described life as a property of higher organization and complexity, which allowed for the organs, tissues and other constituents of the organism to exist only as a consequence of their protection in an "interior environment" which functioned as a kind of greenhouse to protect against "the ever-changing cosmic environment."[53] Although he did not refer to single-celled organisms, his ideas proved influential in the breweries as we will see.[54] These two environments of the organism, "an *outside environment* in which the body is placed, and an *interior environment* in which the tissue items live" constituted a compromise for biological forms to be explained as both protected and penetrable, from and by a reductive chemistry.[55]

By the 1880s, the chemical research agenda with yeast was clear. It would evaluate the reactions of organisms with their external environments while also moving to the cell's interior to investigate fermentation as a physiological process. "That yeast is the agent which causes the decomposition of sugar into alcohol and carbonic acid is indisputable, and that it appropriates

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[52] Originally, "la levûre de bière s'endormant comme l'homme sous l'influence de vapeurs éthérées." In the "Discours de M. Paul Bert" reprinted in ibid., xxix. I provide a detailed analysis of the power of yeast as a metaphor and model of human biology in a later chapter of this work.
[53] Originally, "C'est un organisme qui s'est mis lui-même en serre chaude" and "il est enveloppé dans un milieu invariable qui lui fait comme une atmosphère propre dans le milieu cosmique toujours changeant." In ibid., 112.
[54] I refer especially to the influence of Bernard's writing on the Danish botanist Wilhelm Johannsen, who worked for the Carlsberg laboratory chemistry department in the 1890s, and later coined the terms "genotype" and "phenotype." Early yeast genetics will be discussed later in this chapter.
[55] Emphasis in the original: "un *milieu extérieur* dans lequel est placé l'organisme, et un *milieu intérieur* dans lequel vivent les éléments des tissus." In Bernard, *Leçons Sur Les Phénomènes De La Vie Communs Aux Animaux Et Aux Végétaux*, 112.

some of this sugar for the purposes of its own nutrition is equally certain, but in what way its power is exerted is a question upon which eminent chemists are still at issue," read one popular English weekly magazine of science in 1882.[56] By this period, the cause of fermentation had many theoretical variations. In one encyclopedic entry, it could be explained by acid theory, contact theory, influence theory, chemical theory, galvanic theory, and germ theory.[57]

Part of the confusion was that the meaning of biological specificity had begun to change over the 1880s and early 1890s from a description of the preferential interaction of organism and environment to the causal mechanism of this interaction. Biochemical investigations refocused the question of specificity onto which material - protoplasm or enzyme - created the "fit" of evolutionary fitness. The two theories sought to explain rather than describe organism-environment interaction as specific. The brewers, meanwhile, already had reason for their practice and would continue to exert control over the brewing environment. At the end of the century, they sought to manipulate yeast variety and variation using microbiological and statistical approaches.

Yeast Races at Carlsberg Brewery

The Carlsberg brewery in Copenhagen had been founded in 1847 with the intention of developing "the art of making beer to the greatest possible degree of perfection."[58] By the 1870s, the newly-established Carlsberg Foundation had begun to operate a laboratory separate from the commercial interests of the brewery. The Carlsberg laboratory had been charged with developing

[56] *Knowledge: A Monthly Record of Science*, (London: Wyman & Sons, 1882), 210.
[57] F.A.P. Barnard and A. Guyot, *Johnson's New Universal Cyclopædia: A Scientific and Popular Treasury of Useful Knowledge* (New York: A.J. Johnson & Company, 1881), 66.
[58] Quoted in "1811-1870: Founding Carlsberg," accessed November 20, 2014, www.carlsberggroup.com.

"as complete a scientific basis as possible for malting, brewing and fermenting operations" and was expected to transform the brewing art into a science of perfection.[59]

Such a science of perfection was newly available in the 1870s, following Charles Darwin's stirring assertions about the deep unity of organic life, as well as recent statistical developments which enabled the characterization of groups. Population thinking was as old as the administrative and surveillance needs of the modern state, but in the hands of Darwin's half-cousin, the statistician Francis Galton, it was given a novel biological interpretation.[60] In the late nineteenth century, the centuries-old elaboration of social statistics was giving birth not just to the modern social sciences, but a metrics of the attributes between and within populations.[61] These metrics were constructed at the same time Galton was deriving a vision of society which had had continual disregard for natural selection and was thus stagnating and "regressing toward the mean." As remedy, he advocated a eugenic science that would lift society by acting at the level of the individual in order to improve population averages.[62] Eugenics would be a statistical 'science of perfection' in its population-based strategy for human improvement.[63]

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[59] Jacob Christian Jacobsen, Carlsberg Foundation Charter, (1876), The J. C. Jacobsen Family Archive, Carlsberg Group, Copenhagen. See also H. Holter and K.M. Møller, *The Carlsberg Laboratory: 1876-1976* (Copenhagen: Rhodos, 1976).

[60] Dorothy Porter, *Health, Civilization and the State: A History of Public Health from Ancient to Modern Times* (New York: Routledge, 1999).

[61] Ian Hacking, *The Taming of Chance* (Cambridge: Cambridge University Press, 1990).

[62] Galton's hereditarian vision for human society first appeared in Francis Galton, "Hereditary Talent and Character," *Macmillan's Magazine* 12, no. 157-166 (1865): 157-166.

[63] Galtonian eugenics has been depicted as a foundational and enduring part of contemporary genetic practice in this population-based strategy. See Nathaniel C. Comfort, *The Science of Human Perfection: How Genes Became the Heart of American Medicine* (New Haven: Yale University Press, 2012), 9. In the eugenic view, as long as they "lifted the average", both positive and negative population-based strategies could contribute to society's improvement by increasing favorable and decreasing unfavorable characteristics of interest. Comfort's analysis comes as a significant critique of a still popular belief offered by evolutionary biologist Ernst Mayr in 1959. Mayr offered that it was Darwin who had innovated population thinking while doing away with typologies. The argument was meant to ground genetics in a respectable

The brewers' art could be made into a science of perfection in the 1870s by borrowing from a statistical tradition that brought population thinking together with yeast "types" to allow comparisons between groups of individual cells. Statistics offered the mathematical rigor of a science. Since improvements to the plants and animals making up the breeders' stock required the comparison of large numbers in order to detect change, such observations could be set on a scientific basis with the use of summary statistics. These developments predate Carlsberg's yeast breeding program by many decades, but this early statistical logic was applied in the brewery laboratories not for strain improvements, but for another purpose. Yeast contributed to applications of statistics which treated biological specificity. We will see that over time, as uncertainty crept in to the fixity of yeast "types," so too did statistical methods emerge to account for this uncertainty and to preserve the standard type concept for the industrial varieties.

In the 1870s, establishment of the laboratory at Carlsberg enabled more frequent and regular experimentation with yeasts, separate from the demands of batch production at the brewery. Even before the laboratory, Carlsberg had conducted fermentation trials. As a young man in the 1860s, Carl Jacobsen - namesake of the brewery and son of Carlsberg founder Jacob Christian Jacobsen - traveled Europe to collect yeasts from various breweries and ship these to

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tradition, while distancing the eugenic impulse toward "types" as a shameful aberration from Darwin's insights. Genetics in the postwar period wanted no ownership of the biased, hierarchical and antiquated form of typological thinking which had come before Darwin, and lingered as an early misinterpretation of his work. Reprinted in E. Mayr, "Typological Versus Population Thinking," in *Evolution and the Diversity of Life: Selected Essays* (Cambridge: Belknap Press of Harvard University Press, 1997), 26-43. Mayr's view that "modern" genetics is free of its eugenic past continues even in very recent genomic practice. Lisa Gannet has noted, for example, that because of its resistance to within-group homogenization, population thinking is frequently characterized as an "ethical" approach to thinking about racial differences in genetic terms. Yet population thinking has not ensured a non-racist and/or anti-racist science of human genome diversity research. In Lisa Gannett, "Racism and Human Genome Diversity Research: The Ethical Limits of 'Population Thinking'," *Proceedings of the Philosophy of Science Association* 2001, no. 3 (2001): S480.

his father back in Copenhagen. During his travels, Carl was instructed to collect especially the English and Scottish yeasts and to learn the methods by which they produced porter and ale fermentations.[64] He observed fermentation tanks made of wood and glass in Vienna, oversaw the processing and shipping operations of a new starter from Edinburgh, and requested that his father send detailed accounts of any failed fermentations so that they might correct flaws in the shipping or brewing processes.[65] Sometimes a yeast failed to complete the journey, and other times it was the methods for its cultivation.

In an effort to master use of foreign yeasts, some method of distinguishing and cataloguing the organisms was required for their systematic study. The development of "pure cultures" by Emil Christian Hansen brought such a method to Carlsberg. Hansen was hired as head of the physiology department in the new Carlsberg laboratory with a charge to study organisms important to the industry. He delighted in this opportunity to work for the "zymotechnologists" and saw himself in the mold of Pasteur, whose direct application of scientific discoveries to "practical life" he greatly admired.[66]

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[64] Jacob Christian Jacobsen, Letter to Carl Jacobsen in Experiments with Fermentation with Yeast Skoktsk, (January 14, 1869), The J. C. Jacobsen Family Archive, Carlsberg Group, Copenhagen; Jacob Christian Jacobsen, Latter to Carl Jacobsen About Yeast, Fermentation and Ice Supplies, (February 1, 1869), The J. C. Jacobsen Family Archive, Carlsberg Group, Copenhagen.

[65] Carl Jacobsen, Letter to Jacob Christian Jacobsen About Yeast and Fermentation Takes Made of Wood and Glass. Clubs and Malt, and More, (January, 1868), Letter 1 of 3 letters, The J. C. Jacobsen Family Archive, Carlsberg Group, Copenhagen; Carl Jacobsen, Letter to Christian Jacob Jacobsen, Carl Sends Yeast Home from Edinburg with the Ship "Gnome", (December 30, 1868), The J. C. Jacobsen Family Archive, Carlsberg Group, Copenhagen; Carl Jacobsen, 8 Pages Long Letter in French to Jacob Christian Jacobsen About Yeast, Ice and Time Grois, the Placing of the Monument of Tycho Brahe, (January 21, 1869), The J. C. Jacobsen Family Archive, Carlsberg Group, Copenhagen.

[66] Pasteur's interest in the "practical life" is quoted in Emil Christian Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms* (London: Spon and Chamberlain, 1896), iv. See also page 9 for Hansen's message to the zymotechnologists

In the 1880s, Hansen found that multiple organisms made up the yeast mixture that Carlsberg reused from brew to brew. Repitching, as it was called, was common practice to begin the next batch of beer with a bit of yeast from the last.[67] Pasteur had observed a variety of physiological differences among the cells that made up repitched mixtures, and believed that bad batches of beer resulted from yeasts that had been contaminated by bacteria and molds. To avoid these bacterial diseases of beer, Pasteur had recommended that breweries use a microscope to sort and suppress bacterial growth in favor of the yeasts, which were distinguishable by their larger cell size.

At Carlsberg, Hansen used a microscope to examine the microbes present in repitched mixtures and counted the number of cells suspended in a liquid drop. He used a method of dilution to separate the cells into flasks of nutrient liquid and then looked for those flasks in which only single "specks" seemed to be growing.[68] These, he determined, were "pure cultures" produced from the replication of a single cell.[69] Next, Hansen sorted his pure yeast cultures into

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[brewers]: "*The best*" - meaning the scientific approach - "*is not too good for practice*." Italics in original.

[67] In London, this practice is believed to have been conducted intentionally since at least the 1650s. See Leeuwenhoek, *The Collected Letters of Antoni Van Leeuwenhoek, Vol. III: 1679-1682*.

[68] In Germany, the physician Robert Koch was isolating microbes on solid media, but Hansen was not yet aware of this technique. The liquid dilution method Hansen adapted was that of the British surgeon Joseph Lister. It was performed by adding drops of sterilized water to a preparation until on average there was expected to be less than one cell per drop. Hansen sought to improve on Lister's precision with the extra step of separating drops into flasks and waiting for the growth of single "specks."

[69] Hansen explained, "The only certain way under all circumstances by which we can obtain a pure culture of a micro-organism, whatever physiological and morphological properties it may possess, is *to sow a single cell in a sterilised nutrient medium*…" In Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*, 142; Holter and Møller, *The Carlsberg Laboratory: 1876-1976*; Staffan Müller-Wille and Hans-Jörg Rheinberger, *A Cultural History of Heredity* (Chicago: University of Chicago Press, 2012), 135-136.

"races" according to the various qualities of the broth important to industry.[70] Some of the yeasts Hansen isolated rose to the top of fermenting brews, and these produced ales. Others could be found gathered at the bottom, and these yeasts made lagers. Decades later Hansen would question whether the yeast transitioned between these varieties or if they indeed represented distinct types.[71]

As Hansen began to assemble a collection of yeasts, he systematically recorded their fermentation outcomes, along with their points of entry into his collection. Such origins included, for example, "From Guiness [*sic*] in Dublin," "From grape, St. Anthon," and "isolated from an ulcer of the hand from Dr. Rasch." While intended for tracking purposes, these pre-Carlsberg origins provided the yeasts with a cultural heritage in the place of natural history. Only their last human contact could be known with certainty. Hansen also distinguished his yeasts using morphological or physiological identifiers, like "Bark sweating," "With odour of ether," or "Tiny." When possible, these data were combined with sourcing information: "Red yeast cells from the wood-work of a green-house," "Red yeast No. 36, mentioned by Janssens and Mertens

[70] "One and the same yeast does not suit all breweries…. there are several species or races of culture yeast… [and] these give beers dissimilar in their character… Every brewer therefore must select, according to a definite plan, a species which suits his brewery." In Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*, 21.

[71] In a 1907 paper (later reprinted), he was inclining toward variation by mutation. Originally, "Die Resultate meiner Untersuchungen, und zwar insbesondere der Nachweis einer so starken Konstanz bei den Oberhefen, könnten vielmehr darauf deuten, daß die Oberhefen die älteren in der Natur seien, die Unterhefen aber die jüngeren, welche sich aus jenen entwickelt hätten. Was die Faktoren betrifft, welche diese Variationsbewegung, hin und her, in Gang bringen, habe ich bis jetzt noch keine eigentliche Aufklärung bringen können. In dieser Hinsicht , läßt sich also von den hier behandelten Erscheinungen eben dasselbe sagen, wie von jener Variation bei den Phanerogamen, welche nach HUGO DE VRIES gewöhnlich Mutation genannt wird, und eben dieser Kategorie werden sie, jedenfalls vorläufig, am besten beizuzählen sein." In Emil Christian Hansen and A. Klöcker, *Gesammelte Theoretische Abhandlungen Über Gärungsorganismen* (Jena: G. Fischer, 1911), 411. See also J. Friis, "The Carlsberg Laboratory: Historical Retrospect and Personal Reminiscence," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 447.

in ‘La Cellule’ 1903,” or “Olive-green; from bumble bee.”[72] This was the first detailed taxonomic system of the yeasts and related the cultural origins and products of yeast “races” to cellular structures and functions.

Hansen discovered that it was not just bacteria but also certain yeasts which could ruin the taste or clarity of a beer. He recommended use of the pure culture method in order to isolate and propagate just the preferred yeast races. Uncharacterized “wild” yeasts would need to be guarded against.[73] The following year, Jacob Christian Jacobsen described the change which had been implemented at Carlsberg: “From now on, all fermentation will be carried out in my brewery with this pure yeast, from a single cell!”[74] The organism had taken on a temporal dimension, extending the “same” cell out in multiple generations through time.[75] The

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[72] See these original designations in Øjvind Winge and Aase Hjort, "On Some Saccharomycetes and Other Fungi Still Alive in the Pure Culture of Emil Chr. Hansen and Alb. Klöcker," *Comptes Rendus des Travaux du Laboratoire Carlsberg. Série Physiologique* 21, no. 1 (1935): 53-57.

[73] For many this was easier said than done. “We have, says the *Brewer’s Guardian*, repeatedly impressed upon brewers the very great importance of obtaining yeast as pure as possible for pitching purposes, and have advised continual and diligent search with the microscope, followed by a system of careful selection; brewers must not, however, be disappointed, if they fail to achieve an impossibility, that is, to obtain a yeast in which no organisms but *Saccharomyces cerevisiae* can be detected.” "Uses of the Microscope in Brewing," *Scientific American*, October 6, 1883, 214.

[74] Jacob Christian Jacobsen, Photo Copy of on Extensive Letter to Gabriel Sedelmyr About J.C. Jacobsen's Experiences with Yeast, (May 7, 1884), The J. C. Jacobsen Family Archive, Carlsberg Group, Copenhagen.

[75] John Simmons Ceccatti has written that “Hansen’s [pure culture] system was based on the belief that [yeast] species and varieties possessed characteristics that remained relatively constant from generation to generation. If the brewer of laboratory scientist could select the correct one and cultivate it under sterile conditions to prevent other organism from infecting it, then the culture would retain these properties and be useful in the brewery.” Ceccatti examined debates over pure yeast culture in late nineteenth century Germany to show the importance of traditional skill and artisanal craft knowledge of the brewer in the reception of scientific knowledge, and while pure yeast culture may have indeed represented the challenge of “pure science” to German craft brewers, it is perhaps overly simplistic to contrast, as Ceccatti has, Hansen’s view of yeast species with the “Lamarckian” manipulation of brewing conditions to maintain useful varieties. Hansen’s uncertainties about yeast heredity, variation and variety continued *despite* the development of yeast pure culture, as we will see. For Ceccatti’s investigation, see John

standardization achieved by use of a pure culture also enabled the consistency and profitability of industrial production.

Around the world, brewers, vintners, pressed yeast factories, and distillers took up the new technique with varying levels of commitment and success.[76] Schlitz Brewery in Milwaukee was an early advocate and introduced pure cultures the same year of their creation in 1883.[77] While Hansen's work is most often invoked for this practical transformation of yeast-based industries, pure cultures also provided a means of differentiating and tracking various yeast types and were thus significant for developments in the developing science of microbiology and especially yeast taxonomy, physiology, and ecology. The yeast "races" also raised questions about biological specificity, variation and variety.

Simmons Ceccatti, "Science in the Brewery: Pure Yeast Culture and the Transformation of Brewing Practices in Germany at the End of the 19th Century" (PhD diss., University of Chicago, 2001), 55, 123.

[76] In 2009, an advertisement for Carlsberg lager which aired in Ireland described how, in 1883, the brewery had a secret. It had developed "a pure yeast other brewers would have done anything to get their hands on," and yet they just gave it away. Owens DDB, *The Secret*, Irish Ads, 2009, Carlsberg. Not all brewers were so eager for "the secret", however. Nearly a decade after Hansen's discovery, the English chemist Percy Frankland noted that, "As far as this country is concerned… Hansen's researchers have hitherto been of little more than theoretical interest; scientific men and brewers have made themselves acquainted with his results, and in some cases have conducted laboratory experiments on the same lines, but in hardly a single instance… have his methods been introduced or adopted on a large scale." Percy Frankland, "Recent Contributions to the Chemistry and Bacteriology of the Fermentation Industries," *Journal of the Society of Arts* 40 (1891): 933. Neil Morgan has described the contested introduction of laboratory technique to the English brewing industry in Morgan, "The Development of Biochemistry in England through Botany and the Brewing Industry (1870-1890)," 155-159. Hansen himself described the difficulty he had in convincing Jacobsen to alter brewing practices at "Old Carlsberg," and it took until 1892 for the invention to reach baker's yeast manufacture at De Danske Spritfabriker in Hansen's native Denmark. In Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*.

[77] Schlitz mechanical engineer William Uihlein brought pure cultures to Milwaukee after studying under Hansen at Carlsberg. In M. Hintz, *A Spirited History of Milwaukee Brews & Booze* (Charleston, SC: History Press, 2011), 16. The yeast vendor Wahl & Henius, Pabst and other large U.S. breweries, followed suit not long after. *One Hundred Years of Brewing: A Complete History of the Progress Made in the Art, Science and Industry of Brewing in the World, Particularly During the Last Century*, (Chicago: H.S. Rich & Company, 1901), 80.

Pre-genetic Yeast Heredity in the Breweries

Brewing outcomes varied by the initial yeast variety, but, Hansen realized early on in his experiments, "appreciable irregularity" could result over time even from pure cultures. In 1883, for example, a bad batch of beer at Carlsberg revealed four yeasts in the broth, only one of which resulted in a normal beer of good flavor and odor.[78] The yeast produced this outcome only when the fermenting broth was aerated. If there were any changes to this condition, the beer was again spoiled. Such observations led Hansen to conclude that, "The characters which we make use of for distinguishing different species of animals and plants have no absolute validity, but are constant only under certain conditions." These were the conditions of the broth in which the cells had been cultivated.[79] After nature and the brewer had done their selecting of a type, Hansen found the broth could produce changes across "numberless" yeast generations.[80] The environment had its own laws and constraints upon biological variability – this time not to variety, but to variation.

The variability of environmental conditions which had allowed Hansen to briefly raise questions about yeast variation among the races *despite* the use of pure cultures could not be

[78] He identified this as the lager species, Carlsberg bottom yeast, No. 1. In E.C. Hansen, "Recherches Sur La Physiologie Et La Morphologie Des Ferments Alcooliques V. Methodes Pour Obtenir Des Cultures Pures De Saccharomyces Et De Mikroorganismes Analogues.," *C. R. Trav. Lab. Carlsberg* 2 (1883): 92–105.
[79] This observation of variability despite the use of pure cultures was grounded in common brewing knowledge relating yeast to its environment, for example: "As soon as yeast is admitted into a medium which contains the nourishment it requires it will at once commence to grow till its full size is reached, and then it will reproduce itself by forming new cells." In C.R. Bonne, *C.R. Bonne's Instructions on Yeast and Ferments* (1885), 1.
[80] Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*, 92, 93 and 187.

accommodated outside the brewery within the biochemical paradigm.[81] Indeed, among academic scientists yeast variation went unrecognized for several decades. Only after the triumph of the enzymatic theory of cell metabolism did yeast variation later resurface with the question of enzymatic adaptation. Biochemists could not study the effects of changing environmental conditions until they could explain the interaction of an organism with a single, stable environment.

Yeast variety was foremost the brewers' concern and the use of pure cultures was meant to purify this key ingredient into a single type. For Hansen, variation was only an occasional concern in the brewing practice and would shortly be explained away by another development in the science of statistics. Hansen warned against the belief that "impure" mixtures could create beers of the same character as those produced by yeast pure cultures. Brewers could "obtain a finer and above all a constant product, but one differing somewhat from their former beer" if they brewed from a single yeast variety. Proprietary mixtures might be a possibility, but, "It would be going too far, should it come about that every brewery wished to have its own species." Really, the industrial yeasts were very few.[82]

Hansen published his scientific system for classifying the yeasts in 1884, and this German edition was translated to English in 1896. In the intervening years, a quote from Charles Darwin had taken on additional significance at Carlsberg and now preceded even Pasteur's endorsement of the "practical life" in the book's opening pages. "No doubt man selects varying

[81] I use 'paradigm' in the Kuhnian sense to refer to the prevailing framework of scientific concepts and practices, although some exceptions should be noted – in particular, general microbiological practices of the Delft School, which will be discussed in detail later in the chapter. On scientific paradigms see Thomas S. Kuhn, *The Structure of Scientific Revolutions* (Chicago: University of Chicago Press, 1962).

[82] "At the present time there is a tendency in this direction [for each brewery to claim for itself a different yeast], and my object therefore it to warn against this." In Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*, 21-22.

individuals, sows their seeds, and again selects their varying offspring. But the initial variation on which man works, and without which he can do nothing, is caused by slight changes in the conditions of life," Darwin had written.[83] For Hansen, the organic broth established the conditions for a narrow range of industrial improvements to yeast pure cultures. There was some room for variation of a type by mimicking evolutionary selection, but the yeast's pre-Carlsberg origins most strongly predicted the productivity of the race.

Yeast in Germ Theory

In the 1890s, a detailed description of the yeast races was also a goal for medical bacteriologists concerned with pathogenic and perhaps even therapeutic varieties of yeast. Their interest related to the practical successes of germ theory, which was an older concept that had taken on new meaning at the end of the nineteenth century. In one sense, germ theory was the old vital or physiological theory of fermentation: as fermentation's "germ" grew it consumed and deconstructed sugar, and this was *analogous* to disease processes. This idea had appeared as early as 1665, with the description of plague, by Dutch physician Isbrand van Diemerbroeck, as a pestilent *leaven* whose hostile germ was a poison diffusing through the air.[84] This analogy was

[83] Charles Darwin, *The Variation of Animals and Plants under Domestication, Vol. I* (London: John Murray, 1868). In Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*, iv. The German edition is Emil Christian Hansen, *Untersuchungen Aus Der Praxis Der Gärungsindustrie* (München: Berlag von R. Oldenbourg, 1884).

[84] He wrote, "the origin of the fumes… is the most malignant, a hidden, poisonous, noxious, germ, most hostile to human nature, and sent down from heaven. The smallest quantity injected into the air, like a subtle kind of ferment, expands itself through the air and, defiling it." Originally, "prima originem fumis, est malignissimum, occultum… venenosum, & naturae humanae infensissimum pestilens seminarium, coelitus… demissum, quod minimia quantitate aëri infusum, instar subtilis cujusdam fermenti sese per aërem dilatat, eumque inquinat." In Ysbrand van Diemerbroeck, *Isbrandi De Diemerbroeck Med. Doct. & Profess. Tractatus De Peste, in Quatuor Libros Distinctus: Truculentissimi Morbi Historiam Ratione & Experientia Confirmatam Exhibens; Ab Auctore Emendatus, Plurimisque in Locis Adauctus* (Amstelaedami:

still evident in the late Victorian poetry of Gerard Manley Hopkins, who wrote of souring yeast – a scourge to both blood and spirit: "Bitter would have me taste: my tasted was me;/Bones built in me, flesh filled, blood brimmed the curse./Selfyeast of spirit a dull dough sours."[85]

To the old analogy, however, a new cause had been identified. The "contagium vivum" worked its effect by the rapid multiplication of microscopic organisms which invaded the systems of healthy humans and animals in order to propagate disease.[86] By the time the "germ theory of disease" came into use as shorthand for the discovery of disease-causing bacteria by the physician Robert Koch, Pasteur and others in the late nineteenth century, yeast microbes were suspected to be *specific* causal agents of a small number of human diseases.[87]

As much as yeast had supplied the analogy, the low hanging fruit of germ theory in the 1880s and its sister science of bacteriology were predominantly disease-causing bacteria. Reports of the harms associated with yeast became more prevalent in the 1890s, and it is in this latter period that *Saccharomycosis hominis* ("the sugar fungus infection of man," later *Cryptococcus neoformans*) and another skin disease-causing yeast (later *Blastomyces dermatididis*) were identified.[88] In 1896, an editor of *Medical News* forecast that, "a flood of literature by a host of

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Typis Joannis Blaev, 1665), 23. See also N. Webster, Hudson, and Goodwin, *A Brief History of Epidemic and Pestilential Diseases: With the Principal Phenomena of the Physical World, Which Precede and Accompany Them, and Observations Deduced from the Facts Stated: In Two Volumes* (Hartford: Hudson & Goodwin, 1799), 13-14.

[85] "I wake and feel the fell of dark, not day", published posthumously in Gerard Manley Hopkins, *Poems*, ed. Robert Bridges (London: Humphrey Milford, 1918), Poem, no. 45.

[86] Compare germ theory as it appears as a subentry to fermentation and as its own entry: Barnard and Guyot, *Johnson's New Universal Cyclopædia: A Scientific and Popular Treasury of Useful Knowledge*, 66, 531.

[87] On the history of medical mycology see A. Homei and M. Worboys, *Fungal Disease in Britain and the United States 1850-2000: Mycoses and Modernity* (Basingstoke, UK: Palgrave Macmillan, 2013).

[88] Otto Busse, "Ueber Saccharomycosis Hominis," *Virchows Archiv* 140, no. 1 (1895): 23-46; T Casper Gilchrist, "A Case of Blastomycetic Dermatitis in Man," *Johns Hopkins Hospital Reports* 1 (1896): 269-283.

investigators working in the new field [of medical mycology] will be poured upon us during the next year or two. Pathology has its fashions, and every one [*sic*] wants to be in fashion."[89]

The sciences to which yeast was related – botany, bacteriology, biochemistry, cytology, and enzymology – were developing rapidly in this period. In the 1890s, the desire to reconcile the older fermentation analogy with new insights into cell biology and theories of infection was at the heart of scientific debate. Yeast was a point of intersection for old theories and the new, sometime simultaneously. A news report out of Milwaukee at this time is illustrative.

Physician Maximilian Herzog had been in town only a week in 1894 when he told the City Council that most vaccines then in use against small pox were "bogus" and did not produce a genuine immunological response. He sought to expose the vaccine producers as murderers. Proper vaccination would have been indicated by an abundance of small pox bacilli circulating in the blood, and this was not the case for most patients in Milwaukee's Isolation Hospital. As a student of Darwinian theory and the pure culture methods of Hansen, Herzog also claimed grounds to profess a "new germ theory" about the agent responsible for the ferment of the blood. He would show that Koch and other modern physicians were mistaken to think that bacilli were the true causes of disease. Just as a granule of yeast protoplasm called the nucleus was responsible for fermentation of beer, similarly, a smaller germ living on the cell walls of microorganisms, a parasitic amoeboid, could be found in infected blood.[90] Herzog and others had

[89] The author does not give this "new field" a name, but summarizes evidence implicating yeast in the production of certain tumors. This new oncologic-mycology was to deal with yeast-caused pathologies, including, variously, infection, parasitology, and the etiology of malignant neoplasms. "The Yeast Plants as a Pathogenic Organism," *Medical News* 68, no. 9 (1896): 246.
[90] Herzog's discovery of the infinitesimally small "Small-Pox ameba" is also reported in "Medical Notes," *Boston Medical and Surgical Journal* 131, no. 23 (1894): 569.

observed these small bodies in yeast pure cultures.[91] Although Herzog's bacteriological revelations now "puzzled learned doctors," Milwaukee's Health Commissioner believed they would rank with the Koch discoveries.[92]

It is not surprising that Herzog could maintain such seemingly inconsistent explanations for disease causation by both the "amoeboids" of yeast as specific germs and by yeast's nucleus as a protoplasmic ferment causing decay. The identities of the yeasts were enormously in flux on either side of the Atlantic. In Europe, at the same time regular consumption of baker's yeast was being recommended in France as a diabetes treatment, *The Lancet* was pinpointing bread from the "insanitary bakehouses" as a probable source of disease since baking did not destroy the vitality of microbes contained in the dough.[93] The English scientific literature was identifying only select species of yeast as beneficial or harmful, while popular publications made no such distinction.[94] In the U.S., *Harper's Bazaar* printed in 1897 that scientists had placed bread "under the ban" and that yeast was to blame, although the scientists themselves had not claimed this. The reporter supposed that yeast germs were passing alive into the stomach, rapidly

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[91] Yeast spores likely account for the "parasitic amoeboids" Herzog observed in culture. He states that the culture preparations lacked nutritive material, which was later found to be a way of inducing a form of asexual reproduction known as sporulation.

[92] He hastened to add that no direct criticism had been levied against the vaccines used by his Health Department. In "Use Bogus Vaccine," *Chicago Daily Tribune*, November 27, 1894.

[93] E. Cassaet, professor at the Bordeaux school of medicine, reported that he observed weight and strength gains among his patients after administration of yeast, along with reductions to sugar in the urine. "Brewers' Yeast in Diabetes," *Medical and Surgical Reporter* 73, no. 11 (1895): 314. The *Lancet* study found 13 microbes still living in baked bread. In F.J. Waldo and David Walsh, "Does Baking Sterilise Bread? Being an Inquiry, on Bacteriological and Other Grounds, as to How Far Baking Affects the Vitality of Organisms in Dough," *The Lancet* 72, no. 2 (1894): 908.

[94] This despite the availability of publications geared toward the lay baker which contained information about species differences. In 1885, for example, C.R. Boone of Manchester offered private yeast cultivation instructions and supplies with the information that, "All kinds of yeast met with in practice – whether it is called brewers' yeast, German, French, Dutch, English, or Scotch – belong strictly to the same species, the latin [*sic*] name of which is *saccharomyces cerevisiae.*" In Bonne, *C.R. Bonne's Instructions on Yeast and Ferments*, 1.

multiplying, fermenting, producing acidity, retarding digestion and causing dyspepsia and other ills. According to "several experts, medical and lay," dough should therefore be raised with Royal Baking Powder lest "the staff of life becom[e] the staff of death."[95] This was a significant change from 1880, when *The New York Times* reported that Tough, Dough & Co.'s Squeezed Yeast made bread so light that it was turning bread-making by the "yeast of our mothers" into a lost art.[96] The earlier reflection was akin to the sanctimony and ceremony surrounding yeast's use in the days of Thoreau.

Therapeutic uses of yeast continued to be studied in the French context, while elsewhere even industrial varieties were considered to be possible pathogens. A medical thesis out of the University of Paris in 1902 called attention to the great variation in brewers' yeasts obtained from different breweries, from different barrels in the same brewery, and from different stages in the fermentation process within the same barrel. "Despite extensive study," the author wrote, "brewer's yeast is not well known therapeutically. It is a medicine of varying composition, and it is this variability that is to blame for a number of failures observed in practice. Its mode of action is unknown; we consider it an active ingredient acting as a modifier of the general condition." Nonetheless, fresh or dried brewer's yeast could be administered for treatment of a variety of diseases including typhoid fever, skin, tonsil and vaginal infections, diabetes, constipation and stomach flu, and acute and chronic bronchitis and pneumonia.[97] As long as its chemical mode of action remained unknown, yeast's treatment efficacy remained plausible if unreliable.

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[95] "The Scientists and the Bread," *Harper's Bazaar*, October 30, 1897, 905.
[96] "Yeast: A Problem," *The New York Times*, October 10, 1880, 6.
[97] Originally, "Malgré de nombreuses recherches, la levure de biêre est très mal connue en thérapeutique. C'est un medicament de composition variable, et c'est à cette variabilité méme qu'il faut imputer nombre d'insuccès observes dans la pratique. Son mode d'action est inconnu; on lui considère un principe actif agissant comme modificateur de l'état general… Ses indications sont: la fièvre typhoīde, l'érysipèle, la furonculose, et certaines dermatoses

Despite the high initial expectations for hygienic breakthroughs, ultimately, the yeasts would not provide a second fertile phase of bacteriological successes. They would instead contribute to another fledgling science then in development. Biochemistry was about to assert the ascendency of an enzymatic rather than protoplasmic theory of life, and yeast was its evidentiary grounds.[98]

By 1904, *Harper's Bazaar* would tell its readers that women could become more interested in their daily routines if they applied the science of the "infinitely little" to household details. Yeast germs floating "forever in the air, seeking what they may devour and when they may develop" could be prepared as a "culture" by the good bread-maker. Within the household walls, she might earn a Ph.D. either in biology or in chemistry.[99] Increasingly, yeast research straddled both subjects.

Brewers' Statistics

The collection of yeast races also motivated eugenic selection efforts for their improvement, and related statistical methods developed to address a pre-genetic concept of yeast heredity. Racial improvement of yeasts at the turn of the twentieth century sought to improve

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suppuratives; vaginite, diabète, angine phlegmoneuse. Les gastro-entérites, constipation habituelle, grippe intestinale. Enfin elle pourra ētre employée dans les pneumonies et bronchitis aiguēs et chroniques des vieillards." In Durdan-Laborie, "Revue Des Thèses. Médicaments Nouveaux. - Médications Nouvelles: De La Levure De Bière Et De Son Emploi Dans Le Traitement De Certaines Affections Pulmonaires Du Vieillard. M. Lardier (1902)," *Bulletin général de thérapeutique médicale, chirurgicale, obstétricale et pharmaceutique* 145 (1903): 623-624. The thesis is Jean Lardier, "De La Levure De Bière Et De Son Emploi Dans Le Traitement De Certaines Affections Pulmonaires Du Vieillard" (Doctorat en Médecine diss., Université de Paris, 1902).

[98] Robert Kohler linked the organization of American medicine around laboratory science to the disciplinary origins of biochemistry since the new "physiological chemistry" could help to explain pathological processes. See Kohler, "The Enzyme Theory and the Origin of Biochemistry," 183, 193-195.

[99] "Housekeeping and Biology," *Harper's Bazaar*, July, 1904, 729.

brewing stock by repeated selection of the "best individuals." "It is not only required that the species or race shall keep all those properties which are of value for the practical man," wrote Hansen's laboratory assistant Albert Klochner in 1903, "but it is desired that at the same time such individuals shall be selected as will vary in a manner serviceable to the brewery concerned, i.e., possess good qualities in a high degree and lose undesirable ones." Yeasts need not be "blood relations" to agree in these botanical characteristics. They need only come from the best products' fermenting vats.[100] Their relatedness was defined, like their identity, by shared environments. Heredity and specificity were two sides of the same coin. The yeasts' "cultural heritage" could be used to order the yeasts hierarchically and to separate the wild yeasts from those with industrial abilities. Once this separation of yeast races had been made, the pure culture method could be used to investigate one yeast at a time, and the brewer could perpetuate the best performers.

Darwin had begun to dissociate the concepts of evolution, heredity and development. After Hansen established a method of distinguishing yeast races by the first criteria, the latter remained questions in the brewers' selection program at Carlsberg. The challenge for Hansen and Klochner was that the organic broth could trigger both temporary and permanent changes to yeast pure cultures over time. Permanent changes pointed toward the existence of laws which sustained the variation "through endless generations" and "all methods of treatment," Klochner observed in 1903.[101]

Systematic observation of these laws required sampling techniques and the use of statistical methods to determine just how representative any given sample of cells was to the

[100] Albert Klockner, *Fermentation Organisms: A Laboratory Handbook*, trans. G. E. Allan and J. H. Millar (New York: Longmans, Green, and Co., 1903), 243-244.
[101] Ibid., 13-14.

larger group. Differences needed to be derived on the basis of individual measurements, made representative of the whole. In this way, yeast standard "types" emerged statistically from the *multi*-cellular representations of a species, over time. In Hansen's words: "Since we take the single cell as our starting point in the preparation of our pure cultures, the growths which we obtain represent the individual particularities occurring in the species…. if we wish to avail ourselves of the behaviour of the cells under external influences for the purpose of characterising species, we must never depend exclusively on the behaviour of the single cell, but we must take the collective behavior of a number of them."[102]

Evidence for the brewers' use of statistics in its connection to variability in a yeast population is apparent in the Dublin brewery of Arthur Guinness, Son and Company, in the early years of the twentieth century. There, a practical problem in the brewery sent Guinness employee William Gosset, to seek statistical advice from Galton's heir and protégé, the biometrician Karl Pearson.[103]

While attempting to calculate the amount of yeast present in a batch of Guinness beer, Gosset was confronted by the limitations of his cell-counting tool, the hemocytometer.[104] The Oxford chemist had prepared his sample of beer by killing the yeast with mercuric chloride to stop cell growth and then setting the cells with gelatin beneath his glass. He had established

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[102] Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*, 95, 97.

[103] Gosset had recommended that Guinness consult a mathematician in 1904, in a report discussing the applications of probability theory to work in the brewery. In Philip J Boland, "A Biographical Glimpse of William Sealy Gosset," *The American Statistician* 38, no. 3 (1984): 179. See also Tonse N. K. Raju, "William Sealy Gosset and William A. Silverman: Two "Students" of Science," *Pediatrics* 116, no. 3 (2005): 732.

[104] The hemocytometer had been developed by German, French, and English physicians the late-nineteenth century to count the number of red and white blood cells in a cubic millimeter of blood. See Jack David Davis and Evan Melhado, *The Hemocytometer and Its Impact on Progressive Era Medicine* (Urbana, IL: University of Illinois, 1995).

counting rules for the distribution which determined that cells settling to the right-hand and lower part of the his counting squares would be considered as belonging to that square, while cells which sank to the bottom of the preparation belonged to a different "population" and should not be counted at all. He planned to shake the samples vigorously to detach the offspring of budding yeast but he expected some buds would be indistinguishable from fully formed yeast and would accidently increase his estimates.[105] Here Gosset faced a statistical dilemma – given that cells occupying any given square affected the chances of other cells appearing there, what was the probable error of his counting method?

In July of 1905, Gosset arranged a meeting with Pearson for advice on his yeast cell counting problem. In attempting to calculate how many cells in a sample of beer needed to be counted before an accurate estimate of the yeast population could be made, Gosset had found the existing tools of statistical analyses lacking.[106] As he later explained, "it is sometimes necessary to judge of the certainty of the results from a very small sample, which itself afford the only indication of the variability. Some chemical, many biological, and most agricultural and large scale experiments belong to this class, which has hitherto been almost outside the range of statistical inquiry."[107] Since different varieties of yeasts grew poorly or well in the same broth, and since growth rate could differentiate one yeast from another, a count of yeast cells could

[105] Carlsberg's approach to this particular counting problem was that it did not matter how the cells were counted as long as the same rule was always followed. In Klockner, *Fermentation Organisms: A Laboratory Handbook*, 128.

[106] Gosset's friend and brewing colleague, Lance McMullen later reflected that "scientific methods and laboratory determinations were beginning to be seriously applied to brewing [at the turn of the century], and [Gosset saw that] some knowledge of error functions would be necessary." This was because "[t]he circumstances of brewing work, with its variable materials and susceptibility to temperature change and necessarily short series of experiments, are all such as to show up most rapidly the limitations of large sample theory." In L. McMullen, ""Student" as a Man," *Biometrika* 30 (1939): 205.

[107] Gosset, writing under the pseudonym, Student, "The Probable Error of a Mean," *Biometrika* 6, no. 1 (1908): 2.

provide indication that brewing was proceeding as expected and that the intended species of yeast was in use, or that the next stage of the process had not yet been reached.

At first, Gosset objected to Pearson's use of the statistical term "population" to express a number of things or people of the same kind. Other related terms such as species, race, or type lacked the suggestion of the individuality of its members who were grouped by some shared characteristic. He sought "a word in common use" to express what "population" could, but he was unsuccessful and the word made its way into his own writing.[108]

Current statistical methods to estimate populations from a sample required large numbers of samples in order to establish reliable estimates of significance, and Pearson had no immediate solution for Gosset. He was irritated with the messiness of the practical problem, later grumbling over variation in the sample size that "only naughty brewers take *n* so small that the difference is not of the order of the probable error of the summation."[109] But more accurate population estimates were not possible during the brewing process since yeast counts could change in the time that it took to draw and prepare large numbers of samples. As the yeast continued to reproduce, extraneous variation would enter the calculation.[110]

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[108] William Sealy Gosset, *"Student's" Collected Papers* (Biometrika Trustees, University Press, 1958). Karl Pearson's son Egon Pearson became an extensive biographer of Gosset, see also Egon S. Pearson, "'Student' as Statistician," *Biometrika* 30, no. 3/4 (1939): 211, 213, 219; Egon S. Pearson, "Studies in the History of Probability and Statistics. X.X. Some Early Correspondence between W.S. Gosset, R.A. Fisher and Karl Pearson, with Notes and Comments," *Biometrika* 55, no. 3 (1968): 445-457; Egon S. Pearson et al., *Student: A Statistical Biography of William Sealy Gosset* (Oxford: Clarendon Press, 1990), 37.

[109] Karl Pearson, September 17, 1912, quoted in Boland, "A Biographical Glimpse of William Sealy Gosset," 181.

[110] Joan Fisher Box, daughter of the statistician Ronald Fisher, later described the problem with applying population parameters to a sample: "You cannot get samples of thousands of experimental points. Any experiment large enough would spread so far out in time and space that extraneous variation would drown out any effects of treatment you might be looking for." In Joan Fisher Box, "Guinness, Gosset, Fisher, and Small Samples," *Statistical Science* 2, no. 1 (1987): 45.

The Carlsberg brewers had not recognized the statistical problem that Gosset was raising at Guinness. They had also wished to generalize from a small number of samples, but did so by rough approximation of a "constant average." Counting cells under the glass of a hemocytomer was done regularly at Carlsberg to seed a certain quantity of yeast cells into liquid culture. The technique was also used to compare the relative number of cells in several cultures or to determine the "multiplying power" of cells in the same culture after varying intervals of time. Often the samples were preserved on ice or with sulphuric acid to prevent reproduction to keep their numbers fixed. Variability in these results was blamed on operator error rather than the methods themselves.[111] Gosset hoped that new calculations might be able to correct for this.

Gosset and Pearson worked together to determine the amount of uncertainty involved in a brewing inference given a small sample size. Their initial 1905 meeting culminated in a year of study abroad in Pearson's Biometric Laboratory in 1906-1907, and a series of publications in the journal *Biometrika* followed.[112] Gosset published under the pseudonym "Student" as was company policy at Guinness, and his solution for small number calculations came to be known at Student's t-test.[113] Together with earlier statistical innovations – such as Pearson's x^2 test for

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[111] "If the counting has not been done with precision, or if the material does not allow of an exactly average sample being withdrawn, the result will not be so good." Klockner, *Fermentation Organisms: A Laboratory Handbook*, 129. "As a matter of course, experiments must also be made in order to determine the number of small squares whose cell contents must be counted in order to arrive at a true average. Such a counting and determination of the average numbers is continued until the number finally obtained is found to have no further influence on the average value. The number of countings necessary, and the accuracy generally, depend on the experience and care of the observer. Hansen found that, as a general rule, it was sufficient to count the cells in 48 to 64 small squares." In A.P.C. Jørgensen, A.K. Miller, and E.A. Lennholm, *Micro-Organisms and Fermentation* (F.W. Lyon, 1893), 35.

[112] *Biometrika* had been established in 1901 by Galton, Pearson and Walter F.R. Weldon for the purpose of developing the statistical theory of biological data.

[113] Gosset's *Biometrika* publications include the following papers. Like the eighteenth-century French mathematician Siméon Denis Poisson before him, Hansen first expressed the distribution of his cell counts under a fixed interval as a measure of probability. In Student, "On the Error of

goodness of fit – this work set statistics on a new course at the turn of the century.[114] Rather than merely a descriptive summary of data, increasingly the discipline was becoming a set of uncertainty calculations which allowed generalizations about unobserved data to be made with varying levels of confidence. Still used widely in biomedical research, including genomic studies, to determine statistical significance in cases of a small number of observations, "Student's t-test" provided Guinness a statistical control to characterize a population from a small sample of yeast culture. The test relied on an assumption of the comparability of data which had been assured by the use of pure cultures in standard brewing practice. Even as it dealt with variation, then, the statistics of yeast treated populations as referent types. Varieties needed to be stable, and population variation minimized, if between-group differences were going to be detected.

At the end of the nineteenth century and the beginning of the twentieth, both Gosset and Hansen were seeking controls over yeast variation in the brewing process. While Hansen developed the "pure culture" by isolating and extending a single cell to define a yeast "type" which could be judged against others for industrial selection, Gosset extrapolated a small number of observations of that yeast's "population" based on its definition as a pure culture type. He ignored observations which were assumed to belong to other populations (i.e., the bottom-dwelling cells) because these characteristics were not part of the standard for a culture. A yeast

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Counting with a Haemacytometer," *Biometrika* 5, no. 3 (1907): 351-360. He then worked out an estimate of the cell "population" and probable error, a calculation which came to be known as his "t-test." In Student, "The Probable Error of a Mean," 1-25. The uses of this test were later described in Student, "An Explanation of Deviations from Poisson's Law in Practice," *Biometrika* 12, no. 3/4 (1919): 211-215.

[114] See C. Radhakrishna Rao, "R. A. Fisher: The Founder of Modern Statistics," *Statistical Science* 7, no. 1 (1992): 34-48.

classificatory system had already been established and formed the cultural and biological basis of the cells which would count. It was now reinforced statistically.[115]

In practice, this gave Guinness greater confidence than Carlsberg about the fixity of yeast types in the opening years of the twentieth century as compared to the 1880s. Population statistics had assumed even more consistency among yeast species and races than did pure cultures. In the early 1890s, Hansen's collaborator, Alfred Jörgensen, director of a private Danish fermentation laboratory, had estimated that the liquid dilution method worked to isolate single cells fifty percent of the time - half the flasks in any given trial would receive single cells. Hansen's pure culture method had improved upon this result by the "exact method" of shaking flasks and watching the points at which cultures grew.[116] The following decade Gosset used probability theory to estimate that closer to one-third of the flasks actually received single cells in the pure culture method, but he could be more certain about which these were. Three of four flasks showing growth contained pure cultures.[117] There was less precision than had been hoped using the pure culture method, but accuracy could be improved upon with statistical calculations. Although one in four batches of beer might be contaminated by the use of multiple yeasts, these impure batches were to be expected mathematically. They no longer indicated variation within a pure culture, but rather the common and measurable contamination of a batch by unintended

[115] In the early 1920s, Fleischmann Yeast Company was interested in funding yeast research to further develop population statistics. Sharon Kingsland has described how Fleischmann's approached biologist Raymond Pearl to run a laboratory there in 1923. Pearl, who had just arrived to at Johns Hopkins, declined the offer but later approached the company to request funding for his university laboratory. The company declined. In S.E. Kingsland, *Modeling Nature* (Chicago: University of Chicago Press, 1995), 61-62.
[116] Hansen's exact method improved upon the probable purity of "fractional cultivation" by liquid dilution. In Jørgensen, Miller, and Lennholm, *Micro-Organisms and Fermentation*, 27-29.
[117] Forty percent of flasks received some cells, and three quarters of those with growths came from single cells. See the table given in Student, "On the Error of Counting with a Haemacytometer," 357.

types.[118] In the coming years, these unintended types would be better defined by an examination of the "wild yeasts" responsible for wine and food spoilage. This would produce chemical controls over species and strain variability in addition to the morphological, physiological and statistical controls over yeast types, races, pure cultures, and populations.

Enzymatic Specificity

Like many of his contemporaries in the 1890s, Hansen had believed that investigations of the yeast protoplasm might reveal "what it is in the cells which effects the changes or which produces this or that result."[119] In England at this time, a hybrid theory had implicated both protoplasm and enzymes in metabolic activity according to a physiological division of labor. Huxley's insistence on an evolutionary role for the protoplasm had produced a compromise: protoplasm ran chemical reactions inside the cell, and enzymes promoted chemical activities outside the cell where they were secreted.[120]

Toward the end of the decade, the enzymatic theory gained significant traction after the German chemist Eduard Buchner demonstrated that a liquid crushed and pressed from the yeast cell could ferment sugar without the presence of a living organism. In 1897, Buchner reasoned

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[118] Although multiple species had only recently come to be defined as an impurity in yeast fermentation, this was said to be based on "the principle which has been recognized and carried out for centuries in horticulture and agriculture, namely, that in order to obtain the desired species of plant, the pure seed should be sown free from the seed of all other plants." In Jørgensen, Miller, and Lennholm, *Micro-Organisms and Fermentation*, 227.

[119] Hansen, *Practical Studies in Fermentation: Being Contributions to the History of Microorganisms*, 102.

[120] Neil Morgan has described how Victorian botanist Joseph Reynolds Green put forward the hybrid theory to account for metabolic change as a consequence of scale and degree of differentiation between lower and higher life forms. Green called for an end to the distinction between organized and unorganized ferments alongside other botanists on the continent. See Morgan, "The Development of Biochemistry in England through Botany and the Brewing Industry (1870-1890)," 160.

that the agent responsible for this independent chemical reaction was smaller than yeast protoplasm. He called the cell-free liquid, "zymase" for the ferment of yeast.[121] Zymase was yeast's enzyme, Buchner argued, and there was no physiological ferment. All ferments were enzymes - both "in yeast" and in every other living thing.

This marked an end for protoplasm theory.[122] Fermentation, which had been "an important *secret*" involving yeast and "an *abracadabra"* at the start of the century, could now be obtained outside of the cell.[123] Moreover, as the German chemist Emil Fischer had shown by the mid-1890s, the chemical reaction of enzymes and sugar molecules were specific. Only certain

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[121] "Es war demnach gelungen, die Gährwirkung von den lebenden Hefezellen abzutrennen; als Träger derselben wurde ein Enzym-ähnlicher Eiweisskörper, die Zymase, angesprochen." Eduard Buchner, "Alkoholische Gärung Ohne Hefezellen," *Berichte der deutschen chemischen Gesellschaft* 30, no. 1 (1897): 1110. For more on the significance of the zymase discovery to developments in biochemistry see Barnett, "A History of Research on Yeasts 3: Emil Fischer, Eduard Buchner and Their Contemporaries, 1880-1900," 363-388.

[122] However, when Buchner received the 1907 Nobel Prize in Chemistry for his discovery, he claimed that "Neither the physiologists nor the chemists can be considered the victors." In Eduard Buchner, "Nobel Lecture: Cell-Free Fermentation," *Nobelprize.org* (1907): 119. Robert Kohler has described how Buchner's discovery of zymase was used to justify biochemistry as a new field only following a much longer period of consensus building. Kohler details number of additional contributions to the formulation and eventual triumph of enzyme theory. In Robert E. Kohler, "The Reception of Eduard Buchner's Discovery of Cell-Free Fermentation," *Journal of the History of Biology* 5, no. 2 (1972): 348. See also Kohler, "The Enzyme Theory and the Origin of Biochemistry," 192. Mikuláš Teich too has argued that when Buchner demonstrated cell-free fermentation in yeast he resolved the biological/chemical debate over the nature of ferments and legitimized biochemistry as a discipline. In Mikuláš Teich, "The Historical Foundation of Modern Biochemistry," in *The Chemistry of Life: Eight Lectures on the History of Biochemistry*, ed. Joseph Needham (Cambridge: Cambridge University Press, 1970), 171-191.

[123] Italics in original. H. Hall, *Hall's Distiller* (Philadelphia: John Bioren, 1813), 55. Hall wrote that "yeast is a necessary ingredient in… fermentation… imperfectly understood. Yet there are men, pretending to great knowledge on this subject, who will describe the various appearance which take place in fermentation, and attempt to account for them by the different kinds of yeast, and different proportions; the manner of making and of using which, is an important *secret*, known only to themselves, there is a particular drug or root, which only they know where to procure, or an *abracadabra* made use of in mixing the ingredients. By these means imposing upon the credulity of some and upon the purses of others desirous of obtaining information on the subject; retailing their secret, which may have the art of doing without detection. Such men are not to be believed…"

enzymes would act on a given substrate. After reproducing this selective activity with synthetic sugars, Fischer hypothesized that some enzymes and sugars had compatible geometrical structures which fit together like a "lock and key."[124] This explained why different species of yeast excelled in different environmental conditions. Substrate utilization differed by yeast type, and yeast type differed by enzymatic specificity.[125] After 1897, biochemists began to lay experimental claims to the *in vitro* diagnosis of the living cell. Yeast's inner environment was going to be turned out.[126] Every organism, in fact, was to be characterized by the specific enzymes it contained.

Since species varied by enzymes, clearly these were the "true bearers" of heredity, explained the German-American physiologist Jacques Loeb in 1898.[127] The pursuit of detailed chemical knowledge of the enzymes was expected to enable the production of new animal and plant forms in the laboratory. Enzymes redefined the ferments as not just destructive but constructive too. "In brief, for every vital function, a ferment. That is the latest word of

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[124] Originally, "Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glucosid wie Schloss und Schlüssel zu einander passen müssen, um eine chemische Wirkung auf einander ausüben zu können." In Emil Fischer, "Einfluss Der Configuration Auf Die Wirkung Der Enzyme," *Berichte der deutschen chemischen Gesellschaft* 27, no. 3 (1894): 2992. For these observations, Fischer was awarded the 1902 Nobel Prize in Chemistry. His Nobel lecture noted that, "The examination of the synthetic glucosides has shown that the action of the enzymes depends to a large extent on the geometrical structure of the molecule to be attacked, that the two must match like lock and key." Nobel Media, "Nobel Lecture: Emil Fischer (1902)," accessed January 5, 2015, http://www.nobelprize.org.

[125] J.A. Barnett, "Beginnings of Microbiology and Biochemistry: The Contribution of Yeast Research," *Microbiology* 149, no. Pt 3 (2003): 565.

[126] The yeast cell membrane remained impenetrable unless the cell was killed. This proved a fascination during the first half of the twentieth century, when other cell types were used to make progress on the membrane permeability of various dyes, nutrients and narcotics. In Barnett and Barnett, *Yeast Research: A Historical Overview*, 167-168.

[127] Loeb was also referring to "zymogens" as bearers of heredity. These were enzyme precursors characterized as the resting ferments, and they too functioned as a kind of species biomarker. Jacques Loeb, "Assimilation and Heredity," *The Monist, A Quarterly Magazine Devoted to the Philosophy of Science*, July, 1898, 555.

biological chemistry," explained the statistician Carl Snyder in 1902.[128] The advent of enzymatic specificity did not readily yield chemical tools to diagnose yeast variation or variety, however, for there was no established basis of comparison. The enzymes' chemical composition remained elusive.[129]

In a speech delivered at a meeting of the Oxford Extension in 1903, the English chemist Raphael Meldola (later president of the Chemical Society of London) detailed the advances that biochemistry had wrought for the yeast-based industries, including brewing, distilling, and chemical manufacturing.[130] In the first place, yeast had become the producer and container of enzymes:

> It is now known, through the work of Buchner, that this chemical transformation of sugar into carbon-dioxide and alcohol is the result of interaction between the sugar and a certain definite substance – an unorganized ferment – which is formed by the living yeast shell, and which can do its work independently of the cell in which it originated.

The "unorganized ferment" had solved the riddle of fermentation, but it had not yet served as a new means of differentiating species. Indeed, the organism's survival and reproduction was still very much dependent on the environmental conditions of the brewers' broth:

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[128] Carl Snyder, "The Newest Conceptions of Life," *Harper's Monthly Magazine*, June 1, 1902, 858.

[129] This remained the case in 1907 at the time of Buchner's Nobel lecture: "all we know of all the enzymes is the way they act, and no way has been found up to now of preparing any of them." In Buchner, "Nobel Lecture: Cell-Free Fermentation," 118. Meanwhile from the late 1870s, the German biochemist Albrecht Kossel had begun to distinguish protein from nucleic acid chemistry in yeast nuclein. See Albrecht Kossel, "Ueber Das Nuclein Der Hefe," *Zeitschrift für Physiologische Chemie* 3 (1879): 284-291. During the period 1885 and 1901, he isolated adenine, cytosine, guanine, thymine, and uracil, whose hereditary role was not understood until much later.

[130] A writer for *The Brewer's Journal and Hop and Malt Trade's Review* celebrated this speech: "have not the mysteries evolved from out test-tube and crucible proved a veritable handmaid to our industry?" he asked his brewing colleagues. W. Stanley Smith, "Technical Papers," *The Brewer's Journal And Hop And Malt Trade's Review* 39, no. 459 (1903): 545.

> The water used by the brewer must be analyzed to ascertain whether it contains the necessary mineral constituents for the nourishment of the yeast, because this plant is subject to the same conditions of growth as any other plant.

Yeast pure cultures were analogous to purified chemicals in this new biochemical formulation. In theory, their enzymatic differences were biologically specific even if the tools did not yet exist to show this. As Meldola reported:

> The recognition of yeast as a vital chemical reagent which is apt to contain impurities in the form of wild or stray organisms which may damage the contents of the brewing vat, has led to further introduction of the process of brewing by what is known as "pure culture yeast"… cultivated in the first place from a single cell of some particular species… as pure in strain as a pedigree horse or a particular breed of dog – a yeast which, by virtue of its purity, can be depended on for giving constant results in the brewing vat.[131]

The species concept was a chemical one. It had become interchangeable with the notion of a yeast pure culture just as yeast races had become statistical populations. Under the enzymatic definition of biological specificity, however, yeast variation and variety had not been distinguished. Yeast thus offered a model of enzymatic specificity which did not differentiate between evolution and heredity.

Brewers after Pasteur had read onto their existing practice a new biological specificity in terms of organismal fitness. They deployed an environmental and relational definition of "type" which suggested that living organisms adapted or could adapt to their environmental conditions, and moreover, that these environments could be conditioned in turn to ensure the health and "fit" of the organism. Hansen had briefly distinguished the signs of yeast variation from variety, but this variable performance of a "type" had come to be seen by the brewers as the predictable contamination of a type by other organisms or the inevitable exhaustion of a type by inadequate nutrition.

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[131] Raphael Meldola, "The Relations between Scientific Research and Chemical Industry," *Journal of the Society of Arts* 51 (1903): 811.

At the turn of the twentieth century, biochemical investigations were redefining biological specificity as the cause of preferential interactions – rather than the mere correspondence – of organisms to their environments just as new statistical measures foreclosed investigations of yeast variation and heredity by anticipating the "impure" mixed culture as a probability.[132] Since the organic broth continued to maintain its significance for yeast identification under practical operations, the scientific question of whether a pure culture might change over time was overshadowed by the question of whether a species interacted with its environment on the basis of protoplasmic or enzymatic metabolic activity. Biological specificity in the yeasts came to mean chemical specification of the cause of yeast variety, and this biochemical turn further foreclosed the investigation of yeast heredity.

The hope of enzymatic specificity gave way to the inconvenient reality at the start of the twentieth century that there was little way to determine a unique identity for the enzymes. Thus, in 1908, when Grove Johnson, a London-based "brewer's analyst" and bacteriologist who had studied with "the Professors at all the principal bacteriological laboratories of Europe" sought to summarize his practical expertise for the non-specialist in *The Student's Manual of Yeast Culture*, he offered advice that had been used for the past half century:

> Assuming that we are at work in a brewery or distillery, it is unlikely that we should be unable to find some yeast at hand from whence we may take a supply of cells in a more or less healthy condition. Even should it be badly infected with bacteria *the type is probably better suited to the locality than any to be obtained from outside sources*, and the bacteria themselves matter nothing to us now that we know how to eliminate them [through use of pure cultures]. Should, however, the yeast be really weakened and exhausted owing to successive sowings in unsuitable wort… it is better to take it with all of its impurities and let all grow

[132] Ceccatti wrote that, "Hansen believed that [the gradual buildup of infection] could explain why brewing diseases often appear so mysterious and why brewers frequently attribute such outbreaks as a bit of bad luck that every brewer must face." In Ceccatti, "Science in the Brewery: Pure Yeast Culture and the Transformation of Brewing Practices in Germany at the End of the 19th Century," 86.

> together in a flask or beaker of wort… in order to secure its return to a healthy and vigorous condition before attempting to isolate a single cell from it… [To do so, feed] the cells upon such food as may strengthen them.[133]

Apart from swapping out Pasteur's microscope for Hansen's pure cultures in the brewing process, Grove Johnson's view of yeast specificity – selecting and supporting the right variety for the job – was not all that different in 1908 from Pasteur's advice in 1857. Practically speaking, a yeast should be diagnosed and controlled in relationship to the brewing environment.

SECTION II.

Yeast Taxonomy from the Culture Collections

At the turn of the twentieth century, brewers could not explain variations in yeast's performance as anything other than expected contamination of the fermenting broth by errant germs. These had been accounted for statistically and confirmed by chemical examination of the spoiled product. The wild yeasts responsible for this contamination were not of interest to the brewers and were instead left to be characterized by medical bacteriologists and general microbiologists. These studies offered new tools of species diagnosis in the opening decades of the twentieth century, which the yeast-based industries would again motivate, adopt, and adapt.

In the absence of synthesized enzymes, one method of characterizing new yeast species was their collection in massive catalogues detailing biological characteristics and the environments in which they had been found. Ironically, greater biological variation rewrote taxonomic species boundaries into fewer categories and the number of unique industrial yeasts declined as more non-industrial yeasts were identified. Later yeasts industrialists, medical bacteriologists and geneticists adopted these classificatory methods to resolve their need for

[133] Grove Johnson, *The Student's Manual of Yeast Culture* (London: The Author, 1908), vii, 93-94. Italics added.

greater chemical specificity among the few yeast species of interest. As we will see, the biological variability held in culture collections was a resource from which they could derive greater chemical control over a new increment of species variation – the yeast strain.

At the end of the nineteenth century, Král's Bacteriologisches Labortatorium established the first public culture collection in Prague, and made available a catalogue of the microorganisms held there in 1899.[134] In 1904, following the Second International Botanical Congress, the Royal Netherlands Academy of Arts and Sciences established a new collection of yeasts in the Centraalbureau voor Schimmelcultures. Universities too began to amass their own microbial culture collections for a range of research purposes.

Systematic collection was an approach Hansen had used to observe the yeasts at Carlsberg. Jörgensen, too, had kept a proprietary yeast collection at his institute in Copenhagen. These early attempts to characterize species had differed from the later collection in that they had only been interested in the brewing yeasts. For example, as a supplier of pure yeast cultures to the breweries and distilleries, Jörgensen collected only the industrial yeasts and investigated morphological and physiological criteria to distinguish them from other disease-causing organisms.

Jörgensen published a review of these industrial species in the 1890s in separate German, French and English editions. The text was intended for chemists, botanists, biologists and technologists as a "complement to the text-books which treat mainly of the chemical side of the subject." It described the use of Hansen's method to achieve pure cultures and took this as evidence that the yeasts occurred as "species, varieties, or races" with stable characters. Since their isolation could be achieved, the next step was to analyze individual yeasts and their

[134] Kral's Bacteriologisches Laboratorium, *Der Gegenwärtige Bestand Der Kral'schen Sammlung Von Microorganismen* (Prague: Selbstverlag, 1899).

conditions of life. Different species under the same conditions behaved differently and had different forms. This could "only be explained by assuming that there are intrinsic, indwelling characters in the special cells which exert an influence of their own." As the yeasts' environments changed, it became more difficult to identify the limits of a species, Jörgensen noted, since the cells' shape, size and appearance were not sufficient criteria to distinguish them. Several common industrial yeasts had been better characterized with regard to their performance under various temperatures, timeframes, and nutrients, but these criteria served only as filters to more accurately identify known species of interest. They did not apply well to the selection of new yeasts. Jörgensen determined that the breweries need not be overly concerned with these classification criteria, however, for "valuable as the analysis of yeast is, it must always remain of secondary importance."[135]

The brewers instead shared practical advice for dealing with well-known species under new environmental conditions. In the tropics, for example, where the colonial brewing industries were expected to grow, brewers' favorite yeasts might behave differently. In 1908, the English bacteriologist Grove Johnson warned English brewers headed to distant countries that life developed at a more rapid pace in hot, tropical climates than it did in the sluggish temperate zones. Regions at the equator were rife with "the lowest forms of life," Johnson noted, such that a seething mass of bacteria could appear in a few hours where none would have back in England. English brewers should therefore take care with sterile practices. There was no expectation that superior yeast species would be found abroad.[136]

Two general approaches to the chemical analysis and classification of new yeast species emerged from the universities at the turn of the century. The most common of these used pure

[135] Jørgensen, Miller, and Lennholm, *Micro-Organisms and Fermentation*, iii, 122, 124, 136.
[136] Johnson, *The Student's Manual of Yeast Culture*, 147-155.

cultures to compare single yeast cells under a set of variable but definable chemical conditions. At the University of Paris, pharmacists Louis Charles Lutz and Fernand Pierre Joseph Guéguen used synthetic media to grow up colonies and study the yeasts' morphology and cytology under different conditions. These pharmacists were studying mycology as part of their training in therapeutic botanicals.[137] Their culture media were tested and standardized to the extent that a majority of yeasts could live long enough for consistent and measurable species diagnoses.[138]

The Dutch botanist Martinus Beijerinck also used selective media to study and differentiate yeast species in a rare example of non-medical microbiology.[139] Beijerinck had visited Carlsberg laboratory in the 1880s to learn how best to prepare his new microbiology

[137] Both men later taught at the Paris Superior School of Pharmacy. Lutz was a professor of cryptogamy who studied the sporulating plants, while Guéguen was a botanist specializing in mycology. They later served, respectively, as the Secretaries General of the French botanical and mycological societies. See Henri Bonnemain, "Mycologie Et Pharmacie En France Aux X.I.X.E-X.X.E Siècles," *Revue d'histoire de la pharmacie* (1991): 381, 386; Direction des bibliothèques de France, *Catalogue Des Thèses De Doctorat Soutenues Devant Les Universités Françaises*, ed. Ministère de l'éducation nationale (Paris: Cercle de la libraries, 1904), 844.

[138] L. Lutz and F. Guéguen, "De L'unification Des Methodes De Culture Pour La DéTermination Des Mucedinees Et Des Levures," in *Actes Du 1er Congrès International De Botanique: Tenu À Paris À L'occasion De L'exposition Universelle De 1900*, ed. É. Perrot (Paris: Imprimerie et Lithographe Lucien Declume, 1900), 415.

[139] Eric Kupferberg has detailed two different phases of American bacteriology. The first was the narrow "hygienic vision" of medical, public health, sanitary and veterinary bacteriologists at the end of the nineteenth century. This phase attended to a limited number of infectious organisms, of which, I have noted, very few were yeasts. In the second phase, dairy and soil bacteriologists expanded upon the bacteriological vision to include study of productive microbes in the first decades of the twentieth century. Kupferberg attributes this shift to efforts to make bacteriology more "biological" by investigating such aspects as microbial associations, individual variations and nutritional requirements. See Eric D. Kupferberg, "The Expertise of Germs: Practice, Language, and Authority in American Bacteriology, 1899-1924" (PhD diss., Massachusetts Institute of Technology, 2001), 157. The chronological transition that Kupferberg describes for bacteria parallels the topical division of the medical and general microbiology of the yeasts. However, because yeast research began with fermentation – a process implicated in both disease putrefaction and industrial productivity – the two "phases" were largely concurrent.

laboratory for the Delft Yeast and Spirit Works.[140] After leading the laboratory for several years, he moved to the Polytechnic School of Delft and began a new microbial culture collection for the school in 1895. Rather than using the pure culture method to study individual cells, Beijerinck tailored the medium to favor the growth of only particular organisms. This preferential support allowed one type of microorganism to outgrow the others and for its culture to be "enriched."[141] The tailored media enabled multiple varieties to be present if they could grow under the chosen conditions. By this pluralistic approach, Beijerinck explained, "we come to know the species not only in the form of special varieties, but also from the point of view of their variability, which is all important for their diagnosis."[142]

Beijerinck later described his chemical approach to microbiology as "the study of microbial ecology, *i.e.*, of the relation between environmental conditions and the special forms of life corresponding to them."[143] In fact he had adapted the brewers' methods to exclude the use of pure cultures and extend beyond the industrial yeasts. He described the hereditary variation of

[140] Müller-Wille, "Hybrids, Pure Cultures, and Pure Lines: From Nineteenth-Century Biology to Twentieth-Century Genetics," 801.

[141] Beijerinck had discovered that chemical sensitivities were *specific* in a study of bioluminescent bacteria which were found to use urea when other bacteria could not. Martinus W. Beijerinck, "Anhäufungsversuche Mit Ureumbakterien. Ureumspaltung Durch Urease Und Durch Katabolismus," *Zentralbl Bakteriol* 7 (1901). He hypothesized that a unique enzyme triggered only some bacteria to use urea – an idea later described as "enzyme induction." In Lesley A. Robertson, Marian J. Figge, and Paul V. Dunlap, "Beijerinck and the Bioluminescent Bacteria: Microbiological Experiments in the Late 19th and Early 20th Centuries," *FEM FEMS Microbiology Ecology* 75, no. 2 (2011): 185-194.

[142] Originally, "De cette manière nous apprenons à connaître les espèces non seulement dans quelques variétés spéciales, mais encore au point de vue de leur variabilité, ce qui est de toute importance pour la diagnose." In Martinus W. Beijerinck, "Expériences Relatives B L'accumulation Des Bactéries De L'urée. Decompostion De L'urée Par L'uréase Et Par Catabolisme," *Arch Néerl des Sci Exact et Nat* 7 (1902): 29.

[143] Quoted in C. B. Van Niel, "The "Delft School" and the Rise of General Microbiology," *Bacteriological Reviews* 13, no. 3 (1949): 163.

microbes from many different environments.[144] By 1920, the French botanist Alexandre Guilliermond was still convinced Hansen's was the most precise method of identifying microbes. Even as he noted various species that Beijerinck had identified by their action toward various sugars, Guilliermond wrote that the use of different media as a possible classificatory method for the yeasts in the style of Lutz and Guéguen still had not proven its value but might someday supplement microscopic and macroscopic observations.[145] Only much later would Beijerinck's classificatory approach be taken up for identification of many new yeast species.

A second general approach to the analysis and classification of the yeasts was developed by pharmacologists exploring the biochemical properties of microbes. This approach to studying the yeasts employed an organic rather than synthetic media using a liquid extract of one variety of yeast to investigate species' nutritional needs. Since this media originated from cells' contents it enabled better survival of new cells, but as a tradeoff the chemical composition of the extract was rather poorly defined and could not generate comparative classificatory criteria. In the Belgian Laboratory of Biological Chemistry at the University of Louvain, professor of pharmacology Manille Ide and undergraduate medical student Eugene Wildiers theorized that the rapid growth of cells which occurred in the yeast extract might be triggered by certain organic stimulants it contained. Wildiers called this growth substance "bios," from the Greek "to live," and hoped to define its chemical properties since this would have important consequences for how yeast was classified as a plant or animal. If the organism did not synthesize its own

[144] Beijerinck's observations on microbial variability fell into three categories: degeneration of a culture, transformation of a culture, and the common hereditary variability of individuals. See Martinus W. Beijerinck, "On Different Forms of Hereditary Variation of Microbes," *KNAW, Proceedings* 3 (1900): 363. His influence in early yeast genetics is discussed later in the chaper.
[145] Alexandre Guilliermond, *The Yeasts*, trans. Fred Wilbur Tanner (New York: John Wiley and Sons, Inc., 1920), 176-177. Guilliermond did not mention Beijerinck's approach but only the new species he identified.

"proteinaceuous materials," then "its synthetic chemistry diverge[d] considerably from that of green plants and approache[d] that of the animals." If on the other hand, yeast was capable of generating its own food like the plants that would radically contrast "the manner of life of yeast cells with our own cells," Wildiers wrote.[146] While the extract had classificatory implications for Wildiers, to his successors "bios" opened the door to research on microbial growth factors which would connect the yeasts' biochemistry to the chemical composition of their external environments.[147] Further, shared growth factor requirements (later vitamins) between the yeasts and animals would make "comparative biochemistry" suggestive of their common evolution.[148]

Outside of these few examples, chemical forays into the yeast cell were still rather limited. In 1910, British botanists noted that chemical characterizations of yeast cell constituents provided only indirect inferences from dead to living cells. Conflicting cytological observations were presumed to be the consequence of various chemical methods for killing and fixing cells in

[146] Eugène Wildiers, "Nouvelle Substance Indispensable Au Développement De La Levûre," *La Cellule* 18 (1901): 313-332. English translatation available in T.D. Brock, *Milestones in Microbiology 1546 to 1940* (Washington, DC: ASM Press, 1999), 241, 244.

[147] Wildiers did not pursue the bios research further, but his mentor Ide did. See M Ide, "The 'Bios' of Wildiers and the Cultivation of Yeast," *Journal of Biological Chemistry* 46, no. 3 (1921): 521-523. Wildiers was reportedly "an immature undergraduate medical student of comparatively mediocre attainments" who had supported Ide's chemical research on yeast and was permitted to submit the bios results for a fellowship competition that he did not win. After graduating, Wildiers did not continue to publish but went on to practice medicine for a short time in Antwerp. There, he contracted scarlet fever from a patient and died at age 30. Based on his characterization as an "otherwise unproductive medical student", a *Science* contributor argued in no uncertain terms that the credit for the discovery of the first vitamin should therefore be given to professor Ide, and not his student assistant. See R. J. Williams, "M(Anille) Ide, the Discoverer of 'Bios'," *Science* 88, no. 2290 (1938): 475. Also reported in "First Vitamin Found by Belgian Doctor," *The Index-Journal*, December 18, 1938. While bios cannot properly be called a vitamin in 1901, Wildiers continues receive credit for its discovery and no historian has yet examined Ide's claim.

[148] See the explanation of "comparative biochemistry" in Joshua Lederberg, Notes for an Entry in the Enciclopedia Italiana Entitled, "History of Microbiology, 1930-1950", (1990), Box 87, Folder 26, Profiles in Science: The Joshua Lederberg Papers, National Library of Medicine, Bethesda, MD.

preparation for observation by microscope. Yet even with standardized preparations, different descriptions of the cell could result because of "the remarkable variability in the behaviour …. [and] contents… found in the yeast at different stages in its development."[149] Varying observations could also be due to the conditions under which yeast lived in a constantly changing external environment.

Many observers believed that the "species concept" might not accurately apply to the yeasts. These organisms appeared to exhibit far more variability than the plants, presumably on account of their more rapid generation time. Many of the characters used to specify yeast type varied simultaneously, and to such an extent that was difficult to establish even what the relevant categories of "character" might be.[150] Morphological distinctions were turning out to be not much help since cells within a species could present in various forms. Researchers hoping to identify the yeasts as late as the 1920s followed such paradoxical instructions as the following: "There usually is a predominant shape which, to a certain degree, is characteristic and may be regarded as normal for the species under question. In certain cases, one may note the predominance of abnormal forms among the normal."[151] Presumably, such distinctions could be made by the investigators' accumulated experience.

Yeasts with industrial applications were still somewhat easier to categorize because they could be more readily distinguished by qualities relevant to their end products. The genus *Saccharomyces* included all brewery, distillery, cider, wine and other industrial yeasts. The

[149] Harold Wager and Annie Peniston, "Cytological Observations on the Yeast Plant," *Annals of Botany* 24, no. 93 (1910): 48.
[150] This formed part of a larger discussion at the time about species as arbitrary units. In 1903, for example, Thomas Hunt Morgan believed that species had been invented for classification at the convenience of taxonomists. Only individuals existed. In J.S. Wilkins, *Species: A History of the Idea* (Berkeley: University of California Press, 2009), 179.
[151] Guilliermond, *The Yeasts*, 179.

baker's yeast *Saccharomyces cerevisiae* also acted as a top fermenting brewer's yeast to make ales and was used in the distillation of spirits. The bottom fermenting *Saccharomyces carlsbergensis* was another brewer's yeast which made lagers, and *Saccharomyces ellipsoideus* (later a variant of *Saccharomyces cerevisiae)* made wines. These yeasts and related species could be grouped according to their fermentation reactions to several different sugars in 1920, but the taxonomic genus to which they belonged also included other yeasts which did not induce fermentations and were grouped by "unknown" sugar reactions.[152] In this way, yeast collections which started with practical applications set taxonomic standards for nonindustrial yeast varieties. New classificatory schemes would emerge on the basis of current practice ideals.

Wartime Innovations with Known Species

The First World War inspired new applications with familiar yeast species. These resulted in few consequences for yeast classification since the utility derived from industrial species came from processing changes rather than additional species. In Germany, chemical engineers of the Vereinigte Chemische Werke altered the conditions of yeast fermentation to produce large quantities of glycerol, a compound then in short supply as a result of the British blockade.[153] After patenting the process, it was reported to the German army for use in the production of nitroglycerin explosives.[154] "The process is a war child, born of the necessity of

[152] Ibid., 195. See also Emil M. Mrak and L. S. McClung, "Yeasts Occurring on Grapes and in Grape Products in California," *Journal of Bacteriology* 40, no. 3 (1940): 395-407.
[153] Pasteur had described glycerol formed in the fermentation of sugars over a half century earlier.
[154] G. Semenza and A.J. Turner, *Selected Topics in the History of Biochemistry: Personal Recollections, IX* (San Francisco: Elsevier, 2005), 45.

the times," one engineer claimed.[155] The Germans also used dried brewer's yeast to replace lost imports of animal fodder, and this made up over 60 percent of the protein consumed by cattle during the war. Decades later, one British brewers' journal reflected that, "War conditions give yeast a special chance to prove its value and open the way for it to the peace rations of our animals."[156]

A third use for a familiar industrial yeast during the war was the German innovation to compress brewer's yeast into a new material called "ernolith." When dried, the substance was of sufficient hardness and elasticity for use in a variety of artistic and technical applications. As reported in the German weekly, *Reclams Universum*, and reprinted in American publications such as *The Western Brewer*, *The American Bottler*, and *Scientific American*, ernolith was replacing materials the war had made scarce, and could be readily molded into any desired shape, including combs, knife handles or buttons.[157] Following the war, French scientists produced these "yeast buttons" from ernolith as well as undergarments made of sour milk. The outrageous fashion news caused a stir as far as New Zealand, and the new buttons were predicted to become a commercial success because of yeast's low manufacturing costs.[158]

As plastic as the yeasts appeared to be, these new applications drew only from a few well-known industrial species. The wild yeasts were minimally of interest except as occasional contaminants. The exception that proved the rule was one "industrially useless menace" which

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[155] Originally, "Das Verfahren ist ein Kriegskind, aus der Not der Zeit geboren." In C. Deite and J. Kellner, *Das Glyzerin: Gewinnung, Veredelung, Untersuchung Und Verwendung Sowie Die Glyzerinersatzmittel* (Berlin: Springer, 1923), 229. See also H. Benninga, *A History of Lactic Acid Making: A Chapter in the History of Biotechnology* (Boston: Kluwer, 1990), 212-213.
[156] R. Braude, "Dried Yeast as Fodder for Livestock," *Journal of the Institute of Brewing* 48, no. 5 (1942): 206.
[157] See "Buttons as a by-Product of Beer," *The Western Brewer* 47, no. 1 (1916): 222.
[158] "Ladies' Blouses Made from Sour Milk: Fabrics of the Future," *Wanganui Chronicle*, May 31, 1919, 7.

did not produce fermentation and which had corrupted production of bakers' yeast during the war. The Germans repurposed the species for food and fodder to make the best of the spoilage which had occurred.[159]

Wine & Dietary Yeasts

The variety of yeast species considered for winemaking and dietary consumption were similarly limited and did not advance yeast taxonomic efforts around the turn of the century. At the University of California College of Agriculture, in Berkeley, the Division of Viticulture and Enology had been established in 1880 for the purpose of experimental winemaking, and began to amass a significant collection of wine yeasts through California's Agricultural Experiment Station. Station scientists imported yeast varieties to the collection from wineries in Italy, the Rhine, Médoc, Burgundy, Sauternes, and Algeria. They began to experiment with these pure yeast cultures beginning in 1893, and initial tests resulted in quicker fermentations and clarifications as well as improvements to the wines' bouquet and flavor. They decided to distribute the yeasts to wineries across the state for large-scale experimentation.

The state's winemakers were generally resistant to change or even to discuss their current practices, and the first large-scale experimentations with pure cultures proved a total failure. Rather than improving the average quality and uniformity of the product, on nearly all accounts the pure cultures produced wines that failed to ferment to dryness. This was supposedly due to the selection of yeasts unsuited to California's "heavy [grape] musts," but later a member of the Agricultural Station argued that, "Most people preferred to learn by their own mistakes rather

[159] Reported in Carl C. Lindegren, *The Yeast Cell: Its Genetics and Cytology* (University of Minnesota: Educational Publishers, 1949), Chapter 2: 3-4.

than to read" so that published bulletins and circulars were not being used.[160] Until the state's "cellar-men" could become more familiar with the pure culture method, the Station would supply only a limited number of yeasts to the wineries. These would include only yeasts from France's Champagne and Burgundy districts since these seemed to perform the most consistently.[161]

The spoilage of wines by wild yeasts and bacteria was a problem that California's Agricultural Station scientists had hoped to address with the introduction of pure yeast cultures. In 1912, they argued that greater adoption of this method could prevent "those strange variations of quality between casks of wine made from the same grapes by the same methods which have so long puzzled wine-makers."[162] Wild yeasts were implicated but not systematically collected since these efforts to control yeast variety attempted its diagnosis only secondarily.

In 1918, a study of the wild microorganisms occurring on the state's grapes found differences in their number and type depending on the locality, ripeness of the grapes, shipment

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[160] Two decades later, the researchers found that pure yeast cultivation could be applied successfully on a practical scale by the average California winemaker. Frederic T. Bioletti and W.V. Cruess, *The Practical Application of Improved Methods of Fermentation in California Wineries During 1913 and 1914*, vol. Circular No. 140 (Berkeley, CA: University of California College of Agriculture, 1915). The suspected aversion to *reading* comes from Maynard A. Joslyn, interview by Ruth Teiser, 1974, "California Wine Industry Oral History Project: A Technologist Views the California Wine Industry," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 20.

[161] Joslyn gives the Bordeaux source as a collection held by Professor Paul Pacottet, head of viticulture at the Institut National de France. In Joslyn, "California Wine Industry Oral History Project: A Technologist Views the California Wine Industry," 2. See also J. Simpson, *Creating Wine: The Emergence of a World Industry, 1840-1914* (Princeton, NJ: Princeton University Press, 2011), 256. Pacottet believed that the winemakers' selection of yeasts could be matched to environmental conditions. Natural selection ensured that yeasts were well adapted to the countries in which they could be found, but there was additional room for selection based on cultural interests – so there were yeasts supporting high temperatures in Algeria as well as high alcohol yield in France. In P. Pacottet, *Vinification: Vin, Eau-De-Vie, Vinaigre* (Paris: Baillière, 1904), 68.

[162] Frederic T. Bioletti and William V. Cruess, *Enological Investigations*, vol. v. 230 (Berkeley, California: University of California College of Agriculture, Agricultural Experiment Station, 1912), 23-24, 64-65.

from vineyard to winery, control in fermentation, and morphological and physiological characteristics. William Cruess, a chemist for the Station and Assistant Professor for the Division in Berkeley, determined the baker's and brewer's yeast *Saccharomyces cerevisiae* was not found growing on grapes, but when added experimentally it gave the wine a beer-like flavor and produced a low alcohol content which left wine open to contamination by bacteria. "True wine yeast type," *Saccharomyces ellipsoideus*, was the only species suitable for wine production found so far, Cruess noted. French wine yeasts consistently gave better results than the wild California yeasts of this variety, so the station would continue to supply just these yeasts to the wineries.[163] There was little need to culture other species.

The following year, the Division abruptly stopped research with the wine yeasts. The Volstead Act prohibited commercial winemaking in the United States, and Station experiments could not continue. Emil Mrak, an undergraduate, graduate, and then faculty member of the Division, recalled the story he had been told about this period: "When Prohibition became law… the yeasts were placed in a cabinet and more or less forgotten. The department [then, a division] that had devoted so much time to wine fermentation suddenly found itself without a purpose in life."[164] This was not entirely true of the University's yeast experiments. The Station continued to supply wine yeasts to specially-designated California wineries that were producing sacramental wines for Catholic, Episcopal, and Lutheran churches after the constitutional ban on

[163] William V. Cruess, "The Fermentation Organisms of California Grapes," *University of California Publications in Agricultural Sciences* 4, no. 1 (1918): 3, 48-49.
[164] Emil M. Mrak, History of Yeast Work in U.C., (1979), Box 87, Folder 33, Emil Mrak Papers (D-096), University of California, Davis Special Collections, Davis, CA.

alcohol.[165] The Division rebranded as Fruit Products, and began to investigate new methods of juice processing, canning and drying for California's surplus fruits.

Across the country, new legal uses for familiar yeasts were being innovated. Some invited purchasers to read between the lines, as was the case for dried concentrated grape products like Vino Sano bricks which included a detailed warning in red letter type about how *not* to achieve fermentation.[166] In another example, a Michigan-based bacteriological laboratory was sending out yeast and bacterial cultures for the price of a quarter in 1920, and housekeepers were instructed that this was enough to prepare vinegar by the barrel. "If alcoholic fermentation has taken place it will be necessary to send for vinegar bacteria only," noted one instructor of home economics in 1920, leaving readers to deduce that this yeast alone fermented the alcohol.[167]

Other novel uses for yeast emerged to replace alcohol profits. Before Prohibition, nearly half of Fleischmann's sales came from the production of gin and blended whisky.[168] Without this income it would be necessary to substantially increase the sale of yeast products to make up for the losses. Home sales of yeast were already on the decline in the years leading up to Prohibition as an increasingly urban population shifted its consumption to the bakeries. Fleischmann's had been preparing a campaign to encourage new home sales of yeast when Prohibition began, and it redoubled these efforts in the 1920s and early 1930s. An extensive promotion of Fleischmann's baker's yeast during these years positioned the product as a medicine to be eaten on its own, dissolved in water or juice, or used as a spread on crackers or bread to provide a rich dietary

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[165] Joslyn, "California Wine Industry Oral History Project: A Technologist Views the California Wine Industry," 33.
[166] "By following the "don't" instructions a wine could be prepared." In ibid., 8.
[167] Lavinia Stinson, *The Use of Vinegar Bee*, ed. A.D. Wilson, vol. 6, Circular (University Farm, St. Paul: University of Minnesota, College of Agriculture, Extension Division, 1920), vii.
[168] Klieger, *The Fleischmann Yeast Family*, 63.

source of vitality and health. Advertisements and essay contests suggested that yeast could treat everything from “run-down” condition, to pimples, boils, constipation and a variety of other ailments attested to by Fleischmann’s essay prize-winners.[169]

The Fleischmann’s dietary yeast campaign benefitted from the steady flow of news from nutrition science in this period as studies of brewer’s yeast were proving consequential for animal and human health. Brewer’s yeast was recommended by physicians to prevent and treat a number of deficiency diseases, including beri-beri, anemia and pellagra.[170] Treatment of the latter disease, known as “sharecropper’s plague” in the rural American South, would later raise questions about chemical variation in the yeasts since bakers’ yeast was also found to be effective but only when consumed in much larger quantities.[171] In the meantime, Fleischmann’s

[169] See, for example, "The New Importance Physicians Are Attaching to a Familiar Little Cake of Food (Advertisement)," *The Sunday Oregonian*, October 10, 1920, 12; "$10,000 in Prizes (Advertisement)," *The Morning Oregonian*, January 17, 1928. As a result, sales of yeast tripled during the period 1917-1924, allowing members of the Fleischmann family dynasty to pursue additional ventures. In 1925, for example, Raoul Fleischmann became the financial backer and co-founder of *The New Yorker* magazine, investing $725,000 in the first few years. He would serve as the magazine’s first president, chairman and publisher. In its early days, the magazine gave all signs of failure, and Fleischmann remained working in the family business. He was later rewarded by the magazine’s great commercial success. In "New Yorker Publisher, Raoul Fleischmann, Dies," *Pottstown Mercury*, May 12, 1969, 7.

[170] See E. S. Edie et al., "The Anti-Neuritic Bases of Vegetable Origin in Relationship to Beri-Beri, with a Method of Isolation of Torulin the Anti-Neuritic Base of Yeast," *Biochem J* 6, no. 3 (1912): 234-242; Casimir Funk, "Studies on Beri-Beri: VII. Chemistry of the Vitamine-Fraction from Yeast and Rice-Polishings," *The Journal of Physiology* 46, no. 3 (1913): 173-179. British troops in Mesopotamia were issued the brewer’s yeast paste, Marmite, as a prophylactic against beri-beri in October 1916. In H.P. Cecil and P. Liddle, *Facing Armageddon: The First World War Experienced* (Cooper, 1996), 484. On pellagra and pernicious anemia see Joseph Goldberger, "The Present Status of Our Knowledge of the Etiology of Pellagra," *Medicine* 5, no. 2 (1926): 79-104; M. M. Wintrobe, "The Antianemic Effect of Yeast in Pernicious Anemia," *The American Journal of the Medical Sciences* 197, no. 3 (1939): 286-310.

[171] "Announces Pellagra Cure," *The New York Times*, March 31, 1925, 4. A later study mentions two types of yeast, Fleischmann’s wort-grown, low temperature dried yeast, which would indicate a low-fermenting lager strain of brewer’s yeast, and a commercial yeast concentrate, “Yeast Vitamin-Harris Powder” from Harris Laboratories. In Joseph Goldberger et al., "A Further Study of Butter, Fresh Beef and Yeast as Pellagra Preventives, with Consideration of the

likely benefitted from the lack of species differentiation and was not incentivized to distinguish baker's yeast as another species.[172]

To assure the public that baker's yeast's could provide the general health benefits claimed in its advertising, Fleischmann's pointed to a study that it had commissioned for the *Journal of the American Medical Association* back in 1917.[173] At the time, observers noted that the study appeared to be the first systematic investigation of the therapeutic value of ordinary baker's yeast. Such research had great promise then because this yeast was more familiar to physicians than brewer's yeast, and first-rate commercial processing meant a fresh, stable and convenient product was readily available. "Compressed [baker's] yeast is generally to be preferred because of the fact that it is carefully standardized and a uniform product is always obtainable," the Florida Medical Association argued. In 1917, it remained unknown, however, whether the therapeutic effect of baker's yeast was due to its value as a bactericide, from a by-product of the fermentation process, or because of the "chemotactic influence" of its high nuclein content.[174] Nutritional research in the 1920s and 1930s would attempt to sort this out.

Relation of Factor Pp of Pellagra (and Black Tongue of Dogs) to Vitamin B," *Public Health Rep* 41 (1926): 298, 302, 308. In 1927, U.S. Public Health Officer Joseph Goldberger advised the Red Cross to add brewer's yeast to human food rations to treat an outbreak of pellagra. The preventive element in yeast was later shown to be nicotinic acid (what is today niacin). Co A Elvehjem et al., "Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Black Tongue," *Journal of the American Chemical Society* 59, no. 9 (1937): 1767-1768. See also Joann G. Elmore and Alvan R. Feinstein, "Joseph Goldberger: An Unsung Hero of American Clinical Epidemiology," *Annals of Internal Medicine* 121, no. 5 (1994): 372-375.

[172] Although it was equally true that baker's yeast products were a sometimes critical source of basic sustenance. In 1935, for example, when winter snow slides knocked out train service to a district in British Columbia, supplies of yeast in the district ran dangerously low. Washington State sent in an airplane to end the shortage, dropping yeast by parachute upon the cities. The Canadian Press, "Airplane Drops Yeast, Ending Bread Famine," *The New York Times*, January 27, 1935, 5.

[173] Philip B. Hawk et al., "The Use of Bakers' Yeast in Diseases of the Skin and of the Gastro-Intestinal Tract," *JAMA* 69, no. 15 (1917): 1243-1247.

[174] "Some Facts About Yeast," *Journal of the Florida Medical Association* 4, no. 11 (1918): 376.

Yeast in Nutrition Science

Following on the "bios" discovery in Belgium, a new line of research had begun to indicate the importance of organisms' shared nutritional needs. Scientists were identifying and isolating common "growth factors" across a variety of species.[175] Discovery of these pure chemical substances in various food sources culminated in the identification of more than a dozen vitamins, largely in the 1930s and 1940s.[176] As brewer's yeast was found to contain many of the B vitamins, physicians recommended it for treatment of a variety of human deficiency diseases and researchers began to investigate new uses for yeast in the diet. One series of studies used irradiated yeast as cattle feed and then tested milk produced by the cows for its vitamin D

[175] Roger J Williams, John L Wilson, and Frank H Von der Ahe, "The Control of 'Bios' Testing and the Concentration of a 'Bios'," *Journal of the American Chemical Society* 49, no. 1 (1927): 228. What began in yeast was extended into bacteria and other organisms. André Lwoff, *Recherches Biochimiques Sur La Nutrition Des Protozoaires* (Paris: Monogr. Inst. Pasteur 1932); H. McIlwain et al., "Glutamine and the Growth of Streptococcus Haemolyticus," *Biochem J* 33, no. 2 (1939): 223-229. The growth factors required by certain organisms were in fact "constituents of *all* living things" and were "indispensable to *all* of life… *every* cell." In François Jacob, *The Statue Within: An Autobiography*, trans. Franklin Philip, Alfred P. Sloan Foundation Series (New York: Basic Books, Inc., 1988), 223. Italics in original.

[176] The tremendous success of germ theory may have delayed recognition of the deficiency diseases as physicians trained to seek bacterial causes were slow to subscribe to the new vitamin theory. In J.K. Loosli, "History of the Development of Animal Nutrition," in *Handbook of Animal Science*, ed. P.A. Putnam (San Diego, CA: Academic Press, 1991), 36. See also Lee R. McDowell, *Vitamin History, the Early Years* (Sarasota, FL: First Edition Publishing, 2013). Cambridge physician Egon Kodicek estimated that 200,000 lives over thirty years might have been saved in the United States alone from pellagra if the identity of the vitamins had been recognized by Cambridge biochemists Frederick Hopkins and Edith Willcock in 1906. In A. Rook, *Cambridge and Its Contribution to Medicine: Proceedings of the Seventh British Congress on the History of Medicine, University of Cambridge, 10-13 September, 1969* (London: Wellcome Institute of the History of Medicine, 1971), 241-242.

potency. Later research examined the ability of this yeast-milk to treat and prevent rickets in human children.[177]

Despite baker's yeast's unappealing taste and the preponderance of research pointing instead to brewer's yeast's as having greater nutritional benefit, by 1937 the personal consumption of baker's yeast for health was adding $10 million to Fleischmann's annual sales. Of the nearly 230 million pounds produced in the each year United States, a significant portion was being purchased to eat.[178] The development of new foil wrapping in this period also helped to encourage baker's yeast consumption by the "dose."[179] Fleischmann's began to bioassay their product prior to sale in order to standardize its vitamin content.[180]

Fleischmann's medical marketing of baker's yeast dropped off precipitously in the late 1930s after outraging the medical profession with exaggerated claims. An investigation by the Federal Trade Commission determined that these endorsements were misleading to the public. *The New York Times* explained that the company (now Standard Brands) had agreed to discontinue certain misrepresentations. The story ran:

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[177] See Byron H. Thomas and Florence L. Macleod, "Increasing the Vitamin D Potency of Cow's Milk by the Daily Feeding of Irradiated Yeast or Irradiated Ergosterol," *Science* 73, no. 1901 (1931): 618-620; Edwin T. Wyman and A. M. Butler, "Antirachitic Value of Milk from Cows Fed Irradiated Yeast," *Archives of Pediatrics and Adolescent Medicine Archives of Pediatrics and Adolescent Medicine* 43, no. 6 (1932): 1509-1518; Edwin T. Wyman et al., "A Comparison of Yeast Milk and Irradiated Milk in the Treatment of Infantile Rickets," *New England Journal of Medicine* 212, no. 6 (1935): 257-262; Henry J Gerstenberger et al., "Antirachitic Cow's Milk: Comparative Study of Antirachitic Value of Irradiated Cow's Milk and of Milk Produced by Cows Fed Irradiated Yeast," *Journal of the American Medical Association* 104, no. 10 (1935): 816-826; R Cannon Eley, EC Vogt, and Mary G Henderson, "The Prophylactic Value of Vitamin D Irradiated and Vitamin D Yeast-Fed Milk," *New England Journal of Medicine* 215, no. 3 (1936): 110-111.

[178] 230 million pounds represents the annual production in 1930. Charles N. Frey, "History and Development of the Modern Yeast Industry," *Industrial & Engineering Chemistry* 22, no. 11 (1930): 1161.

[179] Klieger, *The Fleischmann Yeast Family*, 54. Sales figures quoted from the same.

[180] Frey, "History and Development of the Modern Yeast Industry," 1161.

> The firm agreed to cease representing that the product will cure or prevent constipation, bad breath, boils, acne, pimples or other manifestations of irregular digestion and that it will "clear" skin irritants out of the blood… prevent or correct underfed blood or increase the capacity of the blood to perform its functions except in so far as competent scientific evidence demonstrates that the vitamins and other constituents of the yeast affect the composition and functions of the blood and supplement and enhance the biologic values of food.[181]

At the turn of the century, the discovery of enzymes had given hope of distinguishing species by their chemical specificity, but this had been slow to happen. Bios, growth factors, and – beginning in the 1920s and 1930s - the vitamins had since pursued chemical specificity by following nutritional conditions of the organisms' environment. By the late 1930s, yeast taxonomists could begin to chemically classify the yeasts by whether or not they grew in vitamin-free media.[182]

An International Taxonomy of the Yeasts

Old practices with the industrial yeasts resumed after the repeal of Prohibition in 1933. The Division at Berkeley returned to intensive study of the wine yeasts. Courses were expanded to include biochemistry and microbiology, as well as fermentation techniques. Winemaking services were offered through the Extension School to reeducate managers of industry. "The first year or two they made a lot of vinegar instead of wine," Cruess recalled.[183] The Extension also taught that the leftovers of wine fermentation could be reused to ferment brandy and extract

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[181] "To Modify Yeast Claims," *The New York Times*, July 29, 1938, 29. While its products were still marketed under the name Fleischmann's, the brand was no longer a standalone company in this period. Fleischmann's had absorbed Royal Baking Powder Company, Gillette, and others to become Standard Brands for a large stock valuation just prior to the market crash in October of 1929.

[182] Herman J. Phaff, M.W. Miller, and E.M. Mrak, *The Life of Yeasts: Their Nature, Activity, Ecology, and Relation to Mankind* (Harvard University Press, 1966), 88.

[183] William V. Cruess, interview by Ruth Teiser, 1967, "A Half Century in Food and Wine Technology," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 50.

cream of tartar. The supply of Burgundy and Champagne yeasts from the University also resumed to the wineries and vinegar factories. The Berkeley Yeast Laboratory was formed in a private home and acted as a yeast distribution center for a short time.[184] Additional suppliers operated out of Chicago and Los Angeles.[185]

The Extension advised winemakers to order pure cultures from these centers several times during the season and not to "stretch" a yeast too far since contamination of the wine was thought to occur over time. This was a problem that pure cultures were supposed to have resolved. In 1902, for example, brewing experts Robert Wahl and Max Henius told students in their Chicago brewing academy that standard cultures could be kept unchanged for years so long as the yeasts were preserved in a dark place, in a sterile vial, and in 10 per cent sugar solution. "In this way," they explained, "…the brewer has at all times at his disposal the same identical yeast type. Consequently, he is able, other things being equal, to produce a beer of constant, uniform character. Even if the yeast should become infected or deteriorate from any other cause, a fresh batch of the identical original yeast can be developed in a few weeks from the reserve culture."[186] But a problem with this expectation was discovered early on in culture collections when the pure yeasts, carefully preserved, seemed to change their characteristics in storage. This

[184] It was later moved and sold. Joslyn, "California Wine Industry Oral History Project: A Technologist Views the California Wine Industry," 3.
[185] These were the American Type Culture Collection and the Western Beverage Corporation, respectively. In Maynard A. Joslyn and William V. Cruess, "Elements of Wine Making," *California Agricultural Extension Service* 88 (1934): 24, 64.
[186] Henius was a Danish chemist who began consulting in Chicago with Robert Wahl in 1886. In 1891, Henius and Wahl founded the American Brewing Academy (which became the Wahl-Henius Institute of Fermentology, and then Wahl Institute), which Wahl later ran with his son. Robert Wahl and Max Henius, *American Handy Book of the Brewing, Malting and Auxiliary Trades*, 2 ed. (Chicago: Wahl & Henius, 1902), 559. See also Robert Wahl and A.S. Wahl, *American Brewers' Review*, ed. United States Brewers' Association (Der Braumeister Publishing Company, 1903); Arnold Spencer Wahl and Robert Wahl, *Beer from the Expert's Viewpoint*, Reprint, 2014 ed. (Chicago: Wahl Institute, 1937).

was the variation that Hansen had noted in his pure cultures. In 1903, Jörgensen had documented its occurrence in baker's yeast: "it sometimes happens that after about six months' preservation changes have set in in the character of the race."[187] Consequently, fresh cultures of industrial species were constantly being prepared but the reason for their changes was still not understood.

Cruess resumed collection of the yeasts under more expansive terms after Prohibition. Yeast descriptions were given in Latin, as was the new international standard in taxonomy. The collection would now include both the wine yeasts and those responsible for fruit spoilage, such as yeasts found on rotting figs in the orchard. Emil Mrak, then a graduate student in the Division of Fruit Products, would also begin to collect the film yeasts which grew on fermented pickle and olive brines as the subject of his dissertation work. Mrak had arrived in Berkeley as an undergraduate in the 1920s. He continued at the University to pursue master's and doctoral degrees in botany and mycology, and the Division encouraged him to study organisms responsible for food spoilage.[188]

Mrak once described himself as having grown up with yeast work at the University of California. "We raised him from a pup," Cruess agreed.[189] But California's yeast work had grown in turn with influence from the Delft culture collection which had been established by Beijerinck. The film yeasts were a topic on which very little was known but fortunately for Mrak, the first comprehensive yeast taxonomy texts had just been published on the Delft

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[187] A.P.C. Jørgensen and R. Grey, *Practical Management of Pure Yeast: The Application and Examination of Brewery, Distillery, and Wine, Yeasts* (London: The Brewing Trade Review, 1903), 59.

[188] The "Latin diagnosis" of new taxa was a requirement of the botanical code after January 1, 1932, following the Fifth International Botanical Congress in England, and was intended to bring together different factions under an "international" nomenclature. In S.C. Datta, *Systematic Botany* (Wiley Eastern Limited, 1988), 14-15; Herman J. Phaff, "My Life with Yeasts," *Annual Reviews in Microbiology* 40, no. 1 (1986): 2; Herman J. Phaff, "Life with Yeasts During Retirement," *Journal of Industrial Microbiology* 14, no. 6 (1995): 432-435.

[189] Cruess, "A Half Century in Food and Wine Technology," 116.

collection and proved to be important references for his work.[190] In the mid-1930s, Mrak finished these studies and graduated to join the Division faculty at Berkeley.

The collection at Delft had from the start included many species known to be of practical importance to industry. Beijerinck's ecological method of yeast classification had grown out of his work for the Delft Yeast and Spirit Works. After 1921, Beijerinck was succeeded as professor of general and applied microbiology at the Polytechnic School, which had changed its name to the Delft Institute of Technology in 1905, and the collection passed to Albert Jan Kluyver. As one of his first actions in the department, Kluyver contacted the Centraalbureau voor Schimmelcultures run by the Royal Netherlands Academy and asked to make a trade: sixty of their yeasts for two thousand of Kluyver's culture tubes and one hundred Erlenmeyer flasks.[191] After this, the Delft Institute of Technology was for a time the world's premier collector of yeast pure cultures.[192]

Although his formal training had been biochemistry, Kluyver took the reins of what has been called "the Delft School of Microbiology," and continued training students in the ecological and applied principles of a general - that is, non-medical - microbiology.[193] Microbiology primarily fell to chemists and physicians at this time as an outgrowth of bacteriology and virology. Pharmacologists and pharmacists studied the yeasts, but it was the biologists who made the biggest advances in taxonomy using this ecological approach. Rather than employing

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[190] These texts proved an exception to the utter scarcity of information on the yeasts at that time. In Mrak, History of Yeast Work in U.C., (1979), Box 87, Folder 33, Emil Mrak Papers (D-096).
[191] "History of the Centraalbureau Voor Schimmelcultures," accessed January 13, 2015, http://www.cbs.knaw.nl/.
[192] C. J. E. A. Bulder, J. W. M. la Rivière, and W. Verhoeven, "Kluyver's Work in Retrospect: Wisdom of Foresight?," *Antonie van Leeuwenhoek* 56, no. 2 (1989): 111; Albert J. Kluyver and A.F. Kamp, *Albert Jan Kluyver: His Life and Work* (North-Holland Pub. Co., 1959), 145.
[193] J. W. M. la Rivière, "The Delft School of Microbiology in Historical Perspective," *Antonie van Leeuwenhoek* 71, no. 1-2 (1997): 9.

morphological identification methods, which had worked for other species such as the filamentous fungi, the Delft School's approach to microbiology was distinctly chemical and grew more so under Kluyver's influence.[194] Following Beijerinck, the Delft yeast taxonomists based their classifications on the yeasts' fermentation abilities and assimilation of certain compounds under different environmental conditions without the use of pure cultures.[195]

Concurrent with American growth factor analyses, Kluyver argued for the commonality of all organisms at the biochemical level and he published his classic "Unity in Biochemistry" in 1926.[196] "From the elephant to butyric acid bacterium--it is all the same!" he wrote, predating a similar statement from French biologist Jacques Monod by nearly three decades.[197] Since enzymes were still not well understood, their involvement in microbial processes was for

[194] Others have made a greater distinction between the methods of Beijerinck and Kluyver - contrasting Beijerinck's ecological vision with a reductionist, biochemical approach from Kluyver. See Carl R. Woese and Nigel Goldenfeld, "How the Microbial World Saved Evolution from the Scylla of Molecular Biology and the Charybdis of the Modern Synthesis," *Microbiology and Molecular Biology Reviews* 73, no. 1 (2009): 15. To the extent that these methods were not mutually exclusive, this may be somewhat of a false comparison - especially given the different periods in which the investigators were working. It is clear however that Kluyver's orientation was uniquely, and influentially, biochemical. Rivers Singleton, Jr. has studied the biochemical "reorientation" of one bacteriological laboratory at Iowa State in the late 1920s and 1930s following Kluyver's visit there. See Rivers Singleton, "From Bacteriology to Biochemistry: Albert Jan Kluyver and Chester Werkman at Iowa State," *Journal of the History of Biology* 33, no. 1: 165-171.

[195] "History of the Centraalbureau Voor Schimmelcultures," accessed January 13, 2015, http://www.cbs.knaw.nl/.

[196] Albert J. Kluyver and Hendrick J.L. Donker, "Die Einheit in Der Biochemie," *Chemisch Zelle Gewebe* 13 (1926): 134-190.

[197] The statement, "Anything found to be true of E. coli must also be true of elephants" is widely said to be a Monod original dating to 1954. It appears in writing as a "well-known axiom" in Jacques Monod and François Jacob, "General Conclusions: Teleonomic Mechanisms in Cellular Metabolism, Growth, and Differentiation," *Cold Spring Harbor Symposia on Quantitative Biology* 26 (1961): 393. On the similarities to Kluyver's phrase and the attractiveness of unifying ideas in science see H. C. Friedmann, "From "Butyribacterium" to "E. Coli": An Essay on Unity in Biochemistry," *Perspect Biol Med* 47, no. 1 (2004): 47-66.

Kluyver a mere paraphrase of the unexplained phenomena.[198] As a way forward, Kluyver suggested that a "comparative biochemistry" might begin to deduce mechanism from the differences between species.[199] The collection of more yeasts would be necessary. Decades later, Kluyver's former student, Cornelis Bernardus van Niel determined, "As Kluyver… emphasized, we cannot hope to obtain more than circumstantial evidence in support of our interpretations of biochemical mechanisms, and the best way to guard against errors in judgment is to increase the probability of our deductions by an ever-increasing body of information."[200]

In the early 1930s, Kluyver called for a comprehensive study of all the yeast species present in the Delft collection. Doctoral students Nellie Stelling-Dekker and Jacomina Lodder undertook the task as dissertation research for their respective institutions.[201] Stelling-Dekker conducted a critical review of existing methods and devised a new system of yeast classification.[202] As the criteria for differentiating species, she used morphological characteristics, fermentation of sugars, and the utilization of nitrate. Lodder contributed assimilation of various sugars as an additional physiological test for classification. The taxonomists understood that the "species" concept was not fixed, but would need to be flexible as the discovery of new yeasts opened up different distinguishing characteristics and methods of

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[198] Kluyver and Kamp, *Albert Jan Kluyver: His Life and Work*, 100.
[199] Albert J. Kluyver, *The Chemical Activities of Micro-Organisms* (University of London Press, Limited, 1931), 5.
[200] C. B. Van Niel, "Introductory Remarks on the Comparative Biochemistry of Microorganisms," *Journal of Cellular and Comparative Physiology* 41, no. S1 (1953): 28-29.
[201] Stelling-Dekker for the State University of Utrecht, and Lodder at the Technical University. Nellie Margaretha Stelling-Dekker, "Die Sporogenen Hefen" (PhD diss., Drukkerij Holland, 1931); Jacomina Lodder, *Die Anaskosporogenen Hefen* (Amsterdam: N.v. Noord-Hollandsche uitgeversmaatschappij, 1934). Lodder had also been appointed at the Centraalbureau voor Schimmelcultures in 1932.
[202] W.A. Scheffers, *Dr. Nellie Margaretha Stelling-Dekker: 28 May 1905 - 24 October 1998*, vol. XLVIII, Yeast: A Newsletter for Persons Interested in Yeast (International Commission on Yeasts of the International Union of Microbiological Societies (IUMS), 1999), Obituary.

identification. Their work has been praised for "creating order in a partly chaotic system and defining species in a number of features established with simple, standardized tests."[203] It also considerably reduced the number of yeast species believed to exist. The same species might be given multiple names in the literature, and often "new" yeasts were found to fit an old description. Delft's yeast species came to be described using lists of synonyms.[204] With the discovery of additional species in new environments, the industrial yeasts appeared to have more in common than previously suspected, and these known yeasts were consolidated under fewer species categories.[205]

The Delft studies resulted in the first comprehensive attempt to standardize yeast taxonomy, and these were the texts which helped Mrak to navigate the wild, spoilage yeasts in Berkeley. The Berkeley yeast collection benefitted from another resource imported from Delft at this time in the form of Dutch doctoral student Herman Phaff. Phaff had trained in chemical engineering at the Delft Institute of Technology, and with Kluyver's encouragement, he had

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[203] N. J. W. Kreger-van Rij, "In Memoriam Dr. Jacomina Lodder," *Antonie van Leeuwenhoek* 53, no. 2 (1987): i.

[204] This remains the case for contemporary yeast taxonomy. The common baker's or brewer's yeast *Saccharomyces cerevisiae* went by 97 synonyms in 1998. Ann Vaughan-Martini and Alessandro Martini, "44 - Saccharomyces Meyen Ex Reess," in *The Yeasts (Fourth Edition)*, ed. Cletus P. Fell and Jack W. Kurtzman (Amsterdam: Elsevier, 1998), 361-362. Barnett and Barnett have suggested that nontaxonomists may arrive at a position of ignoring new names "because they are too ephemeral to be useful." In Barnett and Barnett, *Yeast Research: A Historical Overview*, 273. At the very least, historians can treat species claims with a heavy dose of contingency.

[205] At mid-century, Lynferd Wickerman described how this had been the tendency in yeast taxonomy for the past 50 years. In one particular case of genera, he summarized, "it may be stated that ever since the creation of *Hansenula* and *Pichia* nearly a half century ago, taxonomists have been attempting to more clearly define and to separate them. Yet the number of distinguishing characteristics has been reduced rather than multiplied. One by one new species have been isolated which possess at least one characteristic that formerly was believed to be characteristics [of the other]… Reduction in the number of distinguishing characteristics has now reached the point where Mrak *et al*… advocate merger of the two genera." In L.J. Wickerham, *Taxonomy of Yeasts* (U.S. Dept. of Agriculture, 1951), 22.

gone on to pursue advanced studies in the University of California Fruit Products Division. He brought with him advanced knowledge of fungal enzymes as well as lifelong familiarity with the yeasts. His family had run fruit wineries, a distillery, and vinegar factory in The Netherlands, and Phaff had grown up observing the budding and growing of yeast cells and spoilage by contaminating organisms. He recalled having been particularly influenced when observing the coexistence of yeast cells in one massive, spontaneous development of acetic acid bacteria in a batch of overripe berry juice. He was a lifelong subscriber to the Delft School's ecological approach to taxonomy, articulating years later that every yeast species had "one or two physiological properties that give them an advantage in their habitats." It was the yeast ecologist's job to determine these.[206]

Phaff arrived in Berkeley in the spring of 1939, taking a position as Mrak's research assistant with funding from the Agricultural Experiment Station. The Division Chair had just retired and Fruit Products had undergone a separation from its work on viticulture and enology, which now moved as a separate division to the University of California in Davis, taking from Berkeley many of the wine yeasts and bacteria which had been collected by Cruess. With an intensified focus on Fruit Products, Phaff and Mrak began to isolate and identify yeasts associated with spoilage of figs and dates in the orchards of central and southern California. They eventually undertook an extensive expansion of Cruess's collection with the identification of yeasts over wide geographies and from different fruits, soils and other hosts like shrimp and fruit flies.[207] After graduating in 1943, Phaff was offered a position in Fruit Products and joined

[206] D. von Wettstein, *Molecular Genetics in Yeast: Proceedings of the Alfred Benzon Symposium 16, Copenhagen 15-19, June 1980* (State Mutual Book & Periodical, 1981), 427.
[207] See Mrak, History of Yeast Work in U.C., (1979), Box 87, Folder 33, Emil Mrak Papers (D-096); Phaff, "Life with Yeasts During Retirement." These ecological studies went hand in hand with biochemical methods of analysis in order to isolate yeasts and their enzymes from far-

the Division faculty. The Nazi occupation of his home country, to which he lost a brother fighting in the resistance, made the American immigration from Delft a permanent one.[208]

From Species to Strains in the Baking Industry

Fleischmann's scientists had by the 1930s begun to recognize the nutritional potential and procedural gains that could be wrought by greater chemical specificity in their yeasts. The concept of a "strain" had emerged to account for chemical variation between yeasts of the same species.[209] Strains of the baker's yeast species *Saccharomyces cerevisiae* could be propagated, they wrote in 1936, to give greater nutrition and efficiency. "In the highly mechanized baking industry, the processes are so timed that it is necessary for the yeast to act almost as a chemical compound and to have a constant and uniform fermentation rate from day to day."[210] Once linked to the vitamins, the strain would be leveraged for product innovations in the 1940s.

The Second World War necessitated new food sources for American troops and civilians. Fleischmann's was praised for aiding the war effort with the development of active dry yeast which could keep well overseas.[211] The company also released a new baker's yeast – this time, with the endorsement of the American Medical Association. The yeast had been "enriched" with

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reaching environments including tree slime exudates and the feces and stomach contents of rabbits. In Sally A. Meyer, "Dedication Herman Jan Phaff," *Journal of Industrial Microbiology* 14, no. 6 (1995): 430. To honor their contributions to yeast taxonomy, the species *Williopsis mrakii*, *Zygosaccharomyces mrakii*, *Phaffia rhodozyma* and the yeast genus *Phaffia* have been named for Mrak and Phaff.

[208] Phaff, "My Life with Yeasts," 4; Meyer, "Dedication Herman Jan Phaff," 430.

[209] C. Rainbow, "The Bios Requirements of Various Strains of Saccharomyces Cerevisiae," *Journal of the Institute of Brewing* 45, no. 6 (1939): 533.

[210] Charles N. Frey, George W. Kirby, and Alfred Schultz, "Yeast: Physiology, Manufacture, and Uses," *Industrial & Engineering Chemistry* 28 (1936): 879.

[211] Klieger, *The Fleischmann Yeast Family*, 111.

vitamin B_1 and was promised to yield white breads equal in vitamin content to whole wheat.[212] Articles in the popular press during this period recommended the administration of dried brewer's yeast or a vitamin B complex interchangeably to prevent and treat a variety of childhood ailments.[213] Small chemical differences between the yeasts were coming to be definitive.

Fleischmann's scientists recommended that microbiologists consider new biochemical tests for the purposes of species diagnosis. The yeasts could be classified by their response to thiamin and vitamin B_6. In 1940, Fleischmann's scientists suggested use of these growth factors in synthetic media to differentiate sub-types among the two most common industrial yeast species, *Saccharomyces cerevisiae* and *Saccharomyces carlsbergenisis*. After examining 44 cultures of these yeasts, they noted differences which would otherwise have been lost under existing species' groupings by sugar fermentation ability. Microbiologists could benefit from these tests, they suggested, to make "a sharp differentiation between otherwise closely related varieties of yeast" since "sub-species, varieties, strains and races" were often identified out of particular processes.[214]

The need for greater specificity in industrial yeast classification arose with the discovery that chemical differences between strains could be marketed for new vitamin-enriched products. Slight chemical differences were argued to have important consequences when consumed on a mass scale. For example, in 1949 it was suggested that the consumption of dried yeast by the German population had made them "notably free from B-vitamin deficiencies" during the Second World War, and perhaps allowed the Germans to continue fighting longer than they

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[212] "New Yeast Is Developed," *The New York Times*, January 30, 1941, 14.
[213] Irving S. Cutter, "How to Keep Well," *Chicago Daily Tribune*, November 11, 1944, 10.
[214] Alfred S. Schultz, Lawrence Atkin, and Charles N. Frey, "The Biochemical Classification of Yeast Strains," *Journal of Bacteriology* 40, no. 3 (1940): 339.

otherwise might have.[215] By employing the methods of general microbiologists to identify variation by modifications in the environment, yeast industrials could better select for top performing strains.

The growing list of characteristics makes evident the push toward greater standardization of baker's yeast in this period. The National Formulary of the American Pharmaceutical Association had defined baker's yeast in contrast to other yeast species back in 1916. At that time, *Saccharomyces cerevisiae* should contain "white or yellowish-white, soft, and easily broken masses, having a characteristic, slightly sour odor, and not more than faintly acid reaction to litmus." The Association advised, "Compressed yeast must not be used unless fresh, and free from mildew and musty or foul odors."[216] By the 1940s, Fleischmann's was greatly expanding on that definition, telling its scientists to strive for the best. Fleischmann's yeast would no longer be contrasted with other species; now differences could be assessed between strains. The ideal baker's yeast was uniform in color ("Should be creaming with and not brown or grey, and free from streaks caused by insufficient mixing or the extruder nozzle"), in odor ("Pleasing, slightly fruity odor, not sour, musty, or putrid, and free from strong H2S odor"), and in taste ("Bland, without bitterness or sourness"). It was firm to the touch and held its shape during shipment and handling. It contained the proper amount of moisture (approximately 70%), and dissolved readily in water to a smooth, creamy consistency. It had good "keeping quality" meaning that it could bake uniformly after two weeks in storage. It was pure and not contaminated by foreign organisms. Finally, it could be used in all types of doughs and resulted in a good product. "Since most yeasts on the market today meet the foregoing requisites, the ability of the yeast to bake satisfactorily is the crucial test in selling our product in competition with other brands,"

[215] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 2: 3-4.
[216] *The National Formulary*, (Philadelphia: American Pharmaceutical Association, 1916), 281.

Fleischmann's scientists noted.[217] They circulated these standards to bakery magazines, encouraging bakers to ask for uniformity along these lines in order to always produce "the same results under the same conditions, and thus… maintain an orderly schedule of bakeshop operation."[218] The standard was set in contrast to poor performing strains of culture, presumably from Fleischmann's competitors.

The Phaff Culture Collection

Like Fleischmann's, the Division in Berkeley had made important contributions to the war effort and had been concerned with the development of dehydrated fruits and vegetables for military rations. This focus on specialty foods persisted as an interest of the Division into the early years of the Cold War with speculation about the need for emergency feeding programs which could be ready to operate under unforeseeable conditions.[219] In 1944, Fruit Products rebranded again, this time as the Division of Food Technology. Mrak became chair of the Division in 1948, and oversaw the next big transition for the Division - its move to the University of California's Davis campus. There, Food Technology was to be housed in a state-of-the-art facility built with funding from the food industry where new processing techniques were expected to yield convenience foods of the future.

American consumers were increasingly distanced from old food preparations methods of the pre-war period. By 1946, 85 percent of American bread came from commercial bakers and

[217] Fleischmann Laboratories, Yeast - All Types (1936, 1948, 1950, 2002), (Undated), Box 16, Folder 22, Ray Thelen Papers (#D-470), University of California, Davis Special Collections, Davis, California.
[218] Frederick W. Nordsiek, Yeast - All Types (1936, 1948, 1950, 2002), (July 18, 1949), Box 16, Folder 22, Ray Thelen Papers (#D-470), University of California, Davis Special Collections, Davis, California.
[219] Emil M. Mrak, "Special Foods for Emergency Situations," *American Journal of Public Health and the Nations Health* 42, no. 4 (1952): 379-384.

home baking was limited primarily to rural, low-income Polish and Scandinavian households.[220] A new television show called *I Love Lucy* reflected on these recent changes to household consumption. In an episode airing in March of 1952, the characters of Lucy and Ethyl bet their husbands, Ricky and Fred, that they can give up the conveniences of modern American life, including such luxuries as store-bought bread. Now faced with the task of making her own dough, Lucy inadvertently adds much more yeast than her recipe calls for – 13 yeast cakes instead of 3 – resulting in a massive loaf of bread which expands from the oven to knock her to the floor.[221] Audiences understood that new modern conveniences saved housewives this drudgery, even as the methods of mass production had distanced them from such relics of the past as baker's yeast.

These were the ambitions which characterized the new Food Technology Division at Davis. Phaff had been in the Netherlands working on yeast taxonomy when news of the Division's relocation reached him. At Berkeley, he and Mrak had taught a pioneering course on taxonomy, morphology, ecology and physiology of the yeasts at a time when other programs offered only general courses in mycology or bacteriology. This course moved with them to Davis.[222] By mid-century, the Division was offering coursework in food processing operations, including food coloring, preservation and spoilage prevention, as well as industrial manufacturing, machinery, the economics of location, and commercial food standards.[223] The University was growing its presence in Davis with a new College of Letters and Sciences and a

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[220] Klieger, *The Fleischmann Yeast Family*, 112.
[221] Marc Daniels, *Pioneer Women*, I Love Lucy, March 31, 1952, Columbia Broadcasting System, Season 1, Episode 25.
[222] Phaff, "My Life with Yeasts," 7. The Mycology Society of American carried news of this course offering amidst a list of other courses on general mycology. *Mycology Society of America News Letter*, vol. 4 (1953), 17.
[223] *General Catalogue, 1950-1951,* vol. 45(7) (Berkeley, California: University of California Press, 1950), 151-152.

more active cultural life, and also moved toward consolidation of its agricultural sciences.[224] In 1959, the University Regents declared Davis a general campus of the University of California. Mrak was appointed chancellor, and Food Technology gained departmental status.[225]

An important source of information on the yeasts during this period was the *Yeast News Letter*, which had begun at the Illinois Institute of Technology in Chicago with biology professor Leslie Hendrick as editor in December of 1950 and passed to Mrak at Davis in 1952. The newsletter had been established "to disseminate information to persons working with yeasts and to stimulate interest in research and teaching with yeasts."[226] Phaff took over as editor at the end of 1953 and continued in the role for another 34 years. The newsletter's circulation grew from 46 American readers in 1950 to become the "Official Publication of the International Council of Yeasts and Yeast-like [M]icroorganisms" in 1969 under the International Union of Microbiological Societies, and by 1988 its mailing list included hundreds of subscribers in 47 countries.[227] The newsletter offered readers pre-publication access to yeast research findings as

[224] Emil M. Mrak, Series II: Correspondence, 1946-1984, (January 4, 1952), Box 8, Folder 14, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.
[225] Emil M. Mrak, This Complicated World, (1982), Box 87, Folder 83, Emil Mrak Papers (D-096), University of California, Davis Special Collections, Davis, CA. Fruit Products, which had become the Division of Food Technology at Berkeley in 1944, rebranded again at Davis as the Department of Food Science and Technology.
[226] See Leslie R. Hedrick, "From the Editor," in *Yeasts: A News Letter for Persons Interested in Yeasts*, ed. Leslie R. Hedrick (1950). Leslie R. Hedrick, "Questions to Be Answered by Persons Interested in Yeasts," in *Yeasts: A News Letter for Persons Interested in Yeasts*, ed. Leslie R. Hedrick (1950); Leslie R. Hedrick, "From the Editor," in *Yeasts: A News Letter for Persons Interested in Yeasts*, ed. Leslie R. Hedrick (1951).
[227] Marc-André Lachance, "Editorial," in *Yeast: A Newsletter for Persons Interested in Yeast*, ed. Marc-André Lachance (International Commission on Yeasts of the International Union of Microbiological Societies (IUMS), 1988), 1. See also Mrak, History of Yeast Work in U.C., (1979), Box 87, Folder 33, Emil Mrak Papers (D-096).

well as updates of new strains found and maintained in the culture centers. As the field became more crowded, it also served as a way for individuals to stake out territorial claims.[228]

The yeast collection which had moved with Mrak and Phaff to Davis continued to expand by thousands of new species over the next few decades as the exploration of yeasts' varied habitats continued.[229] In 1966, Mrak and Phaff published *The Life of Yeasts* about many of these species, together with Martin Miller who was another graduate of Food Technology who joined the faculty at Davis.[230] In time, the extensive collection came to be known as the Phaff Culture Collection, and is today the fourth largest yeast collection in the world with over 6,000 strains. The Enology Culture Collection, which had also started at Berkeley and moved to Davis, also ranks highly with over 2,600 strains of wine yeast, including 85% from a single species. It continues to serve as a resource to the wine industry in and beyond California. Larger yeast collections are held by the United States Department of Agriculture, the American Type Culture Collection, and the Centraalbureau voor Schimmelcultures, but these have grown primarily through acquisitions.[231] Two large acquisitions by the Centraalbureau voor Schimmelcultures

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[228] Christopher Kelty has also discussed the role of newsletters in producing "collaborative competition" in his study of the *Drosophila* community newsletter. Kelty has claimed that the twentieth century newsletters of model organisms represent the success of these research communities and functioned as coordinating tools. In Kelty, "This Is Not an Article: Model Organism Newsletters and the Question of 'Open Science'," 147, 148, 158.

[229] In Phaff, "My Life with Yeasts," 18-19. See also Phaff, "Life with Yeasts During Retirement." One interesting species collected in the late 1960s as part of Phaff's involvement in the U.S.-Japan Cooperative Science Program was identified as containing a red pigment that could give the flesh of farm-raised salmon the coloring of their wild counterparts when added to the fish's diet. See Gary W. Sanderson and Setsuko O. Jolly, "The Value of Phaffia Yeast as a Feed Ingredient for Salmonid Fish," *Aquaculture* 124, no. 1–4 (1994): 193-200; Eric A Johnson, "Phaffia Rhodozyma: Colorful Odyssey," *International Microbiology* 6, no. 3 (2003): 169-174.

[230] Phaff, Miller, and Mrak, *The Life of Yeasts: Their Nature, Activity, Ecology, and Relation to Mankind*.

[231] Kyria Boundy-Mills, "Yeast Culture Collections of the World: Meeting the Needs of Industrial Researchers," *Journal of Industrial Microbiology & Biotechnology* 39, no. 5 (2012): 675, 677.

were Hansen's original yeast collections and the Delft culture collection.[232] In the year 2000, the yeasts which had been curated by Beijerinck and Kluyver were returned there, and placed back under the control of the Royal Netherlands Academy.

For years, research in the Delft collection had served to produce and revise the definitive texts of yeast taxonomy.[233] A major benefactor of this work was the Davis yeast community. Like the Delft collection, the Phaff Culture Collection at Davis adopted an expansive general microbiological vision which propelled it to become an international center for research on yeast taxonomy, physiology and ecology and allowed it to serve as a resource to the yeast-based industries.[234] Species differences determined by chemical relationships between the yeasts and their varied environments gave greater specificity than other physiological, cytological or morphological criteria and enabled a broad demarcation of species. The Delft and Phaff collections were unique for collecting a wide range of wild yeasts for this purpose at a time when many other culture collections focused on deriving potentially useful yeast strains from just a few industrial species.[235]

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[232] I. N. Roberts and S. G. Oliver, "The Yin and Yang of Yeast: Biodiversity Research and Systems Biology as Complementary Forces Driving Innovation in Biotechnology," *Biotechnol Lett* 33, no. 3 (2011): 478.

[233] In "History of the Centraalbureau Voor Schimmelcultures," accessed January 13, 2015, http://www.cbs.knaw.nl/. The best known text evaluated 1317 strains maintained in Delft. See Jacomina Lodder and N. J. W. Kreger-van Rij, *The Yeasts: A Taxonomic Study* (New York: Intersci. Publ., 1952).

[234] In recent years, culture collections are believed to serve a number of additional purposes. "[C]ulture collections are considered to be a means to preserve microbial diversity ex situ…. [They] provide a link to the past…[and to] future biotechnological applications." In F. Uruburu, "History and Services of Culture Collections," *Int Microbiol* 6, no. 2 (2003): 101-103.

[235] Wine yeasts of the Davis Enology Culture Collection offer an example of the latter. Only a few species are represented in this collection which had originated with the wine yeasts of California's Agricultural Experiment Station, and split off in the move to Davis. Slight chemical differences among the strains have been extensively catalogued as the variants in this collection. See Phaff, "Life with Yeasts During Retirement," 434.

As knowledge disseminators of material practice, culture collections helped to produce biological variation among the yeasts as a resource from which to select chemical standards – both for classificatory and industrial purposes.[236] Kluyver recognized the need for culture collections to fulfill this role of "knowledge dissemination" as early as mid-century. By "providing scientists all over the world with authentic cultures of organisms discovered or described by their colleagues elsewhere," collections which disseminated material also transferred concepts and techniques that had been grounded by research on taxonomy and systematics.[237] By 1953, most of that work contained knowledge of comparative biochemistry developed by the general microbiologists.[238] The yeasts moved with this information to pervade all scientific and industrial practices with the organisms. As Mrak told a correspondent of the culture collection in 1952, "Herman [Phaff] will send you 6-8 cultures in the very near future. He will also send you the dope on these cultures."[239]

Early culture collections had been designed to serve the needs of brewers, winemakers, and yeast manufacturers like Fleischmann's, who were concerned with classificatory criteria but only in so far as they helped to differentiate industrial species from the wild yeasts. Once microbiological research into microbial growth factors and the vitamins began to connect the

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[236] Attention to this use of variation as an industrial resource is evident in contemporary efforts to preserve yeast biodiversity. Today, the Phaff Culture Collection advertises that it attempts to conform to the expectations of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, which went into effect in October of 2014. Although the United States has not signed this U.N. treaty, the American Phaff collection contains many microbes of international origin and acknowledges the efforts by national governments to conserve and promote sustainable use of their countries' biodiversity in the face of "commercial biopiracy." "University of California, Davis Phaff Yeast Culture Collection," accessed February 4, 2015, http://phaffcollection.ucdavis.edu/.

[237] Albert J. Kluyver, "Three Decades Progress in Microbiology," *Antonie van Leeuwenhoek* 13, no. 1 (1947): 4.

[238] Van Niel, "Introductory Remarks on the Comparative Biochemistry of Microorganisms," 12.

[239] Mrak, Series II: Correspondence, 1946-1984, (January 4, 1952), Box 8, Folder 14, Sol Spiegelman collection (MSC 561).

yeast metabolism to the chemical variation of their environments for which there was now a repertoire of classificatory tests, yeast industrialists sought greater chemical specificity from the few species which had already proven their utility.[240] The classification of yeasts from a great variety of habitats served to regroup the industrial yeasts into ever fewer species categories even as the number of known species and strains continued to grow overall. Industrial standardization was aided by these taxonomic revisions.[241]

Using just a few industrial species, yeast manufacturers and winemakers sought to control variation not just of yeast types, cultures, races, or populations, but also with the more precise chemical control within species, by strain. As we will see, by the 1930s and 1940s, these standardized strains were no longer just selected – they could also be bred.

SECTION III.

Pure Cultures and Pure Lines

With little agreement as to how the yeasts could be classified at the start of the twentieth century, yeast pure cultures were unreliable as the subject of hereditary research, and yeast did not become the subject of genetic study until the mid-1930s. The diagnostic tools of general microbiology were central to this transition. Since their development by Carlsberg physiologist

[240] This path dependency might be invoked as the right yeast for the job with reference to Clarke and Fujimura, *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences*. In the words of the current curator of the Phaff Culture Collection, “Just as the prudent employer should interview multiple candidates for a job, the prudent yeast researcher should compare multiple yeast species or strains before selecting the best one for their application. Culture collections are arguably the best place to find these candidates.” In Boundy-Mills, "Yeast Culture Collections of the World: Meeting the Needs of Industrial Researchers," 673.

[241] The same can be said today. “In the post-genome era, culture collections have taken on an expanded role as genetic resource centres... [for] a multitude of new applications in fundamental research, biotechnology, sustainable agriculture, and human healthcare.” In Roberts and Oliver, "The Yin and Yang of Yeast: Biodiversity Research and Systems Biology as Complementary Forces Driving Innovation in Biotechnology," 485.

Emil Christen Hansen in the early 1880s, yeast "pure cultures" had not implied the fixed heritability of "pure lines" for use in the brewing process. Although yeast reproduced itself from cell to cell, its purity as a "line" was inconsistent, and perhaps environmentally-modifiable. Yeast "pure cultures" could be variable in their short-term development and long-term evolution, and had from the 1880s exhibited both "temporary" and "permanent" changes in the brewers' broth. Yeast evolution and heredity were undifferentiated by pure cultures, and their use ensured only the exclusion of other species.

"Pure lines" developed out of research with other organisms and was a concept that implied a homogeneous line of descent vis-à-vis an organism's self-fertilization. The bean plant experiments of Danish botanist Wilhelm Johannsen had established such a model in the opening years of the twentieth century. Johannsen had been a research assistant in the chemistry department of Carlsberg laboratory during the years when Hansen led physiological research on the yeasts. While studying the barely plant at Carlsberg, Johannsen was said to have been heavily influenced by Bernard's writings on the commonalities between various forms of life.[242] He may have adapted the concept of a pure culture to his thinking about pure lines.[243] After taking a position at Denmark's Royal Veterinary and Agricultural University to teach plant physiology, Johannsen began his experiments with bean plant "pure lines." He sorted distinct groups of self-

[242] In the 1890s, Johannsen was reading the text in which Bernard proposed the two external and internal environments of the organism, which may have helped him to speculate on how biology could be shared by organisms in ways both visible and invisible. See Øjvind Winge, "Wilhelm Johannsen: The Creator of the Terms Gene, Genotype, Phenotype and Pure Line," *Journal of Heredity* 49, no. 2 (1958): 84-85.

[243] Staffan Müller-Wille has claimed that Johannsen's pure line studies of plant inheritance were modeled on the precision of yeast pure cultures. In Müller-Wille, "Hybrids, Pure Cultures, and Pure Lines: From Nineteenth-Century Biology to Twentieth-Century Genetics," 801.

fertilized bean "seeds" by their weights and began to detect a pattern.[244] The variation in their weight could not be explained by different inheritance since all the plants were "pure," so it was therefore a matter of hidden differences controlling how that heredity manifested due to possible selection pressures from the plants' environment.[245] Johannsen conceptualized two modes of biological variability and offered the concepts of "genotype" and "phenotype" to describe, respectively, the invisible and visible properties of individual organisms. Both concepts dealt with the variability inherent to the organism itself, for Johannsen did not believe that environments could create racial varieties, only select among interracial variants.[246] He had trained under the Danish botanist Eugenius Warming, and had at first agreed with his mentor's ecological views, but after 1900, the two grew increasingly distant. He criticized the imprecise

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[244] W. Johannsen, *Ueber Erblichkeit in Populationen Und in Reinen Linien: Ein Beitrag Zur Beleuchtung Schwebender Selektionsfragen* (Jena: G. Fischer, 1903); W. Johannsen, *Elemente Der Exakten Erblichkeitslehre. Deutsche Wesentlich Erweiterte Ausgabe in FüNfundzwanzig Vorlesungen* (Jena: G. Fischer, 1909).

[245] Kohler has written that this distinction sharpened the line between geneticists in the laboratory working with "safe and scientific" pure lines, and biologists of the field whose work was risky and even unscientific because it dealt with environmentally-modifiable traits. In Robert E. Kohler, *Landscapes & Labscapes Exploring the Lab-Field Border in Biology* (Chicago: University of Chicago Press, 2002), 91.

[246] Johannsen had claimed that selection could not improve upon evolution, and was useful to modify only "intraracial heredity" by changing the average traits exhibited by populations. See a partial English translation, summary and analysis of Johannsen's bean experiments in G. Udny Yule, "Professor Johannsen's Experiments in Heredity: A Review," *New Phytologist* 2, no. 10 (1903): 237. "[O]n the whole nothing whatever is attained by the process of selection within the pure lines", Johannsen wrote. Originally "im großen und ganzen ist durch Selektion innerhalb der reinen Linien gar nichts erreicht worden." In Johannsen, *Ueber Erblichkeit in Populationen Und in Reinen Linien: Ein Beitrag Zur Beleuchtung Schwebender Selektionsfragen*, 39. See also Nils Roll-Hansen, "Commentary: Wilhelm Johannsen and the Problem of Heredity at the Turn of the 19th Century," *International Journal of Epidemiology* 43, no. 4 (2014): 1010; Nils Roll-Hansen, "The Holist Tradition in Twentieth Century Genetics. Wilhelm Johannsen's Genotype Concept," *The Journal of Physiology* 592, no. 11 (2014): 2433. The latter suggests: "Johannsen found that within each of these [pure line] sub-populations selection had no effect on the average property (e.g., weight of the beans). Thus Galton's ancestral law [of continuous variation to produce gradual evolution] did not hold. However, if all the pure lines were added together to make one big population, the law gave a correct description of the result of selection. Johannsen concluded that this was due to a selection between stable genotypes."

methods of ecology and became strongly opposed to the neo-Lamarckian arguments for which they could be used.[247]

The distinction of phenotype with genotype leant itself to investigations which believed that heredity could be marked by subtle, hidden discontinuities. At the turn of the century, following Beijerinck's "rediscovery" of the pea plant breeding experiments of the Austrian monk Gregor Mendel in the mid-nineteenth century and their broader corroboration, this was the position of a small group of scientists who argued that Mendel had proven the inheritance of "factors" passing between generations in specific proportions.[248] This new mathematical genetics could depict the likely outcomes of individual breeding experiments.[249] It was taken up by professional societies such as the American Breeders' Association, which met for the first time in 1903 to explore the implications of Mendelism for practical, theoretical and, increasingly, social concerns of genetics.

Questions about heredity lay just under the surface of research into biological variability in the yeasts but could not be studied in terms of distributed "factors."[250] In terms of their purity

[247] Jean-Baptiste Lamarck was an eighteenth-century French biologist who proposed a theory of evolution in which organisms could lose or develop characteristics in response to their environments and pass these to their offspring. Early twentieth century proponents of his theory used it to argue for the inheritance of individually-acquired characteristics.

[248] It was Beijerinck who "rediscovered" Mendel's experiments in 1899, sharing this early paper with the Dutch botanist Hugo Marie de Vries who used it to interpret his experiments. In Müller-Wille, "Hybrids, Pure Cultures, and Pure Lines: From Nineteenth-Century Biology to Twentieth-Century Genetics," 802.

[249] The French biologist François Jacob once described genetics, by which he meant Mendelian genetics, as "a logical system that worked like an exact science, a combinatorial system of "factors" and "characters." From the visible, the "phenotype," one inferred the invisible, the "genotype." These abstractions required no reference to their origin and composition." In Jacob, *The Statue Within: An Autobiography*, 259.

[250] Staffan Müller-Wille has written that researchers in the brewing industry were predisposed to the Mendelian mindset since they had long reduced microbial species to simple specificity. This was a kind of "protogenetic thinking", which could reliably predict the effects of organisms upon

as hereditary “lines,” yeasts were on the one hand presumed to be very ancient. Breweries perpetuated the best races, and scientists believed that some yeasts had distinguished cultural lineages. In 1905, for example, the Pasteur Institute reportedly traced the origin of some living yeasts to the breweries of ancient Egypt, claiming, whereas there was probably left no “single human descendant who can follow his genealogical tables to the days of the Ramses,” yeast was able to maintain this pedigree since it was everyday made anew.[251] On the other hand was the species problem. In the early twentieth century, the yeasts were distinguishable primarily by their cultural heritage and industrial output, but their performance could change over time. If Ramses’ yeast now failed to produce a good beer, would it still remain a brewer’s yeast? There was far too much uncertainty about what a yeast line was to be able to study it with any certainty.

From Mendelian to Morganian Genetics

The “classical” period of genetics superseded early Mendelian genetics with a new experimental practice and the theory that genes could be co-located as physical objects arrayed along the chromosomes. In 1910, the Columbia University biologist Thomas Hunt Morgan began mapping genes to specific chromosomal locations after noticing a single white-eyed male fruit fly in a normal population of red-eyed *Drosophila*. As he bred more flies from this mutant, Morgan realized that he had observed an exception to Mendel’s laws of genetic segregation since two or more characters were inherited together. The eye color mutation was linked to the sex-determining factor. This and additional examples of genetic “linkage” in mice, corn and other plants, provided cytological evidence for a new gene theory of the chromosome. In Morgan’s

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one another and their environments. In Müller-Wille, "Hybrids, Pure Cultures, and Pure Lines: From Nineteenth-Century Biology to Twentieth-Century Genetics," 802.

[251] A. M. Krecker, "World's Smallest Factory Strange and Mysterious," *Chicago Daily Tribune*, October 29, 1905.

words: “we find coupling in certain characters, and little or no evidence at all of coupling in other characters… [It is] a simple mechanical result of the location of the materials in the chromosomes.”[252] Linkage maps could be made to track structural changes of the chromosome and connect the physical gene to statistical variations in heredity as observed by Mendelian rules. *Drosophila* - which bred rapidly, took up little space and were inexpensive to maintain - turned out to have an additional simplifying advantage for these mapping studies, in that the fly possessed only four chromosomes.[253]

The yeasts were not among these early experimental organisms used to demonstrate linkage for there was little way to know what might constitute a yeast mutant by the existing cytological evidence. In Berkeley during this period, the wine yeasts occasionally overlapped genetic study of *Drosophila* going on in other areas of the University but only as fungal food for the flies.[254] Even more critically, the yeast life cycle was not understood, and it was unclear whether the yeasts had sexuality required for breeding experiments. The yeasts exhibited a range of reproductive behaviors without any clear organization. Some yeasts appeared to undergo reproduction by budding or fissure, while others germinated into new yeasts with or without visible “fusion.” Many of the industrial yeasts seemed to be asexual and appeared to generate spores.

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[252] Thomas Hunt Morgan, "Random Segregation Versus Coupling in Mendelian Inheritance," *Science* 34, no. 873 (1911): 384.
[253] F.H. Portugal and J.S. Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance* (Cambridge: MIT Press, 1980), 121.
[254] Later at Davis, several studies related the yeast flora present in a particular area to wild species of the *Drosophila* who fed on them. In the 1970s, for example, Phaff studied the evolutionary and ecological relationship between the yeasts and *Drosophila* by exploring the chemistry and genetics of wild organisms in the context of various cacti hosts. “The cactus-*Drosophila*-yeast ecosystem has given us a wealth of information on the evolution and speciation of yeasts,” argued Phaff. In Phaff, "My Life with Yeasts," 25.

Danish scientists of the nineteenth century had studied yeast sporulation for the breweries. At Carlsberg laboratory in Copenhagen, Emil Christen Hansen had considered sporulation a parasitic survival tactic of the yeast in 1889. Alfred Jörgensen, founder of the Laboratory of Fermentology, also in Copenhagen, had noted that yeast spore formation was affected by temperature and could be induced by harsh environmental conditions. In 1893, Jörgensen wrote that he considered sporulation a possible morphological criterion of species differentiation.[255] More than three decades later, the French botanist Alexandre Guilliermond wondered if sporulation was an evolutionary trait lost to some yeasts "by a series of unknown circumstances" or whether the lack of sporulation by some species represented their possible origin from "more highly developed fungi."[256] The place of sporulation in the yeast life cycle remained unclear. Without a better understanding of yeast reproduction, chromosomal studies in the style of the *Drosophila* breeding experiments were not a possibility.

Yeast Sexuality

Two Czech fermentation scientists, Karel Kruis and Jan Šatava, were immersed in study of the industrial yeasts. In 1918, they gave an account that linked sporulation and sexuality in the yeasts to the content of the genetic material. Kruis was an organic chemist who had established a research institute for experimental brewing and malting in Prague. The institute had gotten its start in the mid-1880s and provided both theoretical and practical assistance to the Czech breweries and malting facilities. In 1896, it received a donation of pure yeast cultures from Alfred Jörgensen's research institute in Copenhagen and began to distribute these to members of industry. Šatava was a chemist and a brewer at Kruis's institute and later succeeded Kruis as

[255] Jørgensen, Miller, and Lennholm, *Micro-Organisms and Fermentation*, 156.
[256] Guilliermond, *The Yeasts*, 3.

director of both the institute and the University of Technology department of fermentation chemistry and mycology, where both men held appointments.[257] Together, their production and study of pure yeast cultures led to an interpretation of sporulation in the top and bottom brewing yeasts. Spores which germinated asexually formed small cultures and did not go on to sporulate again, they reported, while spores that fused with one another gave rise to cultures with the reverse effect. They related this fusion of spore nuclei to sexuality in the yeasts.[258] In 1920, this publication was unknown to Guilliermond who believed that the variations of sporulation were hereditary mutations and that many yeasts exhibited evolutionary loss of sexual reproduction.[259] The report from Kruis and Šatava sat in relative obscurity as other experimental organisms continued their prolific breeding.

Following Morgan's reports on the chromosomes of the fruit fly, the Danish biologist Øjvind Winge quit his early studies of the fungi and began to study animals and higher plants whose chromosomes were available to a cytogenetic approach as the basis of his doctoral thesis.[260] In 1917, Winge observed that interbred plants could have more than more than two paired sets of chromosomes and he theorized that this phenomenon of "polyploidy" represented the summation of parental chromosomes which did not undergo a reduction division of the genetic material. It was this doubling of the chromosomes, he proposed, which might account for

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[257] O. Hanč, *100 Years of the Czechoslovak Chemical Society: Its History and Development, 1866-1966*, ed. Československá společnost chemická (Academia, Pub. House of the Czechoslovak Academy of Sciences, 1966), 7; Gabriela Basarová and Ivo Hlavácek, *Ceské Pivo* (V Pacove: Nuga, 1999); "Institute History," accessed February 8, 2015, http://www.beerresearch.cz/.

[258] Karel Kruis and J. Satava, *O Vývoji a Klícení Spór Jakoz I Sexualite Kvasinek, Etc* (V Praze: nákladem Ceské akademie císare Frantiska Josefa pro vedy, slovesnost a umení, 1918).

[259] Guilliermond, *The Yeasts*, 25-28, 180-181.

[260] His dissertation is Øjvind Winge, "Studier over Planterigets Chromosomtal Og Chromosomernes Betydning" (PhD diss., H. Hagerup, 1917). See also his genetics textbook, Øjvind Winge, "Arvelighedslaere Paa Eksperimentelt Og Cytologisk Grundlag, Af O. Winge ... Med 147 Figurer I Teksten," (1928).

the evolution of new species.[261] Johannsen was a member of Winge's dissertation committee. Although he appreciated Mendelian logic in hereditary research, Johannsen balked at the chromosomal approach of the Morgan school.[262] That he accepted a thesis about the importance of the chromosomes in evolution may have indicated just how separately he viewed the laws governing evolution and heredity.[263] Winge corresponded with the English zoologist Reginald C. Punnett about these studies, and Punnett sent Winge pea plant flowers for cytological examination.[264] When nearly two decades later Winge moved into study of the yeasts these early influences would prove influential to his genetic analyses.

Punnett had been an early proponent of Mendelian genetics, and even though Morgan had indicated that genes were more than the abstract units of heredity that Mendelian geneticists were working with, and were in fact physically arrayed units, they could still be visualized mathematically. The Punnett Square was a tool developed by Punnett to illustrate the variety of possible genetic combinations following a cross between two individuals, and represented Mendel's discovery of the segregation of parental traits into discrete hereditary units. In its simplest form, the Punnett Square showed the distribution of parental traits in a 2 x 2 tabular format. Each pair of parental factors was segregated to form four possible breeding outcomes of

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[261] This hypothesis was contested decades later. See Jack R. Harlan and J. M. J. deWet, "On Ö. Winge and a Prayer: The Origins of Polyploidy," *The Botanical Review* 41, no. 4 (1975): 361-362.

[262] The "school" consisted of a small group of U.S. practitioners at this time under Morgan's leadership. Stephen Brush has estimated that between 1911-1926, "20 or 25 other students and collaborators published at least one paper using or testing Morgan's theory" and "thus could be considered part of Morgan's school." In S.G. Brush, *Making 20th Century Science: How Theories Became Knowledge* (New York: Oxford University Press, 2015), 403-404.

[263] Mogens Westergaard found Johannsen's involvement in chromosomal research odd and wrote that he likely had to be persuaded to accept the findings. In M. Westergaard, "Ojvind Winge (1886-1964)," *Genetics* 82, no. 1 (1976): 3.

[264] Øjvind Winge, "On the Relations between Number of Chromosomes and Number of Types, in *Lathyrus* Especially," *Journal of Genetics* 8, no. 2 (1919): 136.

genetic recombination. These variable outcomes of heredity had consequences for the tabular way Punnett described human biological variation. In 1911, for example, he wrote, "People generally look upon the human species as having two kinds of individuals, males and females, and it is for them that the sociologists and legislators frame their schemes. This, however, is but an imperfect view to take of ourselves. In reality we are of four kinds, male zygotes and female zygotes [representing the earliest stage of the gendered embryo], large gametes and small gametes [representing egg or sperm], and heredity is the link that binds us all together."[265]

Yeast in the Modern Synthesis

Karl Pearson's biometrical school was investigating these hereditary links in the distribution of phenotypes across a population. As Johannsen was differentiating the idea of phenotypes and genotypes in the individual, he was also reading Pearson's research using population statistics. Johannsen was skeptical of scientific methods that claimed to allow multiple sources of variation to enter an experiment. This is what had led him to condemn ecological work, even as he considered the influence of the environment in the production of biological variation. These conflicting perspectives were in close dialogue with one another in the opening decades of the twentieth century such that Beijerinck, who led an ecological approach to the classification in the yeasts, could in 1912 start using Pearson's term "population" after picking the word up from Johannsen.[266] He used it to describe microbial groups defined by

[265] R.C. Punnett, *Mendelism* (New York: The Macmillan Company, 1911), 183-184.
[266] Martinus W. Beijerinck, *Mutationen Bei Mikroben*, Folia Mikrobiologica (Delft: [s.n.], 1912). reprinted in Martinus W. Beijerinck, *Verzamelde Geschriften Van M.W. Beijerinck Ter Gelegenheid Van Zijn 70sten Verjaardag, Met Medewerking Der Nederlandsche Regeering Uitgegeven Door Zijne Vrienden En Vereerders* (Delft: F. Bruckmann A.G. und J.B. Obernetter, 1922), 36.

their response to the chemical composition of the tailored medium.[267] This "accumulation method" allowed for the multiplication of the microbial population of interest. Then individual traits could be related to group definitions using the pure culture method of isolating a single cell.

The variability of hereditary phenomena was also at the heart of arguments about the evolutionary mechanism at this time. At Britain's Rothamsted Experimental Station, Ronald Fisher, a young student of both Mendelian genetics and of the biometricians' problem of natural selection, held a temporary statistician appointment in 1919. He was observing the widespread variability of experimental data from agricultural research. These practical problems were being tackled by investigators using a mostly theoretical large-sample statistics which was still not all that useful.[268] Fisher had been inspired by "Student's" 1908 paper on the distribution of small samples. He met the author, Gosset, in 1912 and struck up a correspondence.[269] Student's t-test

[267] Angela Creager has argued that the shift in focus from an emphasis on adaptation in the single cell to the cell in culture occurred as a result of postwar studies of antibiotic resistance after the discovery of nutritional mutants. See A. N. Creager, "Adaptation or Selection? Old Issues and New Stakes in the Postwar Debates over Bacterial Drug Resistance," *Stud Hist Philos Biol Biomed Sci* 38, no. 1 (2007): 160. I place this transition earlier. Andrew Mendelsohn has argued that as early as the 1880s, medical bacteriologists performed cell culture experiments to investigate questions about variation and evolution in their quest for reliable vaccines. In Andrew Mendelsohn, "Message in a Bottle: The Business of Vaccines and the Nature of Heredity after 1880," in *A Cultural History of Heredity III: 19th and Early 20th Centuries*, ed. Max Planck Institut für Wissenschaftsgeschichte (Berlin: Max Planck Gesellschaft, 2005). This was also the intent of Beijerinck's species' diagnoses.

[268] As Fisher put it in 1925, "the traditional machinery of statistical processes is wholly unsuited to the needs of practical research. Not only does it take a cannon to shoot a sparrow, but it misses the sparrow!" In R.A. Fisher, *Statistical Methods for Research Workers* (Edinburgh: Oliver and Boyd, 1925), vii.

[269] See A. W. F. Edwards, "What Did Fisher Mean by "Inverse Probability" in 1912-1922?," (1997); Stephen Stigler, "Fisher in 1921," *Statistical Science* 20, no. 1 (2005). Fisher soon established another connection to the Guinness brewery where Gosset worked. In 1917, he married Eileen Guinness the great, great granddaughter of founder Arthur Guinness. In Darryl Lundy, *The Peerage: A Genealogical Survey of the Peerage of Britain as Well as the Royal Families of Europe* (Wellington, New Zealand: Lundy Consulting Ltd., 2013).

was not yet widely used outside of Guinness, and Fisher began to promote the work.[270] In time, Fisher would become a strong critic of Pearson's biometrical tradition and would produce a series of highly influential papers introducing alternative methods of model-based induction to statistics.[271] He spent his adult career working to make the pattern of Mendelian inheritance observed in individuals compatible with the biometrical pattern observed in populations.[272] Pearson's tradition held that evolution progressed gradually by the continual selection of the best adapted individuals.[273] Heredity in this formulation was characterized by an apparent blending of parental traits.[274] The population perspective conflicted with Mendel's observation that just a few

[270] Boland, "A Biographical Glimpse of William Sealy Gosset," 180.
[271] The disagreements between Pearson and Fisher have been extensively covered. See, for example, Joan Fisher Box, *R. A. Fisher, the Life of a Scientist* (Wiley, 1978); Box, "Guinness, Gosset, Fisher, and Small Samples," 45-52; Theodore M. Porter, *Karl Pearson: The Scientific Life in a Statistical Age* (Princeton, N.J.: Princeton University Press, 2004). For an example of how Fisher's work has been extended to recent genomic practice, see Guillaume Martin and Thomas Lenormand, "A General Multivariate Extension of Fisher's Geometrical Model and the Distribution of Mutation Fitness Effects across Species," *Evolution* 60, no. 5 (2006): 893-907.
[272] This began in 1918 with the concept of analysis of variance which allowed multiple factors in an experiment to vary simultaneously (i.e. multivariate analysis). See R.A. Fisher, "The Correlation between Relatives on the Supposition of Mendelian Inheritance," *Transactions of the Royal Society of Edinburgh* 52 (1918). Today the analysis of variance technique, or ANOVA, is a set of statistical models still widely used in the behavioral, social, population and life sciences to compare between-group and within-group variance.
[273] The biometricians claimed a basis for their views in the Darwinian theory of natural selection. They were opposed by early Mendelists such as the English geneticist William Bateson, who believed that different species originated, not gradually, but by evolutionary jumps as "discontinuous variations." See W. Bateson, *Materials for the Study of Variation: Treated with Especial Regard to Discontinuity in the Origin of Species* (London: Macmillan, 1894), 17; G.E. Allen, *Life Science in the Twentieth Century* (New York: Wiley, 1975), 52.
[274] Pearson had been influenced by Galton's law of ancestral heredity which proposed that variations of heredity were continuous: the heritage of an individual was equal to the sum of proportional contributions of each generation which preceded them. "Thus the sum of the ancestral contributions… being equal to 1, accounts for the whole heritage." Francis Galton, "The Average Contribution of Each Several Ancestor to the Total Heritage of the Offspring," *Proceedings of the Royal Society of London* 61, no. 369-377 (1897): 402.

discrete traits varied among individual generations of the pea plant.[275] In 1930, Fisher combined Pearsonian and Mendelian approaches and explained inheritance in terms of the variance of populations. This laid the foundation for evolution to become a theory of gene frequencies within populations, a statistical compromise enabling study of both individual heredity and natural selection at work on populations which, in the 1940s, was termed the "Modern Synthesis."[276]

Yeast's multiplication power had raised the question of uncertainty in small sample calculations, and from this Gosset had merged Hansen's culturally-defined concept of the yeast "races" with a scientific species concept now used interchangeably with the statistical concept of "populations." By 1912, Beijerinck was using this term to classify microbes ecologically, chemically and statistically. The yeasts' own 'modern synthesis' was their taxonomic standardization as species and strains across these disciplines.

Carl Lindegren & Microbial Genetics

The Morgan laboratory had begun to study microbial genetics. Morgan had relocated from Columbia to the Biology Division at the California Institute of Technology (Caltech) in the late 1920s, and he had continued to advance his physical brand of particulate Mendelian heredity

[275] Nils Roll-Hansen has argued that Johannsen's bean selection experiments echoed Mendel's findings on the consistency of quantitative characters, and that Johannsen also opposed the evolutionary gradualism of Galton and Pearson. These bean selection experiments formed the basis of Johannsen's definitions of the concepts of genotype and phenotype, which referred not to statistical averages, but to the properties of individual organisms. In Nils Roll-Hansen, "Sources of Johannsen's Genotype Theory," in *A Cultural History of Heredity III: 19th and Early 20th Centuries*, ed. Max Planck Institut für Wissenschaftsgeschichte (Berlin: Max Planck Gesellschaft, 2005), 43.

[276] R.A. Fisher, *The Genetical Theory of Natural Selection* (Clarendon Press, 1930); Julian Huxley, *Evolution: The Modern Synthesis* (London: George Allen & Unwin, 1942); Raphael Falk, "Mendel's Impact," in *A Cultural History of Heredity III: 19th and Early 20th Centuries*, ed. Max Planck Institut für Wissenschaftsgeschichte (Berlin: Max Planck Gesellschaft, 2005), 22.

in *Drosophila* in studies increasingly oriented to development and evolution.[277] There he was approached for a biological research problem by Carl C. Lindegren, a young plant pathologist and part-time student in organic chemistry. Morgan encouraged Lindegren to develop chromosomal mapping in other experimental organisms. Morgan had obtained several cultures of the multicellular bread mold *Neurospora* while at Columbia, as part of a study for the U.S. Department of Agriculture. He gave these to Lindegren for study of the organism's genetics and life cycle.[278] *Neurospora*, which reproduced sexually, allowed visualization of chromosomal division during the stages of reproduction known as meiosis and mitosis. It was known that the four products of meiosis were duplicated in mitotic division and were then available as eight haploid spores in a sac called the ascus. This octad of "ascospores" could be grown up into cultures which seemed to perfectly demonstrate the segregation of Mendelian factors. Since the haploid cell could undergo no further chromosomal division, there could be no dominance or recessiveness of traits. The phenotype gave access to the genotype. Not only could all products of a breeding experiment be recovered physically, but the spores were lined up in the order of their formation, which suggested chromosomal mapping in *Neurospora* as a possible alternative to *Drosophila.* To investigate this possibility, Lindegren began the dissection of *Neurospora* asci and analyzed the morphological differences of cultures grown from individual spores.[279]

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[277] See Kohler, *Lords of the Fly: Drosophila Genetics and the Experimental Life*, 177.
[278] Carl C. Lindegren, "Reminiscences of B.O. Dodge and the Beginnings of Neurospora Genetics," in *Neurospora Newsletter* (Fungal Genetics Stock Center, 1973). Although *Neurospora* and the yeasts are both classified as eukaryotic fungi, they are not related at the phylum level. By analogy, *Neurospora* and the yeasts are even more different in taxonomic terms than mammals and reptiles which share a phylum, Chordata.
[279] Carl C. Lindegren, "Genetic Study of Sex and Cultural Characters in Neurospora Crassa," (1931); Carl C. Lindegren, "The Genetics of Neurospora-II. Segregation of the Sex Factors in Asci of N. Crassa, N. Sitophila, and N. Tetrasperma," *Bulletin of the Torrey Botanical Club* 59, no. 3 (1932): 119-138. For more on the early genetic study of Neurospora, see Portugal and

As early as 1895, Beijerinck had described how study of the microbes would bridge the tensions between biological continuity and differentiation – or what he called the different questions of historic, static and dynamic biology.[280] In his inaugural lecture at the Polytechnic School of Delft, he claimed that bacteriological studies would someday identify the hereditary processes which explained biological variation:

> There can be no doubt that in some bacteria changes in the external conditions of life bring about deeper changes in the hereditary characteristics than has been observed to occur in higher organisms, and that therefore it will be the bacteria which will provide the building blocks for the erection of a theory of variability, which until now has mainly been supported by creations of the imagination.[281]

At the turn of the century, Beijerinck's chemical enrichment studies indicated that "microbes are an extremely useful material for the investigation of the laws of heredity and variability" due to their rapid generation, widespread variability, and competitive nature.[282] Lindegren's work in *Neurospora* seemed in part to support this.[283]

Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*.

[280] One might be tempted to note the similarities with the three major aspects later drawn together under the umbrella of genetic science: evolution, heredity, and development.

[281] Translation from Bert Theunissen, "The Beginnings of the "Delft Tradition" Revisited: Martinus Beijerinck and the Genetics of Microorganisms," *Journal of the History of Biology* 29, no. 2 (1996): 210. Originally, "Het laat zich verder ook niet ontkennen, dat bij sommige bacteriën, wijzigingen in de uiterlijke levensvoorwaarden diepere veranderingen teweegbrengen in de erfelijke eigenschappen, dan men dit ergens bij de hoogere organismen heeft waargenomen, en dat het derhalve wel de bacteriën zullen zijn, welke de eerste steenen zullen aandragen voor de opstelling eener theorie van de veranderlijkheid, tot nu toe bijna geheel en al door de scheppingen der verbeeldingskracht wordt gedragen." In Martinus W. Beijerinck, *De Biologische Wetenschap En De Bacteriologie: Redevoering Gehouden Bij De Opening Der Lessen in De Bacteriologie Aan De Polytechnische School Op Donerdag 26 September 1895* (Van Markens Drukkerij-Vennootschap, 1895), 22-23.

[282] Beijerinck, "On Different Forms of Hereditary Variation of Microbes," 352.

[283] Beijerinck's call for the use of microbes as experimental organisms of genetic study has been said to have gone unanswered until the 1930s with the development of identifiable and reproducible microbial strains. In Müller-Wille, "Hybrids, Pure Cultures, and Pure Lines: From Nineteenth-Century Biology to Twentieth-Century Genetics," 803. But *Neurospora* provides an earlier exception.

Late in the 1930s, the study of the rapid replication of the phage was independently taken up as a question of basic biological principles by the German physicist Max Delbrück, the American bacteriologist Alfred Hershey, and Italian microbiologist Salvador Luria. Like the yeasts, the tiny size and properties of bacteria and the phage had at first seemed to exclude them from the laws of genetics.[284] In the 1910s and 1920s, the phage had held promise as a possible therapeutic tool against bacterial infection, but hope for their widespread application had begun to fade by the 1930s.[285] Most geneticists had turned to other experimental organisms like the mouse to develop animal models of the genetics of human cancer.[286] The phage became favorable organisms for the study of variation once they were found to contain genes, exhibit conjugation, and acquire properties from other bacteria.[287] In this period, such studies were also enabled by new powerful magnifications of the electron microscope.[288]

By the mid-1930s, genetics was undergoing a transition to make compatible related observations in physics and biology. In 1935, German physicists Max Delbrück and Karl Günther Zimmer, together with Russian biologist Nikolai Timoféeff-Ressovsky, published a novel theory of gene mutation and structure, which held that all biological processes occurred at

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[284] Jacob, for example, said that he dreamed of performing experiments that "overturned the biological landscape, modified the problem of cancer", in Jacob, *The Statue Within: An Autobiography*, 208-210.
[285] W.C. Summers, *Félix D`Herelle and the Origins of Molecular Biology* (New Haven, Connecticut: Yale University Press, 1999).
[286] See Rader, *Making Mice: Standardizing Animals for American Biomedical Research, 1900-1955*.
[287] Jacob, *The Statue Within: An Autobiography*, 226-227.
[288] The American biophysicist Thomas F. Anderson recalled, "In 1940, when I first heard of the electron microscope which was said to have been developed in Germany it almost seemed to be a hoax perpetrated on the rest of the world by the Nazis." In Thomas F. Anderson, "Electron Microscopy of the Phages," in *Phage and the Origins of Molecular Biology*, ed. J. Cairns, J.D. Watson, and G.S. Stent (New York: Cold Spring Harbor Laboratory of Quantitative Biology, 1966), 63.

the atomic level.[289] Genes were at once both stable and variable. They could pass along heredity in a physical form while at the same time accounting for the fluctuations observed as variation.[290] This biology of the physicists was molecular.[291]

In the 1940s, the "phage group" consisted of an informal network of physicists and geneticists who were studying biological phenomena as time-ordered sequence of chemical events. They approached the study of life and heredity in a bacterial population as a set of molecular transformations. Reproduction of the phage occurred by the synthesis of new particles constantly in flux: "The animal or plant or micro-organism he [the physicist] is working with is but a link in an evolutionary chain of changing forms, none of which has any permeant validity… The organism he is working with is not a particular expression of an ideal organism, but one thread in the infinite web of all living forms, all interrelated and interdependent," Delbrück claimed. "[A]ny living cell carries with it the experiences of a billion years of experimentation by its ancestors."[292] In this formulation, variation could be explained as the

[289] N.V. Timoféeff-Ressovsky, K.G. Zimmer, and M. Delbrück, "ÜBer Die Natur Der Genmutation Und Der Genstruktur," *Nachrichten von der Biologie der Gesellschaft der Wissenschaften Göttingen* 1 (1935): 189-245.

[290] This theory gave biology a logical structure that operated similarly to physics, such that, for example, "[S]pontaneous mutations were considered to arise from quantum-statistical fluctuations in the isomeric states of the genetic molecules." In Robert H. Haynes, "My Road to Repair in Yeast: The Importance of Being Ignorant," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 146.

[291] The concept of "molecular biology" implied by Delbrück, Zimmer, and Timoféeff-Ressovsky's 1935 paper was greatly popularized by E. Schrödinger, *What Is Life?: The Physical Aspect of the Living Cell* (Cambridge: Cambridge University Press, 1944). More will be said about the molecularization of biology and the cracking of the genetic code in later chapters of this dissertation.

[292] Max Delbrück, "A Physicist Looks at Biology," *Transactions of the Connecticut Academy of Arts and Sciences* 38 (1949): 173-175.

hereditary “reassortment of characters in the thread of generations.” Evolution established the molecular properties of a species.[293]

The First Yeast Breeding Experiments at Carlsberg

In the years leading up to the transformative molecularization of biology, the yeasts’ sexuality was further characterized in ways that began to enable their genetic analyses. During his research on the chromosomes of higher organisms, Øjvind Winge had held positions at Denmark’s Royal Veterinary and Agricultural University and the University of Copenhagen. In 1933, he accepted an offer to direct physiology for Carlsberg laboratory in the position once held by Hansen. In the intervening years, the Carlsberg physiology department had moved away from the laboratory’s mission and had been studying problems of oceanography. Winge now returned it to the study of industrial organisms and resumed Hansen’s research with the yeasts. He was amazed to find that Hansen’s yeast strains which had been stored in a simple sugar solution more than four and a half decades earlier could be coaxed to grow again. His first paper on yeast described this revival, which he later described to a colleague as an almost “religious” experience.[294] Two identically dated and stored yeast cultures with no perceivable macroscopic differences had resulted in the death of one culture and the survival of another. “[A]pparently the life-span of the culture is largely a matter of chance,” Winge wrote. Group survival was a bleak aspiration, however, because in each culture there were “but a very few cells that have survived

[293] See Jacob, *The Statue Within: An Autobiography*, 271.
[294] Waclaw Szybalski, "My Road to Øjvind Winge, the Father of Yeast Genetics," *Genetics* 158, no. 1 (2001): 1-6; Robert K. Mortimer and John R. Johnston, "Genealogy of Principal Strains of the Yeast Genetic Stock Center," *Genetics* 113, no. 1 (1986): 35.

the hardship they have been exposed to."[295] Within a culture there was variation such that some individuals did better than others under the same conditions. Later, the revival of Hansen's yeasts attained a kind of mythology among other yeast researchers. For one, it proved yeast's value as an organism that could be readily and inexpensively circulated and stored across long periods of time, as Bernard's example of life in a latent state. But it also extended their research tradition and inherited material that much further into a distant past where yeast had already demonstrated its legitimacy and utility in research and practice.[296]

In his first year of laboratory work with the industrial yeasts, Winge extended his chromosomal studies from the higher organisms. He found that the life cycle of *Saccharomyces*, like other fungi, appeared to alternate between diploid and haploid phases. That is; that there were instances of yeast containing two sets of chromosomes - one from each parent - and other times at which it contained a single, unpaired set of chromosomes. Fertilization did occur in the species he examined as this was the mechanism by which the haploid returned to the double chromosomal state of the diploid. This alternation between different chromosomal states conformed to the spore fusion and variation in sporulating cultures that Kruis and Šatava had reported in 1918, although Winge learned of the Prague brewers' contribution only as his publication was going to press.[297] Yeast sexuality entailed the fusion of spore nuclei which doubled the genetic material and prompted further reduction division.

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[295] Winge and Hjort, "On Some Saccharomycetes and Other Fungi Still Alive in the Pure Culture of Emil Chr. Hansen and Alb. Klöcker," 58.

[296] Winge explained, "The… still surviving material of original cultures will in part form the basis for the investigations into the biology of the Saccharomycetes which this laboratory has taken up." In ibid.

[297] Winge commented on the obscurity of the Czech journal in which Kruis and Šatava had published. See his footnote in Øjvind Winge, *On Haplophase and Diplophase in Some Saccharomycetes* (Hagerup in Komm., 1935), 81. Their report remained buried in the literature for many years and is still frequently overlooked. Winge is most often credited for first relating

Winge studied several of the industrial yeasts and found that when they sporulated, the asci most frequently formed a four-spored tetrad. Using a glass needle to prevent the haploid spores from mating, Winge dissected the asci to separate each spore in the tetrad. This micromanipulation allowed the four spores to be grown up into different haploid cultures. The distinct morphological features of these cultures could be used to investigate genetic segregation, as Lindegren had done with the *Neurospora*.[298] Mendelian segregation seemed thus to extend to yeast since the four ascospores carried the segregated alleles, or alternative versions of the same gene that had separated in the two chromosomal divisions of meiosis.[299] Chromosomal irregularity, which had made yeast challenging and unpredictable as a genetic system, was beginning to conform to certain well-known rules of Mendelian genetics.

Winge's early studies had been intended to give order to the perceived "lawlessness" of the yeasts, and to a certain extent they did. It was now clear that the yeasts had sexuality during a certain phase in their life cycle. But on the other hand, it was not clear to what if any patterns this sexuality adhered. Spores mated with other spores, or with budded cells. "A striking feature is the absence of an established system governing the zygote formation," he wrote in 1935. "Every combination appears to be possible."[300]

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sexuality to the yeast life cycle in 1935 due largely to his later contributions to yeast genetics. See, for example, a recent publication by Carlsberg yeast geneticists Rosa Garcia Sanchez, Natalia Solodovnikova, and Jürgen Wendland, "Breeding of Lager Yeast with Saccharomyces Cerevisiae Improves Stress Resistance and Fermentation Performance," *Yeast* 29, no. 8 (2012): 344.

[298] This process is also described in first-person accounts in Hall and Linder, *The Early Days of Yeast Genetics*, 100.

[299] Winge, *On Haplophase and Diplophase in Some Saccharomycetes*; Øjvind Winge and Otto Laustsen, "On Two Types of Spore Germination, and on Genetic Segregations in *Saccharomyces*: Demonstrated through Single-Spore Cultures," *Comptes Rendus des Travaux du Laboratoire Carlsberg. Série physiologique* 22 (1937): 99-117.

[300] Winge, *On Haplophase and Diplophase in Some Saccharomycetes*, 77, 106.

The "rules" of yeast diagnosis began to change in the late 1930s and early 1940s given recent revisions to their taxonomy, which had opened up the possibility of new types of genetic characters. Mutant phenotypes like *Drosophila* eye color or the morphologic colonies of *Neurospora* began to make way for additional genetic characters that had been established in chemical classifications of the yeasts. In 1939, Winge and his research assistant Otto Laustsen began to use genetic fermentation markers to characterize yeast sugar utilization. Unlike Hansen's separation techniques to identify and isolate the desired yeast pure cultures, Winge and Laustsen's genetic crosses could in theory combine desirable fermentation characteristics between individual organisms. While taxonomy was "a delicate matter" and "absolute identification" was "generally impossible," there was enzymatic specificity in the yeasts' ability to ferment various carbohydrates which could be used to diagnose mutants from the culture medium. "The ability to produce a definite enzyme was always found to be dominant," they found in the initial experiments. "If a yeast type with the ability of forming one of these enzymes [saccharase, raffinase, or melibiase] is hybridized with another yeast type lacking this ability, the hybrid will always possess the ability of forming the particular enzyme."[301]

Winge continued his investigations of yeast genetics as German troops arrived to occupy Copenhagen in the spring of 1940. Although he had noted that different yeast colonies grew on different chemical media, and that hybrids typically gained rather than lost new fermenting properties, he did not follow up on the genetic utilization of sugars by the yeasts until after the war but remained focused on their morphology. While Carlsberg continued research and

[301] Winge and Laustsen had not yet produced a better brewer's yeast, but one of their baker's yeast hybrids had been adopted by a British baking company. See Øjvind Winge and Otto Laustsen, "On 14 New Yeast Types, Produced by Hybridization," *Comptes-Rendus des Travaux du Laboratoire de Carlsberg, Ser Physiol* 22, no. 21 (1939): 344, 351-352. In 1976, Winge's biographer, Mogens Westergaard claimed that "Strangely enough, Winge's methods never produced better strains of brewer's yeast." See Westergaard, "Ojvind Winge (1886-1964)," 6.

production on behalf of occupying forces, elsewhere, the persecution of European intellectuals greatly arrested scientific practice on the continent.[302] In 1939, the Senegalese poet Léopold Sédar Senghor foresaw the loss of another of Europe's promising young generations in the march to war. "Europe is burying the nations' leaven / And the hope of new races," he wrote.[303] The metaphorical value of yeast as something full of the potential of transformation intersected the day's eugenic ideals both in and outside of the laboratory. Like Carlsberg's earliest yeasts cataloged by country of origin, a generation of the "nations' leaven" were also being racialized and subjected to the tenuous promise of biological improvement.[304]

Biochemical characterizations were applied during these years to other experimental organisms more familiar to geneticists. At Stanford University, the geneticist George Beadle had recently moved from Caltech and was joined by the biochemist Edward Tatum, who was just returning from a postdoc in the Netherlands where he had had an opportunity to meet Kluyver. Beadle had worked on *Drosophila* for Morgan at Caltech, and had obtained some of Morgan's

[302] Germany ensured the supply of malt and corn to Carlsberg in exchange for beer for the occupying forces. In M.J. Iversen, "Carlsberg and the Cartels," *Journal of the Brewery History Society*, no. 131 (2009): 64. At the time, Carlsberg's beer labels contained an unfortunate design choice – the swastika logo – use of which the brewery tried to phase out over the 1940s in an attempt to minimize its association with the Nazis. The logo had been chosen decades earlier for its ancient association with prosperity and good fortune. See "Carl Jacobsen's Trademark 1881," accessed April 22, 2015, www.carlsberggroup.com.

[303] Originally, "L'Europe qui enterre le levain des nations et l'espoir des races nouvelles." In Léopold Sédar Senghor, ed. *Luxembourg 1939*, The Collected Poems (University of Virginia: The Rector and Visitors of the University of Virginia, 1998). In 1960, Senghor became the first president of Senegal following independence from France.

[304] The yeast metaphor for humans often became a human metaphor for yeast. Anthropomorphic language is apparent in the advice of Carl Lindegren to yeast industrialists in 1945 when he suggested to minimize the "era of good feeling" when "large numbers of a weaker type of cell manage to gain a foothold" by forcing a competition for nutrients. See Carl C. Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," *Bacteriological Reviews* 9, no. 3-4 (1945): 130.

Neurospora stock from Lindegren.[305] At Stanford, he and Tatum began to investigate the effect of x-ray exposure on *Neurospora* genetics. They tried to induce new nutritional needs among the offspring indicating the occurrence of a mutation.[306] Such biochemical changes would be taken as evidence that offspring failed to produce the enzymes once made by their parents for genetic reasons. In 1941, Beadle and Tatum published this work, which was expanded to articulate their "one-gene-one-enzyme hypothesis."[307] If genes controlled the production of enzymes involved in metabolic pathways, genes could be mapped in breeding and mutation studies by using enzymes as their markers.

While Tatum and Beadle had provided a successful link between genetics and biochemistry in *Neurospora*, they were not operating in isolation.[308] Their work moved quickly into other organisms for replication, but it did so not merely because of the correctness of the genetic logic.[309] Instead, the success in *Neurospora* had been predicated on much prior extensive

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[305] Lily E. Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology* (New York: Oxford University Press, 1993), 197; Joshua Lederberg, "Edward Lawrie Tatum: December 14, 1909-November 7, 1975," *Biographical memoirs. National Academy of Sciences (US)* 59 (1990): 357.

[306] N. H. Horowitz, "One-Gene-One-Enzyme: Remembering Biochemical Genetics," *Protein Sci* 4, no. 5 (1995): 1018.

[307] G. W. Beadle and E. L. Tatum, "Genetic Control of Biochemical Reactions in Neurospora," *Proc Natl Acad Sci U S A* 27, no. 11 (1941): 499-506.

[308] The origins of biochemical genetics have been argued to predate Beadle and Tatum's 1941 paper by decades. Medical geneticists, for example, can point to the inborn errors of metabolism recognized in the physiological chemistry of Archibald E. Garrod, "The Incidence of Alkaptonuria: A Study in Chemical Individuality," *The Lancet* 160, no. 4137 (1902): 1616-1620. "Garrod's vision is the idea that there is no "normal." Variation itself is the norm." In Comfort, *The Science of Human Perfection: How Genes Became the Heart of American Medicine*, 21. Jann Sapp wrote, "Although textbooks assert that Beadle and Tatum were the first to use microorganisms for biochemical genetic studies, the German biologist Franz Moewus and his collaborators preceded them… on the unicellular green algae *Chlamydomonas*… There were several other model organisms for microbial genetics." In Jan Sapp, *Genesis: The Evolution of Biology* (New York: Oxford University Press, 2003), 164-166.

[309] This logic is upheld by geneticists themselves. In 1965, James Watson, for example, saw that "the tools of Mendelian geneticists, organisms such as the corn plant, the mouse, and even the

chemical study, especially in the yeasts where the notion of enzyme specificity had been established. In 1941, the British geneticist J.B.S. Haldane predicted that "since yeasts have been very extensively studied from a biochemical standpoint, their genetics will be of great interest for a variety of metabolic problems."[310] Yeast was an obvious place for the genetics of metabolism to be linked to well-defined chemical processes because the organism had helped to establish to possibility of these connections. It would soon be made to conform to them.

Motivated by the industrial interests at Carlsberg, Winge had sought to classify and breed the yeasts to produce better industrial standards. He and Laustsen noted that a lack of objective standards made it difficult to judge the outcomes of yeast breeding experiments, for example, "The problem of the aroma for one is so important that it may often be literally a matter of taste."[311] Despite these doubts about yeast breeding, the Carlsberg experiments led the Polish chemist Adolf Joszt to credit Winge with the development of a new field of "genetic engineering."[312] Winge had preempted Tatum and Beadle in the use of chemical diagnostic tests

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fruit fly, *Drosophila*, were not suitable for chemical investigations of gene-protein relations. For this type of analysis, work with much simpler microorganisms became indispensable." In J.D. Watson, *Molecular Biology of the Gene* (New York: W.A. Benjamín, 1965), 31. In 1988, François Jacob also subscribed to this view. See Jacob, *The Statue Within: An Autobiography*, 224. Historians too have applied this internal logic by arguing that microbes provided the logical next step because their reproduction and development could be controlled in a way that was impossible for the higher organisms of classical genetics. See Sapp, *Genesis: The Evolution of Biology*, 161.

[310] John Burdon Sanderson Haldane, *New Paths in Genetics* (London: Allen and Unwin, 1941), 82.

[311] Winge and Laustsen, "On 14 New Yeast Types, Produced by Hybridization," 348, 351.

[312] A number of sources credit Danish microbiologist, A. Jost (also given as Joost or Justin) with the first use of this phrase in 1941 during a lecture (others say a conference) in Lwów. This claim appears to be a historical hybridization of sorts. The Danish microbiologist was Winge. A. Jost was the Polish chemist Adolf Joszt, who studied yeast fermentation and the genetics of microorganisms. Joszt taught at the Technical Institute during the Nazi occupation of Lwów, before the Soviet reoccupation when he was deported and "repatriated" to Gliwice in the Silesian part of Poland. In the 1943-1944 academic year, he introduced then-chemistry student Waclaw Szybalski to the yeast breeding experiments of Winge, which had begun before the war, referring

to define genetic mutants, but he had not attempted a formal yeast gene mapping program. This work was instead left to an American scientist trained in the Morgan school.

Yeast Gene Mapping

Following his years at Caltech with Morgan, Lindegren had moved to the Henry Shaw School of Botany at Washington University in St. Louis and switched from the study of *Neurospora* to the yeasts beginning in 1941. His laboratory was well-funded with support from Anheuser-Busch, Inc., a major supplier of yeast that reached consumers under other brand names.[313] Early funders also included the United States Public Health Service, the American Cancer Society, and the American Philosophical Society.[314] When Lindegren took up study of

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to the work as "genetic engineering." Szybalski later visited Winge in 1946, and using his teacher's description, proceeded to confuse the scientist whose work it was meant to characterize. See Szybalski, "My Road to Øjvind Winge, the Father of Yeast Genetics."; Waclaw Szybalski, interview by Mila Pollok, 2001, "Waclaw Szybalski on Studying Science in Poland During World War II," New York, Oral History Collection, Cold Spring Harbor Laboratory Archives; Waclaw Szybalski, "Recollections of 1939-1949: From Politechnika Lwowska to Politechnika Gdańska," *Acta Biochimica Polonica* 50, no. 2 (2003): xviii. One of the first appearances of this "A. Jost" claim in print is S.C. Witt, *Biotechnology, Microbes and the Environment* (Center for Science Information, 1990). In 2001, A. Jost featured on a timeline of biotechnology on the website "Access Excellence", a program which had been launched by Genentech Inc. in 1993. See "How Old Is Biotechnology? (2001)," accessed May 11, 2015, www.accessexcellence.org. The mistaken claim has since spread widely. See, for example, Martina Newell-McGloughlin and Edward Re, "The Dawning of the Age of Biotechnology 1970–1990," in *The Evolution of Biotechnology* (Springer Netherlands, 2006), 47; Gulzar A Niazi, "Genetics and Biotechnology in Historical Perspective: A Review," *World Journal of Medical Sciences* 2, no. 2 (2007): 72.

[313] Anheuser-Busch first sponsored Carl Lindegren to work at Washington University on a yeast genetics fellowship. In "Notes, News, and Comment," *Journal of the New York Botanical Garden* 43, no. 506 (1942): 55.

[314] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, vii. Genetic research on yeast was funded from an early period in the U.S. by groups interested in the cause of cancer. In the 1960s and 1970s such funding underwent a substantial expansion for work with model organisms as will be discussed in a later chapter. Prior to that expansion, Lindegren had been receiving $40,000 per year for yeast-based cancer investigations from cancer societies and the United States Public Health Service. See "Yeast Yields Secrets," *Popular Mechanics*, October, 1962, 8.

the yeasts, the tetrad analysis Winge had developed was familiar to him by the analyses he had done of *Neurospora* octads. Spore counts invariably differed by species, and among the yeasts, some - like the one Beijerinck had found growing on Greek currants in 1894 - produced eight-spored asci.[315] Others, like the pathogenic yeasts which had found in clinical practice, appeared to be nonsporulating. Under the right conditions, many varieties of yeast could be induced to sporulate however. Winge had selected the four-spored asci because it appeared to be fairly common among the industrial yeasts. In their simple statistics, tetrads also bore a distinct resemblance to that of the four products of a Punnett Square.[316]

In 1945, Lindegren noted for the yeasts that, "Ideally, each ascus contains four ascospores, but this ideal is not invariably attained; in fact, one much more frequently encounters two- and three-spored asci than four-spored asci, while one-spored asci abound in some cultures and on rare occasions one finds asci with more than four spores."[317] The analysis of the four-spored asci became so central to yeast genetic practice that standard growth media were developed to ensure that yeast regularly produced asci with this number of spores.[318] Lindegren

[315] Martinus W. Beijerinck, "Schizosaccharomyces Octosporus, Eine Achtsporige Alkoholhefe," *Centralblatt für Bakteriologie und Parasitenkunde* 16 (1894): 49-58.
[316] The English psychologist Charles Spearman was also applying the statistics of tetrad analysis in psychometric studies of intelligence and evoking criticism from Pearson for his misapplication of the normal sampling distribution to small samples. In C. Glymour, R. Scheines, and P. Spirtes, *Discovering Causal Structure: Artificial Intelligence, Philosophy of Science, and Statistical Modeling* (Elsevier Science, 2014), 234-239.
[317] Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," 132.
[318] At California's Agricultural Experiment Station, Mrak and Phaff developed a mixture of vegetable extracts which produced regular sporulation by many different yeasts. Lindegren noted that "media were judged on their ability to produce large 4-spored asci and on their comparative percentages." In Carl C. Lindegren and Gertrude Lindegren, "Sporulation in Saccharomyces Cerevisiae," *Botanical Gazette* 105, no. 3 (1944): 306. By 1955, one English brewer's analyst was claiming that, "The most suitable sporulation medium for a given yeast is one that… yields a high proportion of 4-spored asci." The reasons given for these preferences were that four-spored asci "are easier to dissect than other asci, yield more spores per ascus so that fewer asci have to

saw yeast tetrad analysis as providing a great and essential genetic advantage over organisms like corn and *Drosophila*.[319] In particular, he noted that *Saccharomyces*, the genus containing the most common industrial yeasts, "produces four viable ascospores and is therefore a *perfect* form."[320] The reliance on the yeast tetrad became so normalized in genetic practice that in later decades unexpected spore counts came to be routinely ignored or discarded as outliers.[321]

Following his studies with Beadle in *Neurospora*, Tatum visited Lindegren at Washington University in 1941 to demonstrate his new biochemical technique for generating mutants and deriving genetic markers. Lindegren had supplied the Stanford team with the bread mold and he now heard a report on their findings. Carl and his wife Gertrude Lindegren began to apply this method for a new yeast genetics mapping program. Gertrude was a full-time collaborator and although the credit frequently fell to her husband, she did all the microdissection of spores and biochemical analyses of the yeasts.[322] Carl saw this work as elevating yeast to "full-fledged membership in the Drosophila-maize-Neurospora hierarchy" because the collection of these unique biochemical phenotypes allowed mapping of single gene

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be dissected, and they are essential for accurate genetical analysis." In R. R. Fowell, "The Hybridization of Yeasts," *Journal of Applied Bacteriology* 18, no. 1 (1955): 153.

[319] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 12: 12.

[320] Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," 131-134.

[321] By the 1980s, specially-designed paper for tetrad analysis had labeled rows A, B, C, and D, because of the expectation that yeast asci sporulated in groups of four. The design implied much more regularity than had been assumed historically. A sample of this paper can be found in the laboratory notes books of the Amar Klar Papers, 1976-2001, (January 23, 1981), Series 1: Lab Notebooks, Box 5, Yeast Collection, Cold Spring Harbor Laboratory Archives, New York.

[322] Lindegren, "Reminiscences of B.O. Dodge and the Beginnings of Neurospora Genetics." Gertrude Lindegren later told a report that the example of Mrs. Morgan at Caltech had inspired her scientific life as wife and co-worker to a "pioneer." She had met Carl Lindegren prior to the years at Caltech at the U.S. Department of Agriculture. In Carol Bradford, "Microbiologist's Wife: Scientist and Homemaker," *Southern Illinoisan*, February 11, 1951, 5.

differences to the chromosomes.[323] In the 1940s, the Lindegrens began a collection of yeast strains which differed in their reaction to specific metabolites thought to be under the control of single genes.

Time and again the yeasts had proven themselves amenable to chemical investigations. From protoplasm to enzymes there had been much speculation about the chemical nature of the heredity material, but such investigations had not proven classificatory. Metabolic research which had followed from the "bios" of yeast revealed that all living things were constructed from the same chemical building blocks.[324] Kluyver's "unity in biochemistry" had been an early articulation of the belief that microbes and humans might share a common evolution apparent just below the surface of their plainly different physical forms.[325] Enzymes, growth factors and the vitamins suggested possible sources for variety, but did not enable its control. In the face of undifferentiated cell morphology, a taxonomy of the yeasts took up chemical classificatory methods for species diagnosis. Only then, when variety in the yeasts had been more expansively defined, could biochemical geneticists apply these classifications to the control of yeast hereditary variation.

Aided by a taxonomy of the yeasts produced by the microbiologists at Delft and food technologists at Davis, yeast geneticists could select and breed yeast strains in the 1940s by their

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[323] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, v; Carl C. Lindegren and Gertrude Lindegren, "The Genetics of Melezitose Fermentation in Saccharomyces," *Genetica Genetica: An International Journal of Genetics and Evolution* 26, no. 1 (1953): 431.

[324] The American geneticist Joshua Lederberg remembered the outcome of these studies as having "humiliated [us] by our species' inferiority to Escherichia coli, [which] in turn is less capable than the green plant!" Lederberg, Notes for an Entry in the Enciclopedia Italiana Entitled, "History of Microbiology, 1930-1950", (1990), Box 87, Folder 26, Profiles in Science: The Joshua Lederberg Papers.

[325] At the time, the "unity in biochemistry" was "not surprising to the more astute biologists, many of whom were largely preoccupied with the consequences of evolutionary theory: Given that a man and a fish are descended from a common ancestor, it should not be surprising that many of their cell constituents are similar." In Watson, *Molecular Biology of the Gene*, 45-48.

chemical differences. Winge's individual spore fusions had established breeding studies in principle but it was the Lindegrens who devised an alternative technique to generate breeding stock. To do this, they continuously inbred strains, crossing them only with themselves, until they had eliminated any "undesirable recessives." Carl had claimed that genes were not good or bad per se, but exerted their effect in relation to the whole.[326] "[I]nferior genetic material" in the industrial yeasts commonly produced rough, dark, small-colonied, or excessively low-yielding cultures, and these could be bred out of a strain by repeat sporulation. Once a generation of yeast showed that all four ascospores produced satisfactory cultures, a genetically stable breeding strain had been established. Since most commercial yeasts carried inferior recessive genes which predictably produced poor cultures, these were inbred repeatedly in order to join the stock of the Lindegrens' formal yeast breeding program.[327]

The Lindegrens learned a lesson in media sensationalism during this period after they were mistakenly credited with having developed yeast into a synthetic meat. *Time Magazine* described the new product as "nearly as succulent as the sirloin steak it takes two years to raise on the hoof, much cheaper, and much richer in proteins and vitamins." Carl Lindegren was supposed to have found "a candidate to upset the world's food economy" - one which the Germans also knew about but lacked the sugar to produce in quantity. "The Army and Lend-Lease are already buying millions of pounds. Postwar possibilities are obviously enormous," the

[326] In this contextual view of the gene, Lindegren differed from some medical geneticists who played off the success of germ theory to treat genes as specific agents of disease and articulate a "germ theory of genes" in which some were distinctly and individually bad or harmful. For more on this position of the medical geneticists, see Comfort, *The Science of Human Perfection: How Genes Became the Heart of American Medicine*, 68.

[327] Carl C. Lindegren and Gertrude Lindegren, "Selecting, Inbreeding, Recombining, and Hybridizing Commercial Yeasts," *Journal of Bacteriology* 46, no. 5 (1943): 412-413, 418.

article reported.[328] Other media outlets picked up the story: While on an Anheuser-Busch fellowship, Carl Lindegren had crossbred cells with his wife Gertrude Lindegren, the newspapers claimed, to develop yeast in a variety of flavors, including "meaty, nutty, or celery."[329] Anheuser-Busch had already demonstrated the yeast-meat could be used in soups, meat loaf, muffins, cheese sticks, and pie. "[T]he chemist appears to have accomplished a still greater step in the betterment of mankind," declared the journal of the American Chemical Society with reference to a number of similar workers exploring new food technologies.[330] Carl Lindegren was embarrassed by the erroneous coverage, which had confused the reach and purpose of his yeast breeding research. Anheuser-Busch "modestly disclaimed" the reports of a new yeast-meat product. "[O]nly God can make a steer," one representative remarked.[331] "It took a long time for me to get it all straightened out," Carl Lindegren later told a reporter.[332]

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[328] "The Last Roundup?," *Time* 42, no. 6 (1943): 50. The title suggested an end to the slaughter of the world's cattle. Similar reference to animal welfare was made 70 years later, in 2013, with the synthesis of the first cultured beef hamburger at Maastricht University in the Netherlands. Grown from cow stem cells, the "test-tube hamburger" was billed as ethically superior to animal slaughter, as well as being more agriculturally efficient and sustainable, potentially safer and healthier. Also headline-worthy was the source of funding for the project, Google co-founder Sergey Brin who provided approximately $300,000. In Alok Jha, "Synthetic Meat: How the World's Costliest Burger Made It on to the Plate," *The Guardian*, August 5, 2013. News of the stem cell burger was quickly followed up on by another bioengineering project, synthetic cow milk brewed in yeast by the Silicon Valley startup Muufri. In Linda Qiu, "Milk Grown in a Lab Is Humane and Sustainable. But Can It Catch On?," *National Geographic*, October 23, 2014.
[329] "Beefsteak Now Has a Synthetic Substitute: Anheuser Busch Have Brought out a New Yeast That Is a Vitamin-Filled Food," *Dunkirk Evening Observer*, August 6, 1943, 2.
[330] Walter J. Murphy, "Editorials: A Modern Day Version of the Loaves and Fishes?," *Industrial & Engineering Chemistry* 35, no. 9 (1943): 925.
[331] "U.S. Company Perfects "Meat Extender"," *The Advertiser*, August 9, 1943, 2.
[332] "Sex in a Cell ...But It's Yeast Cells," *Mt. Vernon Register-News*, September 6, 1951. It is not clear to what extent Carl Lindegren may have participated in or encouraged the 1943 report in *Time*.

The incident was a reminder of the excitement and interest that could attend a major breakthrough in genetics, and gave Carl Lindegren a taste of the public attention enjoyed at that time by his Nobel-winning mentor, Thomas H. Morgan, back at Caltech.[333]

Industrial Sponsorship & Commercial Opportunity

When, in 1948, the Lindegrens moved their laboratory to the Department of Biology at the University of Southern Illinois in Carbondale, they were the first to bring research grants to the University. The following year, Carl contemplated the reasons a researcher might choose a particular microorganism as the object of "genetical" research. "One important factor which cannot be ignored is the amount of capital invested in a given project," he wrote.[334] Like Pasteur, who had studied yeast for the improvement of France's beer, Hansen and Winge who had worked for Carlsberg, and the Davis food technologists who worked for both the wine and baking industries, the Lindegrens' yeast work was linked from the start to their relationship with industry.[335] In 1943, for example, the Lindegrens were investigating the requirements of a good commercial baker's yeast, including the shortest reproduction time measured by the transformation of nutrients in the fermenter into more yeast. Their breeding program attempted

[333] Morgan won the Nobel Prize in Physiology or Medicine in 1933 for his chromosome theory of heredity which had been established in *Drosophila*. Although Carl Lindegren completed his PhD with Morgan in biology in 1931, and went to work for Western Pennsylvania Hospital, Morgan's Nobel made its way into Carl Lindegren's conversations with the press for decades afterwards.

[334] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 12: 11.

[335] Sponsorship of the Lindegrens' research was an ongoing concern. In 1973, Carl claimed that for over more than three decades, he and Gertrude had dissected and analyzed over 100,000 yeast spores, all without compensation. In Lindegren, "Reminiscences of B.O. Dodge and the Beginnings of Neurospora Genetics." He had made a similar claim in 1951 at which time the number had been 20,000 "types" of a single species. He likely meant asci. See Bill Lyons, "Release: Immediate," news release, (Carbondale, Illinois: Southern Illinois University Information Service), July 5, 1951.

to improve upon this property by devising a "yield test" to select the fastest reproducing strains and "reject inferior cultures." The strains' "hereditary vigor" was defined in relation to industrial needs.[336] This sponsorship was a big impetus for the continuation of much research on the yeasts and led to the selection of industrial species as the prime breeding material, and thus, the dominant experimental species in the laboratory.

By the late 1940s, new yeast species were expected to be bred from strains with predetermined properties such as the type of sugar fermented, the ability to synthesize vitamins, the amount of alcohol produced, and the influence on alcohol flavor.[337] "The power of bio-synthesis contained within this little laboratory called yeast cell has reached the threshold of scientific revelation and is ready for greatly enlarged utility to man," reported scientists at Anheuser-Busch, Inc. in 1948.[338] This greater specificity also meant that yeast industrialists now replaced "pure culture" *species* with "pure line" *strains* in brewing practice. Pure cultures no longer gave precise control in the brewing process because species behaved too variably. One brewing scientist at the University of Birmingham claimed in 1947 that:

> The single cell culture accepted since the days of Hansen as biologically pure can no longer be regarded as such… spores upon germination will transform our "pure" culture into a mixture of different yeast types. A yeast culture, however, which has been derived from the germination and diploidization of a *single spore*… can only be homozygous, *i.e.*, a truly pure line.[339]

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[336] Carl C. Lindegren and Gertrude Lindegren, "Environmental and Genetical Variations in Yield and Colony Size of Commercial Yeasts," *Annals of the Missouri Botanical Garden* 30, no. 1 (1943): 71-79.

[337] There was already some encouraging evidence for this possibility in 1945, when Carl and Gertrude Lindegren found that "a vitamin-synthesizing deficiency" could be corrected in yeast hybrids. In Carl C. Lindegren and Gertrude Lindegren, "Vitamin-Synthesizing Deficiencies in Yeasts Supplied by Hybridization," *Science* 102, no. 2637 (1945): 34.

[338] Anheuser-Busch Inc., Yeast - All Types (1936, 1948, 1950, 2002), (July, 1948), Box 16, Folder 22, Ray Thelen Papers (#D-470), University of California, Davis Special Collections, Davis, California.

[339] R. S. W. Thorne, "Inheritance in Yeast," *Journal of the Institute of Brewing* 53, no. 1 (1947): 30.

At mid-century, the biochemically-defined strains of the yeast geneticists had become the new gold standard in commercial processes. Only yeast spores gave control over variation when grown up into cultures because as “pure line” strains they had been stabilized genetically.

Conclusion

The question of biological specificity in the yeasts arose within nineteenth century industrial practices, and resulted in the collaborative development of statistical and chemical controls by craft brewers and academic scientists in an effort to standardize yeast industrial processes. These controls emerged to diagnose yeast varieties but had resulted in a pre-genetic treatment of yeast variation. The emergence of the notion of enzymatic specificity in the yeasts offered a chemical model of heredity that would be taken up in the genetic study of other organisms. In order for yeast industrialists to operationalize a chemical definition of biological specificity, they drew from the yeast taxonomy developed by general microbiologists. Microbiological studies of the rich diversity held by the culture collections allowed for the first major advances in yeast taxonomy which had hitherto been stalled by few observable morphological or physiological differences among the yeasts. The yeast-based industries dedicated their own scientists and funding to these investigations with the expectation that better-characterized yeast species and (later) strains would be a profitable investment. While it is difficult to determine the high-level economic consequences of efficiency gains made by greater chemical specificity in the industrial yeasts, there is evidence of profitability on the mere promise of this scientifically-driven innovation. New products were marketed and sold on the basis of greater chemical purity, efficiency, suitability, or efficacy of the new yeast type. Unstable classifications were not so much disruptive to the yeast-based industries as they were

opportunities to expand the yeast product line. Standardizing yeast categories was then a collaborative effort to stabilize various scientific, craft and market knowledges simultaneously.

The chemical diagnostic methods produced by yeast taxonomists were used by later biochemical geneticists in the diagnosis of biochemical mutants which could be reliably defined against the stable evolutionary background of a standardized laboratory strain. A statistical tool to estimate variation in the breweries was leveraged to make individual hereditary variation compatible with that observed within populations. Taxonomic research on the yeasts resulted in fewer and more stably-defined industrial varieties, and it was these varieties that were taken up in experimental genetic practices as a result of industrial sponsorship. Over the next few decades, a number of controversies in yeast genetics moved researchers toward further standardization of their experimental material. The next chapter will explore how conflicting observations in early yeast genetics pointed toward additional *molecular* differences among strains such that geneticists began a common exchange of materials in order to reproduce one another's findings. Later chapters will argue that the rapid growth and success of yeast genetics at that time was produced not merely by the progressing "internal logic" of the science, but rather the existing material culture of yeast genetics which had enabled it to thrive. By then, the resulting strain of laboratory yeast for yeast genetics – an industrially- and molecularly-standardized experimental organism – was the consequence of a science that many other yeasts had helped to produce.

Chapter 2

Yeast Geneticists and the Standard Strain, 1935-1956

> Thus, yeast which has long been a favored source of experimental information for the physiologist and the biochemist, is now coming under the scrutiny of the geneticist and we may hope will be as rewarding to him [sic].[1]

By the mid-1930s, a revised taxonomy of the yeasts was emerging from Delft which defined microbial species in biochemical terms, relating them not merely to their places of origin, but their ecological relationships and cultural utility. Fewer species categories had collapsed the yeasts into broad industrial categories, and research on the vitamins was redirecting attention to the performance differences between strains. Genetic research had identified sexuality in the yeasts and for the first time breeding new yeast species for purposeful strain improvements actually seemed to be a possibility. Perhaps new yeasts would be invented by the end of the decade as the raw manufacturing material for a variety of industries. A few familiar species had already proven their utility in the production of nitroglycerin explosives, vitamin-enriched foods, and even a malleable material for combs and buttons.[2]

The first systematic yeast hybridization experiments began by inbreeding strains with the intent of establishing a breeding stock. Ideally, this approach would generate a complete catalog of types – representing the total variation among species – for the selection and combination of superior traits in a single organism. No sooner had these efforts begun, however, than the yeasts started misbehaving and appeared to be changing their characteristic traits. Studies out of

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[1] Or *her*. Female co-investigators ran the two major yeast genetics laboratories at this time in Carbondale and Copenhagen. Quote from Pomper, "Recent Developments in Yeast Genetics," 21.

[2] These examples produced from the few known industrial species were discussed in the previous chapter. See Deite and Kellner, *Das Glyzerin: Gewinnung, Veredelung, Untersuchung Und Verwendung Sowie Die Glyzerinersatzmittel*, 229; Braude, "Dried Yeast as Fodder for Livestock," 206; "Buttons as a by-Product of Beer," 222.

Carlsberg laboratory in Copenhagen and Washington University in St. Louis were reporting that yeasts were refusing to mate, or that they would not form spores, or that their spores were dying quickly. Others found just the opposite. Some investigators reported hybrids offering a perfect reflection of their parents; others found offspring behaving wildly unexpectedly. Conflicting observations led to conflicting explanations, and the disagreements about yeast appearance and behaviors led to more disagreements about the yeasts' hereditary mechanism.

In the late 1940s, genetic laboratories in Paris and Seattle found provocation in the disordered state of yeast research, and thought they might make an original contribution given the early successful record of *Neurospora*. An informal network of exchange began to share genetic characterizations of the yeasts, and investigators shared experimental material to minimize discrepant observations. By the mid-1950s, the resolution of their conflicts had forged a compromise in S288C, a shared laboratory strain of the industrial baker's yeast *Saccharomyces cerevisiae*, which served as an experimental "wild-type" in the decades which followed.[3] This laboratory strain and the mutants derived from it began to circulate out of the University of

[3] Others have found that organisms embody particular amalgamations of theories, beliefs and practices and are "co-opted and deployed by scientists in the support and defense" of these. See Gregg Mitman and Anne Fausto-Sterling, "Whatever Happened to Planaria? C.M. Child and the Physiology of Inheritance", in Clarke and Fujimura, *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences*, 176. Experimental organisms have been investigated as constructed artifacts. See Clause, "The Wistar Rat as a Right Choice: Establishing Mammalian Standards and the Ideal of a Standardized Mammal."; Kohler, *Lords of the Fly: Drosophila Genetics and the Experimental Life*.

California at Berkeley to set experimental standards worldwide.[4] The yeast geneticists had bred their superior organism. It was the material culture of a flourishing scientific community.[5]

The present chapter charts the development of S288C as a series of conceptual, cultural, and material compromises that followed on industrial selection of the laboratory yeasts with a second phase of genetic standardization. In tracing the "biography" of this particular strain, the chapter moves between a number of early laboratories in yeast genetics. Beginning with a series of unusual yeast behaviors encountered over the 1940s in breeding experiments by Øjvind Winge at Carlsberg laboratory in Copenhagen and Carl Lindegren and Gertrude Lindegren at Washington University in St. Louis, the chapter explores conflicting hereditary interpretations in light of the scientists' differing cultural and political commitments. Next, the chapter examines shifting alliances over the 1950s, which produced two important compromises. The first was the development of a new international center for yeast genetics in Herschel Roman's department at the University of Washington in Seattle. Here, the relationship of the Seattle yeast geneticists is drawn, not only to the few other yeast genetic laboratories then in existence, but also to other laboratories in biochemistry, microbiology, and biophysics where yeast was used in research. The second important compromise was the development of laboratory strain S288C by biophysicist Robert Mortimer at the University of California in Berkeley as the genetic "wild-type." The material compromise provided by this standard reconciled the conflicts of an older generation of yeast geneticists with ascendant practices of the new. The chapter concludes with

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[4] Robert Kirk has claimed that "standardization discourses within science are inherently internationalizing." In R. G. Kirk, "A Brave New Animal for a Brave New World: The British Laboratory Animals Bureau and the Constitution of International Standards of Laboratory Animal Production and Use, Circa 1947-1968," *Isis* 101, no. 1 (2010): 62.

[5] On the ability of material technology to crystalize forms of social organization see Steven Shapin, Simon Schaffer, and Thomas Hobbes, *Leviathan and the Air-Pump: Hobbes, Boyle, and the Experimental Life: Including a Translation of Thomas Hobbes, Dialogus Physicus De Natura Aeris by Simon Schaffer* (Princeton, N.J.: Princeton University Press, 1985), 25.

some of the institutional efforts to promote and maintain a shared material culture as the strain circulated to other laboratories. The next chapter will examine the development of yeast as a model eukaryotic for molecular biology by the groups in Seattle and Berkeley. The emergence of molecular biology over the 1930s, 1940s, and 1950s depended crucially on the shifting meaning of biological specificity during this period – the same years which witnessed production of the standard laboratory strain as a specific configuration of molecules.

Individual and Population-Based Breeding Analyses

At the end of the 1930s, Danish biologist Øjvind Winge had been the first to conduct yeast breeding experiments on the upper floor of Carlsberg laboratory. He and laboratory assistant Otto Laustsen had used a method of hybridization which allowed them to observe the mating of individual spores under a microscope. For a small international group of practitioners, this spore-to-spore mating method remained the uncontested approach to yeast breeding experiments until 1943.[6] It was then that husband-and-wife research team Carl and Gertrude Lindegren developed a new experimental technique for the mass mating of yeast at Washington University in St. Louis. The Lindegrens had moved their genetic research program into yeast from *Neurospora* in 1941. They had tried Winge's spore-to-spore mating method initially, but it was not working well for them. In 1942, for example, the Society of American Bacteriologists'

[6] Early yeast hybridization was performed, for example, at the Dai-Nippon Beer Company in Japan, where investigator Yukio Yamamoto referenced Winge's research at Carlsberg, described hybrids by their morphology, and discussed the potential impact of new strains for the brewing industry. Yamamoto began his investigations in the department of agriculture of Kyoto Imperial University. See Yukio Yamamoto, "Genetical Investigations on Saccharomycetes I. Segregations in Saccharomyces Saké Yabe," *The Botanical Magazine* 53, no. 634 (1939): 449; Yukio Yamamoto, "Varietal Hybrids in Japanese Saké Yeast," *Japanese Journal of Genetics* 15 (1939): 353-355; Yukio Yamamoto, "On Some New Yeast-Types Produced by Hybridization," *The Japanese Journal of Genetics* 16, no. 6 (1940): 302-304.

Journal of Bacteriology published a mixed review of work being done at its eastern Missouri branch in St. Louis. The report indicated that Carl Lindegren had successfully mated a stable and relatively stable form of *Saccharomyces* with support from Anheuser-Busch, one of a number of industrial laboratories of microbiology which supported the Society. Unfortunately, "[t]he hybrid proved to be exceptionally unstable, producing mutants in great abundance, with the general characteristics of the two parents as well as a large number of inferior types."[7]

Winge was identifying new yeast hybrids at this time on basis of their colony formations, but the Lindegrens, following Edward Tatum's lead, were interested in a greater range of phenotypes that could be defined biochemically. Rather than the spore-to-spore fusions that Winge had observed, they soon determined that mass mixtures of yeast haploid cultures could result in large numbers of hybrids, and they argued that these would be more useful for generalizing about a range of genetic characters. The biological complexity present in such mixtures was manageable once it was reduced through biochemical description.[8] According to Carl Lindegren:

> The economy that is achieved in describing living organisms by genetical terms is enormous, for with morphological characters that can only be designated descriptively, one cannot present a pedigree involving many hundreds of individuals unless some shorthand "all-or-none" designation can be discovered. If each culture differs from every other one it is not feasible to develop categories to fit them all… Descriptive characters are simply too difficult to handle. However, biochemical characters such as ability to ferment carbohydrates are easier...[9]

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[7] "Proceedings of Local Branches of the Society of American Bacteriology," *Journal of Bacteriology* 44, no. 5 (1942): 623; "Administration: Sustaining Members," *Journal of Bacteriology* 43, no. 5 (1942): 1.

[8] Science philosopher John Dupré has explored the opposing tendencies of reductionism and pluralism in science, in John Dupré, *The Disorder of Things: Metaphysical Foundations of the Disunity of Science* (Harvard University Press, 1995); John Dupré, "It Is Not Possible to Reduce Biological Explanations to Explanations in Chemistry and/or Physics," *Contemporary Debates in Philosophy of Biology* (2010): 32-47.

[9] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 20: 26-27.

Biochemical characters were economical because they were discrete and categorical (e.g., either able to ferment carbohydrates or not able), rather than continuous (e.g., the possibly infinite number of morphological permutations). Carl Lindegren described their use as a convenience in the development of "a pedigree involving many hundreds of individuals" which would be used to characterize the parental genotypes. That the mass mating method characterized parental genotypes by the distributed properties of a hybridized *culture* did not mean that these characters were also exhibited at the level of each individual progeny. In fact, he deemed his own mass mating method "hazardous" for commercial production because any single haploid cell selected might involve an "enormous degree of variability" once it began replicating.[10]

In the Lindegrens' laboratory, the mass mating of two yeast cultures had the benefit of allowing the original spores to be stored for later experiments since they had not been fused in the mating process.[11] The ability to then repeat "identical" crosses fulfilled the important ideal of experimental reproducibility by appearing to arrest the temporal dimension of developmental and evolutionary progression. With the original haploids on hand to generate more of "the same" pure cultures, scientists could iterate their experiments until they found the best combination of characters. The wartime press proclaimed mass mating a technological advance and sign of American progress: "The lowly yeast bud, that until just recently had been associated only with the making of beer and bread, may have a postwar future as important as the airplane's."[12] In a modern world it was possible that superior products would be bred to "enable overpopulated

[10] Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," 130.
[11] Lindegren and Lindegren, "Selecting, Inbreeding, Recombining, and Hybridizing Commercial Yeasts." See also Herschel Roman, "The Early Days of Yeast Genetics: A Personal Narrative," *Annu Rev Genet* 20 (1986): 4.
[12] "Now They Are Inter-Breeding Yeasts," *The Morning News*, November 22, 1943, 6.

nations to build a permanent defense against famine."[13] Still, the new method was not appreciated by everyone.

Winge saw the Lindegrens' mass mating technique as cheating. To him, the only "honest" mating technique was to observe individual spores under a microscope to ensure that each new pairing yielded an original product. Only this intentional hybridization technique could ensure that new yeasts occurred by a selection process that was, not natural, but scientific.

At stake between the two laboratories was the proper role of statistics in genetic practice. In the early 1940s, the "Modern Synthesis" was just beginning to make individual Mendelian patterns of inheritance statistically compatible with the Darwinian evolutionary changes predicted for populations. This methodological union was aided by extrapolation from small yeast sample sizes which "Student" had investigated with the biometrician Karl Pearson. The compromise struck by statistician Ronald Fisher had enabled inferences to be made from population-level outcomes such as the Lindegrens' mass mating experiments. Natural selection could be seen acting upon *populations* in the changes to allele frequencies which determined genetic variation.[14] Since haploid yeast was defined by unpaired alleles allowing direct observation of genotype, the variation observed by the Lindegrens after mass mating haploid cultures resulted, presumably, from many individual hybridizations relating to the parent spores.[15] This method was not satisfactory to Winge, who continued to argue against the

[13] "2 Yeast Sexes Found; Food Is Their Offspring," *Chicago Daily Tribune*, February 6, 1944.
[14] An "allele" was understood to be a variant form of a gene that was inherited from a single parent. By the 1930s, diploid yeast was described as having two alleles, one from each parent, co-located at each gene loci along the chromosomes.
[15] "Genetical analyses of the hybrid are made by picking and dissecting 4-spored asci at random… the tetrad analyses usually yield surprisingly regular results. This was supposed at first to be the result of statistical sampling; in the enormous population of cells, the chances that a given zygote had been derived from the two preponderant genotypes is presumably very great." In Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 27: 28-29.

imprecision of mass mating as late as 1950, and was still using his own spore-to-spore breeding method in 1960.[16] A classical Mendelian, he had little use for population statistics which assumed the relationship between individuals.

Sex and Species Differences

The Lindegrens were equally critical of Winge's method since it had failed to work for them. Using the industrial yeast species, *Saccharomyces cerevisiae*, the Lindegrens found that haploid spores frequently failed to hybridize with one another under the microscope, and they attributed this to the spores' sexual preferences which were known to exist in other fungi. The Lindegrens proposed that yeast had two different mating types, akin but not identical to male and female sexes, which they initially designated '+' and '-' in 1943.[17] Winge had explicitly ruled out this possibility in 1935, writing that, "It is not a question of + and - cells… nay, it is even hard to point out anything whatever that may conceivably elicit attraction between two conjugating haploid… cells…"[18] The Lindegrens argued that Winge's microscopic preparations had been held between the slide and cover-glass so tightly that they "may not have permitted

[16] In 1950, Winge's co-investigator Catherine Roberts characterized the spore-to-spore method as more precise than that of the Lindegrens': "for exact genetic studies this technique [Winge's] is by far the preferable one." In Catherine Roberts, "Methods in Yeast Genetics," in *Methods in Medical Research*, ed. Ralph W. Gerard (Chicago: Year Book Publishers, Inc., 1950), 43. See also Szybalski, "My Road to Øjvind Winge, the Father of Yeast Genetics," 1-6; Friis, "The Carlsberg Laboratory: Historical Retrospect and Personal Reminiscence," 449.

[17] Lindegren and Lindegren, "Selecting, Inbreeding, Recombining, and Hybridizing Commercial Yeasts," 406. These mating types were renamed **a** and **α** in 1945. See Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," 122. Joshua Lederberg identified sex in bacteria three years later than yeast, in 1946, at the University of Wisconsin. Lederberg shared the 1958 Nobel Prize with Edward Tatum (who had been his teacher) and George Beadle for their work on the mechanisms of bacterial genetic recombination.

[18] Winge, *On Haplophase and Diplophase in Some Saccharomycetes*, 107.

sufficient freedom of contact to make preferences in copulation obvious."[19] In contrast, the freedom and "preferences" permitted by their test tube mixtures brought + cells into contact with - cells for mass mating to yield new products.

The Lindegrens had calculated that there were only two yeast mating types by observation of a single four-spored ascus of *Saccharomyces cerevisiae*. Although there was no phenotypic indication of sex in the individual yeast cell, they diagnosed cultures for mating type in response to a pre-designated tester strain. They designated four-spored asci the "perfect" form in 1945, and the "standard" form in 1953, even though, they had observed, "asci containing fewer than 4 spores are usually more abundant."[20] When the four spores were grown into separate cultures for mass mating crosses they observed that two of the possible combinations failed to hybridize. These infertile pairings, they assumed, must have been of the like-mating types, '+' crossed with '+', and '-' crossed with '-'.[21] Carl Lindegren later gave a genetic justification for the mating type binary he had seen in yeast. Like-mating types did not mate by definition as a consequence of their "self-sterility genes" which limited the amount of inbreeding which could occur.[22] Lindegren found it important not to refer to mating type as sex, saying, "I prefer to define sex… only in terms of true male and female sex organs. When we use this

[19] Carl C. Lindegren and Gertrude Lindegren, "Segregation, Mutation, and Copulation in Saccharomyces Cerevisiae," *Annals of the Missouri Botanical Garden* 30, no. 4 (1943): 453.
[20] This had resulted, presumably, from the degeneration of one or more nuclei. In Carl C. Lindegren and Gertrude Lindegren, "Asci in Saccharomyces with More Than Four Spores," *Genetics* 38, no. 1 (1953): 74. The "perfect" form is described in Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," 131-134.
[21] Carl C. Lindegren and Gertrude Lindegren, "A New Method for Hybridizing Yeast," *Proceedings of the National Academy of Sciences of the United States of America* 29, no. 10 (1943): 308.
[22] Sarah Richardson has explored the history of sex as a binary in genetic research while tracing the influence of twentieth century cultural gender norms upon sex chromosome research, see S.S. Richardson, *Sex Itself: The Search for Male and Female in the Human Genome* (Chicago: University of Chicago Press, 2013).

definition, mating type, self-sterility alleles, and plus-minus factors take on their true significance. They are not essential to the sexual mechanism but are simply means of assuring cross-fertilization."[23] This nuance was more often than not left out of descriptions of yeast sexuality in both popular and scientific accounts not specifically investigating the phenomenon. Carl Lindegren himself gave a talk on "Sex in Yeast and Flavor in Beer" to the American Society of Brewing Chemists in Milwaukee in 1946.[24] Newspapers covering the mating type story played on the sexual innuendo of "Sex In A Cell" in headlines with a photo of the "man and wife" team, where "[s]mall, comely Mrs. Lindegren" was shown seated at the microscope with her husband presiding.[25]

Once exceptions were found in some strains' self-fertilization ("selfing" between haploids presumed to be of like-mating type), the Lindegrens maintained their mating type definition by stipulating that "legitimate" copulation would result in the regular production of viable four-spored asci. "Illegitimate" copulation could occur between like-mating types, but the offspring of these pairings, they anticipated, would be recognizable by their failure to multiply indefinitely and could then be excluded from analysis.[26] If like-mating type pairs were not

[23] Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," 125. Max Delbrück drew similar conclusions for his early mating theory of the phage which held that reproduction appeared contemporaneously with, but was not dependent upon, recombination. In Frank Stahl, "The Phage Mating Theory, with Lessons for Yeast Geneticists," *Genetics* 180, no. 1 (2008): 2; N. Visconti and M. Delbruck, "The Mechanism of Genetic Recombination in Phage," *Genetics* 38, no. 1 (1953): 5-33.
[24] Carl C. Lindegren, "Sex in Yeast and Flavor in Beer," *Am. Soc. Brewery Chemists* 11 (1946): 76-82; "Brewery Chemists' Meeting in Milwaukee," *Chemical & Engineering News Archive* 24, no. 10 (1946): 1379-1380.
[25] "Sex in a Cell ...But It's Yeast Cells," 3.
[26] "We define viability of ascospores in the same manner as Winge, namely, if (1) an ascospore fails to germinate or (2) grows to produce a small haploid colony of cells which is not capable of indefinitely continued growth in culture, the ascospore is considered nonviable." In Lindegren and Lindegren, "Selecting, Inbreeding, Recombining, and Hybridizing Commercial Yeasts," 410, 415, 418. Roberts did not accept Lindegren's characterization of the definition she used with

infertile, their offspring eventually would be. Yeast which might "inaccurately" be described as asexual, bisexual, or (later) transsexual, was to be, preferentially heterosexual.

Among the yeast strains that had been isolated by Hansen at Carlsberg many years earlier, Winge observed the reduced ability of some of his hybrids to return to budding in the diploid state. This was not a sign to him of illegitimate hybridization, however, but rather just the opposite: it was an indication that the experimental cross had been successful and a new species had been formed. Winge theorized that while same-species copulations yielded "variety hybrids" with normal vigor, the mating of two *distinct* species yielded "species hybrids," identifiable by their reduced fertility.[27] This distinction appeared to enable a rational approach to yeast taxonomy so that true species could be properly classified, and new species recognized. Reduced fertility in the yeasts was thus a contested sign at the start of the 1940s either of same-sex identity or species difference.

Lindegren, however, had the support of a new biological species concept then being proposed by U.S. evolutionary biologists. Winge's idea of yeast "species hybrids" would find no support in the Modern Synthesis since species were coming to be identified as reproductively-isolated gene pools.[28]

Winge, later writing, "…it is not true that self-diploidized single spore cultures usually sporulate poorly and produce spores with poor germination; we have in our work generally found the opposite to be the case." Catherine Roberts, "The Inheritance of Enzymatic Characters in Yeasts," *Friesia* 5 (1956): 162.

[27] Winge's definition of "reduced fertility" was more conservative than the Lindegrens' in that 'fertility' indicated budding in the diploid state and was reduced even by the continued sporulation of a haploid. See Winge and Laustsen, "On 14 New Yeast Types, Produced by Hybridization," 345.

[28] Evolutionary biologists saw speciation as part of a larger problem to be worked out at this time with Mendelian geneticists, and their ideas on the species concept further supported the Modern Synthesis. See Theodosius Dobzhansky, *Genetics and the Origin of Species* (New York: Columbia University Press, 1937); Ernst Mayr, *Systematics and the Origin of Species* (New York: Columbia University Press, 1942).

Early Material Standards for Gene Mapping

A program of yeast breeding that could map individual chromosomes in the style of the Morgan school required the possibility of genetic linkage. Morgan had identified sex-linked traits related to X and Y chromosomes (i.e. as in *Drosophila*, eye color and the "mating type" of male flies). While yeast had no "sex chromosomes," yeast mating type could be linked to the centromere and to other genes by the phenotypic patterns displayed in the tetrad (extrapolating, for example, from two spores exhibiting and two spores lacking a given characteristic of interest, or a "2:2 ratio"). By comparing observed patterns to their expected frequencies, the relative distances between genes could be mapped along the chromosomes which comprised the distinct "linkage groups," but this could only be done in the haploid organism showing stable mating types.

Among the Carlsberg brewing yeasts, Winge's "illegitimate" diploids had masked binary yeast sexuality, it was suggested, because with paired chromosomes these yeasts contained both "mating type alleles."[29] The genetic stability which had made diploid strains valuable to the Carlsberg brewers now made them unserviceable to a gene mapping program.[30] Although Winge's strains formed abundant spores for genetic analysis, chromosomal mapping was neither a possibility nor a priority. It was both things to the Lindegrens, however. As former contributors

[29] Winge's stable diploid sporulated into haploids where mating type was potentially observable, but these haploids quickly returned to the diploid state. In Winge and Laustsen, "On Two Types of Spore Germination, and on Genetic Segregations in *Saccharomyces*: Demonstrated through Single-Spore Cultures," 99-117.

[30] "[S]train stability… may have been selected by the brewers." In Mortimer, Technical Documents, 1950-1999, (November 13, 1997), Box 5, Folder 16, Robert K. Mortimer Collection (ARO-5425). Brewers likely selected for traits contributing to a low mutation rate. See Robert K. Mortimer, "Evolution and Variation of the Yeast (Saccharomyces) Genome," *Genome Research* 10, no. 4 (2000): 403. See also John F.T. Spencer and Dorothy M. Spencer, *Yeast Technology* (Springer-Verlag, 1990), 31.

to the Morgan laboratory, the Lindegrens wanted to locate genes on the yeast chromosomes. As it turned out, one lucky break enabled them to do so. They obtained stable haploid mating type strains from the spontaneous division of a diploid culture in their laboratory.

While training under Morgan, Carl Lindegren had used stable haploid mating type strains of the bread mold *Neurospora* to begin a gene mapping program. His work had aided George Beadle and Edward Tatum with their one-gene-one-enzyme hypothesis in 1941, in the same year that the Lindegrens began studying the yeasts. Tatum, too, explored yeast genetics hoping to begin a gene mapping program like *Neurospora*. In 1945, he moved to Yale as an assistant professor of botany (later professor of microbiology) and began to mentor student Joshua Lederberg in microbial genetics. Tatum and Lederberg began inducing mutations in the yeasts. In April of 1946, Lederberg wrote to Lynferd Wickerham, a zymologist in the Northern Regional Research Laboratory of the U.S. Department of Agriculture at Peoria, Illinois, to ask if he might recommend a yeast with distinct mating types. “I suppose that question has been put to you before,” Lederberg wrote.[31] Wickerham had no suggestion for them, and Lederberg moved forward instead that spring with work sexual conjugation in the bacteria *Escherichia coli* (*E. coli*).[32] He was later awarded one half of the 1958 Nobel Prize in Physiology or Medicine for these efforts with Beadle and Tatum sharing the other half for their work on biochemical genetics.[33]

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[31] Joshua Lederberg, Letter to Lynferd J. Wickerham, (April 9, 1946), Box 6, Folder 79, Profiles in Science: The Joshua Lederberg Papers, National Library of Medicine, Bethesda, MD.
[32] Lynferd J. Wickerham, Letter to Joshua Lederberg, (April 29, 1946), Box 6, Folder 79, BBAMUS, Profiles in Science: The Joshua Lederberg Papers, National Library of Medicine, Bethesda, MD.
[33] Their early experiments were reported in Joshua Lederberg and E. L. Tatum, "Gene Recombination in Escherichia Coli," *Nature* 158, no. 4016 (1946): 558; Joshua Lederberg, "Joshua Lederberg - Biographical," in *Nobel Lectures, Physiology or Medicine 1942-1962* (Amsterdam: Elsevier Publishing Company, 1964).

The Lindegrens, meanwhile, had been sent a diploid culture collected by the microbiologist Emil Mrak who was then studying the yeasts responsible for food spoilage at the University of California in Berkeley. In 1938, Mrak was involved in a project to sample trees in 10 different California districts. He isolated 115 yeasts as part of this study, including a sample of the baker's yeast *Saccharomyces cerevisiae*, which was notably common in an orchard of rotting figs in Merced, California, but likely not responsible for the fruit's spoilage. Mrak categorized the species he collected by their ability to sporulate and ferment different sugars, but otherwise he had found the current yeast taxonomy "meager and useless" for identification purposes.[34] The *Saccharomyces cerevisiae* sample was a diploid which seemed unusual for its ability to produce an abundance of viable ascospores. It was for this reason that he provided it as fertile material to the Lindegren laboratory in the early 1940s as they began to set up their yeast breeding program.

The Lindegrens reported that Mrak's culture was "among the most vigorous" they had ever seen.[35] Although its spore production was matched by the "D" strain they had inbred from four generations of Fleischmann's commercial bakers' yeast, they later reported that Mrak's yeast underwent a spontaneous division in their laboratory into two stable haploid mating types. These quickly became the most useful strains among their experimental stock and served as

[34] The microbiologist Herman Phaff would not arrive on the Berkeley campus with his knowledge of the Delft yeast taxonomy until the spring of 1939. Emil M. Mrak et al., "Yeasts Occurring in Souring Figs," *Journal of Bacteriology* 44, no. 4 (1942): 441; M. W. Miller and H. J. Phaff, "Successive Microbial Populations in Calimyrna Figs," *Applied Microbiology* 10, no. 5 (1962): 394-400.

[35] Carl C. Lindegren, "Chromosome Maps of Saccharomyces," *HRD2 Hereditas* 35, no. S1 (1949): 339; Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 18: 11.

tester strains against which to identify mating type in other cultures. They also allowed the possibility of gene mapping work as it was being conducted in other organisms.[36]

Since the stable haploid variants were deemed superior for use in gene mapping, the use of two mating type strains quickly became integrated into American yeast genetic practice in laboratories influenced by the Morgan school.[37] The Lindegrens began to share the strains with other U.S. academic and commercial laboratories, including, by 1949, with colleagues at Yale. There, Tatum and another doctoral student Sheldon Reaume exposed the Lindegrens' strains to mustard gas treatment and found a mutant with pink colonies.[38] Seymour Pomper, too, who was on a Standard Brands fellowship in microbiology at Yale used the mating type strains in his 1949 doctoral research.[39] Over the next few decades, these unusual yeasts would become a small legacy of mainstream legitimacy for the Lindegrens, whose other research contributions were increasingly being challenged as illegitimate.

"Eliminating Natural Selection"

[36] "…unless a heterothallic condition exists, it is rather difficult to establish breeding programs and follow the segregations of genes in an organism." In Pomper, "Recent Developments in Yeast Genetics," 7.

[37] There were multiple appraisals of the haploid strains' utility by mid-century including from Carlsberg laboratory. See Roberts, "The Inheritance of Enzymatic Characters in Yeasts," 162. A more recent assessment is provided in George Sprague Jr., "Differentiation: Mating and Filamentation," in *Landmark Papers in Yeast Biology*, ed. P. Linder, D. Shore, and M.N. Hall (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 142.

[38] They reported that the mutant was adenine-dependent. See S. E. Reaume and E. L. Tatum, "Spontaneous and Nitrogen Mustard-Induced Nutritional Deficiencies in Saccharomyces Cerevisiae," *Arch Biochem* 22, no. 3 (1949): 331-338.

[39] Pomper completed his Ph.D. with support from Standard Brands, then the parent company of Fleischmann's Yeast. See Pomper, "The Biochemical Genetics of Yeast." See also the companion article to the dissertation, which references Lindegren's mating type strains. Seymour Pomper and P. R. Burkholder, "Studies on the Biochemical Genetics of Yeast," *Proceedings of the National Academy of Sciences of the United States of America* 35, no. 8 (1949): 457.

The use of different genetic material and methods created a rift between the early yeast breeding programs of Winge and the Lindegrens. But it was their conceptual divergence that began to catch the attention of geneticists working in other organisms. The Lindegrens had followed the Morgan school in terms of linkage studies, biochemical analyses, and the move into population statistics, but their yeast work soon broke from these mainstream practices in several critical ways.[40] One of their first investigations was designed for the purpose of "eliminating natural selection," a task that some yeasts performed better than others.[41]

When Carl Lindegren and graduate student Sol Spiegelman first observed the changing rate of fermentation in *Saccharomyces cerevisiae* in the mid-1940s, they raised questions about the genetic basis of yeast adaptation.[42] The yeast was able to ferment a new sugar after a considerable, but variable, amount of time. If cell growth could be detected, they theorized, yeast "adaptation" was a genetic phenomenon exhibited at the population level because they would be observing hereditable change as the result of random variation and selection in mutant offspring. If no new growth was involved, however, it was a physiological phenomenon because the original cells were changing in response to the new set of environmental conditions.

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[40] See Mogens Westergaard, "Øjvind Winge. 1886-1964," *Biographical Memoirs of Fellows of the Royal Society* (1964). Jan Sapp has treated the Lindegrens' work on cytoplasmic inheritance in the context of the larger disciplinary controversy. See Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, 102, 161.

[41] This phrase was used in a later review of their work by Roberts. Although she was explaining the investigators' choice of yeast in the experimental design, Roberts did not hide her disapproval in this article of Carl Lindegren's claims of non-Mendelian patterns of inheritance. In Roberts, "The Inheritance of Enzymatic Characters in Yeasts," 165.

[42] The adaptation they were investigating was "not concerned with adaptation to galactose utilization *per se*, but with the development of a particular enzyme system leading to a fermentative oxidation of the sugar." In Sol Spiegelman, Carl C. Lindegren, and Loyd Hedgecock, "Mechanism of Enzymatic Adaptation in Genetically Controlled Yeast Populations," *Proceedings of the National Academy of Sciences of the United States of America* 30, no. 1 (1944): 22.

Prior investigations had shown heritable adaptation in the yeasts. In 1912, for example, researchers at the California Agricultural Experiment Station in Berkeley sought to test "the alleged possibility of training a yeast" to resist a series of chemical exposures over time. What they encountered was the reverse effect; the wine yeasts negatively adapted. The yeasts became less active and developed a persistently slow rate of fermentation.[43] In 1920, the French botanist Alexandre Guilliermond recalled Louis Pasteur's observations on yeast growth in the presence or absence of oxygen and concluded that the yeasts which took oxygen from sugar rather than the air were adapting to resist suffocation. Fermentation was respiration, a property the yeasts possessed in common with other organisms, Guilliermond noted. They were rapidly flexible when it came to switching to use of the sugar.[44]

Different strains showed different adaptation outcomes, Carl Lindegren and Sol Spiegelman noted, in terms of whether the change occurred in the presence or absence of cell growth. This implied that while some yeasts change as a result of mutation and natural selection, others individually acclimated to their environment. At stake was the belief that natural selection was the only mechanism of evolutionary change. Their evidence suggested that haploid yeasts could not change without cell division, while diploid yeasts still could. Diploids adapted in the absence of growth, suggesting a sensitivity and responsiveness of the individual cell to its environment for which there was yet no explanation.

Although the Lindegrens had determined that diploids with poor viability were "illegitimate" for use in experimental breeding analyses and useless for gene mapping, diploid yeasts became advantageous in adaptive fermentation experiments because their slowed division "eliminated," or nearly eliminated, the possibility of natural selection acting upon the next

[43] Bioletti and Cruess, *Enological Investigations*, v. 230, 58-63.
[44] Guilliermond, *The Yeasts*, 100.

generation.[45] It is little surprise, then, that Spiegelman and Carl Lindegren thought the adaptive fermentation could be "studied *safely* only in [the] genetically stable and homogenous population" of yeast diploids.[46] These yeasts were already "artificial" since they had come from the breweries where their evolution had been subject to the brewers' selection, not "nature's." If the diploids now failed to produce spores or engage in "legitimate" heterosexual yeast behaviors that was all the more reason to suspect "natural" selection was not in operation.

As early as 1900, the French microbiologist Frédéric Dienert had reported in his doctoral thesis the phenomenon of yeast "acclimation" allowing fermentation of a new sugar. Dienert observed that the duration of this change varied with the yeast. Although there were specific patterns of adaptation, the phenomena were thought to be shared by all organisms. Dienert had hypothesized significant changes in the interior of the yeast cell that were similar to those seen in the mammalian immune response, for example.[47] The Delft microbiologist Albert Jan Kluyver had also examined the adaptation of yeast to ferment a new sugar in a chapter of his 1914 doctoral thesis. Kluyver experimented with temperature to inhibit growth but still permit fermentation in *Saccharomyces cerevisiae* but he produced inconclusive results.[48] More than two

[45] Spiegelman did not use the Lindegrens' term "illegitimate" in this article since he had observed the pair-wise copulation of two spores in the tetrad to form the diploid and presumed them to be opposite mating types. However, the conditions of his experiment produced the Lindegrens' definition of "illegitimacy" since failure of a diploid to multiply indefinitely was supposed to define this state.

[46] In Spiegelman, Lindegren, and Hedgecock, "Mechanism of Enzymatic Adaptation in Genetically Controlled Yeast Populations," 23. Italics added.

[47] Originally, "La fermentation du galactose n'est possible que lorsque la levure s'est acclimatée à ce sucre. La durée de l'acclimatation varie avec les levures… Il doit en être de même des toxines agissant sur les leucocytes." In M. Frédéric Diénert, "Sur La Fermentation Du Galactose Et Sur L'accoutumance Des Levures À Ce Sucre," *Annales de L'Institut Pasteur (Journal de Microbiologie)*, no. 14 (1900): 187.

[48] Kluyver concluded, "so it seems to me that one cannot assign value to the explanation of this phenomenon as adaptation." Originally, "[Z]oodat het mij voorkomt, dat men aan dit verschijnsel geen waarde voor de verklaring der aanpassing mag toekennen." In Albert J. Kluyver,

decades later, the Cambridge biochemist Marjory Stephenson and graduate student John Yudkin reopened the matter to show adaptive fermentation in the absence of cell growth. They concluded that "adaptation occurs, not as a result of natural selection, but as a response of the cell to its chemical environment."[49] The change was physiological since it seemed to occur for the entire culture.

After confirming this absence of cell growth seen by Stephenson and Yudkin using a diploid yeast and noting the other inconclusive evidence, the Lindegrens and Spiegelman found that, "the contradiction noted between the results and those of earlier workers is only an apparent one and is probably due to the differences in the genetic background and phenotypic constitution of the strains employed."[50] Adaptive enzymes were linked to genetic specificity. Lindegren and Spiegelman wanted to understand how. They began a series of experiments on controlled adaptation in the yeasts which had the potential to recommend many new raw materials in the fermentation process.[51]

Carl Lindegren's "New Gene Theory"

The Lindegrens and Spiegelman took up the question of yeast adaptation in university laboratories with funding from Anheuser-Busch, Inc. As a consequence, their research stayed

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"Biochemische Suikerbepalingen (Proefschrift)" (PhD diss., Technische Hoogeschool Te Delft, 1914), 110. See also Kluyver and Kamp, *Albert Jan Kluyver: His Life and Work*, 76.

[49] Marjory Stephenson and John Yudkin, "Galactozymase Considered as an Adaptive Enzyme," *Biochemical Journal* 30, no. 3 (1936): 514.

[50] Sol Spiegelman and Carl C. Lindegren, "A Comparison of the Kinetics of Enzymatic Adaptation in Genetically Homogeneous and Heterogeneous Populations of Yeast," *Annals of the Missouri Botanical Garden* 31, no. 2 (1944): 231.

[51] Kluyver had noted the "sometimes divergent demands of pure science and technology" which needed to be satisfied simultaneously by such projects. Originally, "aan de soms zoo uiteenloopende eischen der zuivere wetenschap en die der techniek." In Kluyver, "Biochemische Suikerbepalingen (Proefschrift)," iv.

focused on industrial yeasts. They began by hybridizing lager and ale brewing yeasts that differed in their ability to ferment whole grain sugars. By performing the tetrad analysis of offspring spores, they found that different alleles could produce the same phenotype. This was an apparent contradiction to Mendelian segregation and the one-gene-one-enzyme hypothesis proposed by George Beadle and Edward Tatum in *Neurospora* in 1941.[52] The Lindegrens and Spiegelman concluded that two dominant genes controlled the rate of fermentation.[53] This surprised them because it meant that even "cosmopolitan" industrial species like *Saccharomyces cerevisiae* could carry multiple recessive alleles.[54]

Multiple gene control challenged the Mendelian logic of genetic analysis, and, after observing a large number of these statistically irregular tetrads, Carl Lindegren soon abandoned this interpretation as "too elaborate to be justified."[55] He began to theorize about a new genetic mechanism at work - the *cytogene*, which was responsible for adaptive fermentation. "The chromosomes have often been called the "bearers" of the heredity factors and the terms "gene"

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[52] Beadle and Tatum, "Genetic Control of Biochemical Reactions in Neurospora."

[53] Multiple gene control is proposed in Carl C. Lindegren, Sol Spiegelman, and Gertrude Lindegren, "Mendelian Inheritance of Adaptive Enzymes," *Proceedings of the National Academy of Sciences of the United States of America* 30, no. 11 (1944): 352. This contradicted the one-gene-one-enzyme hypothesis because it held that the gene-enzyme relationship was not specific. "The original gene-product which becomes specific by contact with the melibiose molecule might presumably become differently specific on contact with some other molecule. Genes are "enzyme factories," but each gene may not necessarily be restricted to the production of a single enzyme." In Carl C. Lindegren, "Mendelian and Cytoplasmic Inheritance in Yeasts," *Annals of the Missouri Botanical Garden* 32, no. 2 (1945): 121-122.

[54] Lindegren, "Mendelian and Cytoplasmic Inheritance in Yeasts," 119. The simple biochemical phenotypes exhibited by microorganisms created a tendency to explain genetic traits in terms of single genes, rather than complex interactions, explained UCSF biochemist William Rutter, looking back on the early postwar period from his vantage point in the early 1990s. See William J. Rutter, interview by Sally Smith Hughes, 1992, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

[55] Carl Lindegren quoted by Catherine Roberts at the 1946 Cold Spring Harbor Symposium "in response to a direct question." Roberts, "The Inheritance of Enzymatic Characters in Yeasts," 167.

and “locus” have been considered synonymous. This terminology was prophetic of the real nature of the hereditary mechanism,” he wrote, for it was the genes which “stored” the cytogenes until they were ready for use under the right environmental conditions.[56] According to this theory, cytogenes moved into the cell cytoplasm where contact with a new sugar could trigger their fermentative action. If these environmental conditions remained constant, cytogenes could self-perpetuate and be passed to the next generation. Heredity was thus a “duality” which had both chromosomal and cytoplasmic components.[57] The gene was still the locus of control but cytogenes could operate “in the absence of the gene.”[58]

When Carl Lindegren presented this “new gene theory” at the 1946 Cold Spring Harbor Symposium on Quantitative Biology, it sounded a lot to his colleagues like a defense for the inheritance of acquired characteristics.[59] Carl Lindegren did not think he was making a neo-Lamarckian claim about the ability of the environment to provoke heritable change, however,

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[56] Carl C. Lindegren, "A New Gene Theory and an Explanation of the Phenomenon of Dominance to Mendelian Segregation of the Cytogene," *Proceedings of the National Academy of Sciences of the United States of America* 32, no. 3 (1946): 68.

[57] Winge and Laustsen had also suggested the possibility of cytoplasmic genetic elements in yeast chondriosomes (later, mitochondria) to account for non-Mendelian patterns of yeast fertility (“inbreeding degeneration”). See Øjvind Winge and Otto Laustsen, "On a Cytoplasmatic Effect of Inbreeding in Homozygous Yeast," *Comptes Rendus des Travaux du Laboratoire Carlsberg. Série physiologique* 23 (1940). Although this paper has been cited as a forerunner of mitochondrial genetics, according to later practitioners, Winge and Laustsen’s early findings “did not have a major impact on the development of th[at] field.” In S.W. Liebman and F. Sherman “Cytoplasmic Inheritance” in P. Linder, D. Shore, and M.N. Hall, *Landmark Papers in Yeast Biology* (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 14.

[58] See Lindegren, "Yeast Genetics: Life Cycles, Cytology, Hybridization, Vitamin Synthesis, and Adaptive Enzymes," 166; Sol Spiegelman, Carl C. Lindegren, and Gertrude Lindegren, "Maintenance and Increase of a Genetic Character by a Substrate-Cytoplasmic Interaction in the Absence of the Specific Gene," *Proceedings of the National Academy of Sciences of the United States of America* 31, no. 3 (1945): 102; Carl C. Lindegren and Gertrude Lindegren, "The Cytogene Theory," *Cold Spring Harbor Symposia on Quantitative Biology* 11 (1946): 115-129.

[59] The annual meeting at Cold Spring Harbor brought the world’s leading quantitative biologists together on New York’s Long Island.

because cytogenes still originated under genetic control. He believed that he had observed in yeast an additional layer of genetic complexity which others had missed.[60]

One of the main reasons Carl Lindegren claimed to be studying the yeasts was to look specifically at those aspects which seemed novel. He claimed that the point was to understand the nuances of the organism for only in this way could yeast be adapted to useful purposes. This contrasted with the perspective, argued by his contemporaries, that the value of studying yeast genetics was limited to "frequently occurring examples of generalizable phenomena."[61] In the late 1940s, Carl Lindegren claimed:

> Geneticists frequently speak of genes as if the fall into two natural categories: "good" and "bad." A "good" gene is easy to diagnose (especially in combination with others), is relatively unaffected by environment, does not diminish vigor to an unusual extent, and usually gives regular ratios [the distribution of phenotypes observed among offspring]... Classical Mendelian genetics is based on the analysis of data involving… combinations of "good" genes... At least part of the difficulties involved in transferring classical genetics to useful purposes has arisen from the fact that what plant and animal breeders consider their "best" organisms are what a classical geneticists would call "poor" genetical material.[62]

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[60] In 1948, Carl Lindegren maintained that "the current views concerning the stability of the gene and the regular segregation of alleles are in need of revision." The gene could be readily affected by the environment, and this effect was then part of the genetic control of heredity. Non-genetic influences were practically non-existent. In Lindegren, *The Yeast Cell: Its Genetics and Cytology*, ix. In the 1920s, the work of Victor Jollos was similarly taken to defend neo-Lamarckian claims about the inheritance of acquired characteristics, but Jollos raised questions about cytoplasmic inheritance while defending the genetic stability. In Christina Brandt, "Clones, Pure Lines, and Heredity: The Work of Victor Jollos," in *A Cultural History of Heredity IV: Heredity in the Century of the Gene*, ed. Max Planck Institut für Wissenschaftsgeschichte (Berlin: Max Planck Gesellschaft, 2008), 146.

[61] Direct response of Boris Ephrussi to a question from Carl Lindegren following Ephrussi's talk at an international symposium in 1955. Carl Lindegren asked if his own work did not support gene mutation as a nonrandom event for certain cases of yeast fermentation. Ephrussi thought the example too narrow. See Boris Ephrussi, "Enzymes in Cellular Differentiation" (paper presented at the Henry Ford Hospital International Symposium on Enzymes: Units of Biological Structure and Function, Detroit, Michigan, November 1-3, 1955), 48.

[62] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 20: 27-28. Despite Carl Lindegren's protests, "good" and "bad" genes continued to characterize genetic practice. A representative of the English Distillers Company declared the task of hybridization in industry "immensely more difficult" than Winge's breeding experiments, given the need to begin with

Carl Lindegren wanted to use the latest statistical, biochemical, and genetic approaches in his practices, but he did not want to routinize yeast behavior for the sake of theory-building.[63] He wanted control over industrial organisms.

The following year, Carl Lindegren called for more critical study of the environment upon yeast behavior. He and research assistant Caroline Raut insisted that different synthetic media of the laboratory in which yeast was grown "may prove very useful for genetical diagnosis but may not give reliable information concerning the synthetic activity of the organism under normal conditions."[64] "Normal" nutritional behaviors governing yeasts' use of the vitamins were the Lindegrens' primary concern, and these were *affected* but not controlled by genes. They found that yeasts would eventually grow on any medium, if left long enough.[65] Their study in a variety of synthetic media produced a dynamic picture of vitamin synthesis and cell growth since yeast appeared to have no *absolute* vitamin deficiencies.[66]

In 1947, the American Cancer Society reported another of Carl Lindegren's findings of asexual but not sexual transmission of mutations from yeast parent cells to their offspring. The

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suitable breeding stocks. "A good deal of attention is at present being devoted, therefore to the task of facilitating the hybridization of 'difficult' yeasts," he noted in 1955. In Fowell, "The Hybridization of Yeasts," 150.

[63] The Lindegrens' laboratory thus provides an exception to Rowland Davis' claim that the "universality of genetic mechanisms became an article of faith" after 1940, resulting in the use of "specific stocks, intraspecific crosses and highly controlled environments" to study individual species. This approach, according to Davis, characterized the "strongest" genetic programs at that time. Rowland H Davis, "The Age of Model Organisms," *Nature Reviews Genetics* 5, no. 1 (2004): 69.

[64] Carl C. Lindegren and Caroline Raut, "The Effect of the Medium on Apparent Vitamin-Synthesizing Deficiencies of Microorganisms," *Annals of the Missouri Botanical Garden* 34, no. 2 (1947): 75. At Washington University, Carl Lindegren had a staff of five research assistants in 1947, including Gertrude Lindegren and Caroline Raut. *Missouri Botanical Garden Bulletin*, vol. XXXV (St. Louis, Missouri: Board of Trustees, 1947), 19.

[65] Carl C. Lindegren and Gertrude Lindegren, "Mendelian Inheritance of Genes Affecting Vitamin-Synthesizing Ability in Saccharomyces," *Annals of the Missouri Botanical Garden* 34, no. 2 (1947): 95.

[66] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 21: 21.

evidence seemed to explain the development of human cancer as the degradation of an individual's genes over time when recombination did not occur. The Society explained that in asexual cells "some cellular by-product may rob a gene of one of its essential components producing a "depletion" mutation."[67] The Lindegrens said they had observed the "running out" of a pink character in asexually reproducing yeasts. "Continuous production of pink exhausts the supply," they hypothesized, but fortunately, this could be restored by crossing to any normal stock.[68] The Society reported that Carl Lindegren was optimistic that chemical agents might be found to repair partially degraded genes and provide cures for cancer.[69]

Fundamental and Applied Research

These studies did little to win Carl Lindegren favor with prominent geneticists of the period for they promoted a picture of an instable and environmentally-modifiable yeast gene with little relevance to generalizable theory. His research did, however, garner steady and consistent extramural funding from varied private, professional and public sources including Anheuser-Busch, Inc., the American Cancer Society, the U.S. Public Health Service, and the American Philosophical Society.[70] In the late 1940s and 1950s, Carl Lindegren's research

[67] *Annual Report*, ed. American Cancer Society (Northwestern University, 1947), 15, 74.
[68] Carl C. Lindegren and Gertrude Lindegren, "Depletion Mutation in Saccharomyces," *Proceedings of the National Academy of Sciences of the United States of America* 33, no. 11 (1947): 318.
[69] Carl C. Lindegren and Caroline Raut, "A Direct Relationship between Pantothenate Concentration and the Time Required to Induce the Production of Pantothenate-Synthesizing "Mutants" in Yeast," *Annals of the Missouri Botanical Garden* 34, no. 2 (1947): 93.
[70] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, vii. Carl Lindegren's 1966 book, *The Cold War in Biology* is dedicated to the late Mr. James Diego Veron of Anheuser-Busch, Inc., "who assumed the responsibility of sponsoring yeast genetics during a most crucial period." See Carl C. Lindegren, *The Cold War in Biology* (Planarian Press, 1966). The variety of these early funding sources is remarkable in contrast to the funding picture in recent years. Today, basic

support was exceptional among his academic peers. On New Year's Day in 1948, when he and Gertrude Lindegren moved to Southern Illinois University in Carbondale with equipment on loan from Anheuser-Busch, they were the first to bring grant funding and to have a campus unit dedicated solely to research at the university.[71] By the time of his retirement in 1964, Carl Lindegren had received a total of $174,486 from the American Cancer Society, he had obtained eight consecutive years of funding from the Damon Runyon Cancer Fund totaling $77,700, and he supported four graduate students on a National Institutes of Health (NIH) training grant.[72] The university later estimated that with other federal and industry sources the Lindegrens had obtained more than $1 million in research grants for their research on yeast, making them Southern Illinois University "notables."[73]

Carl Lindegren was greatly valued by his institution and was the highest paid professor on the Carbondale campus in 1948. He was director of biology, and later microbiology, beginning at a twelve-month salary of $6,720.[74] Stories of Carl Lindegren's research awards made the university newspaper, which regularly boasted about the comings and goings of the

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research in yeast is sponsored almost entirely by the National Institute of General Medical Sciences (NIGMS). David Morgan, Conversation with the Author, April 28, 2015.

[71] "The first formal research conducted at SIU began in 1948 with [the] appointment of internationally known geneticist Carl C. Lindegren as a research professor of biological science. Today, one of the University's buildings, Lindegren Hall, stands as a memorial to the scientist who first brought in research grants." See "Southern Illinois University Hall of Chancellors: President Chester F. Lay, 1945-1948," accessed May 29, 2015, http://chancellor.siu.edu/hall-of-chancellors/lay; Eli G. Lentz, *Seventy-Five Years in Retrospect, Southern Illinois University, 1874-1949* (Carbondale, Illinois: University Editorial Board, Southern Illinois University, 1955), 110.

[72] Daily Egyptian Staff, "Lindegren's Research Boosted by $66,216," *Daily Egyptian*, June 5, 1964, 5.

[73] "SIU Notables," *Southern Illinoisan*, August 21, 1987, 49.

[74] Gertrude Lindegren was a faculty assistant starting at $3000 per year. In Frank G. Thompson and Vernon L. Nickell, *Proceedings of the Teachers College Board (Formerly Normal School Board)* (State of Illinois, 1947), 157, 192. This gendered difference in position and income related to their credentials. While Gertrude had contributed equally to their research program since Carl's student days at Caltech in *Neurospora*, only Carl received the Ph.D.

university's "international authority." In September of 1949, for example, after explaining that yeast cytogenes had been found to account for non-Mendelian patterns of heredity, the paper ran the impressive claim that: "Lindegren, who has pioneered in studying genetics by means of the yeast cell, after having successfully discarded the fruit fly and *Neurospora* as subjects, has reached his new theory after some eight years research."[75] Although Gertrude Lindegren had done the bulk of experimental manipulations during this time, Carl Lindegren was recognized as the leading expert on yeast genetics within U.S. borders. Scholars from Bombay to Jerusalem came to train and publish with him at Southern Illinois University in the early postwar years.[76]

The Lindegrens also enjoyed a very positive reputation with the local Carbondale press. Gertrude Lindegren was profiled by *The Southern Illinoisan* in February of 1951. With quiet mannerisms and a modulated voice, she was described as the active, patient, and personable wife and co-worker of a "pioneer." The Lindegrens lived across the street from Southern Illinois University, where Mrs. Lindegren did all the cooking. They owned a farm just outside of Carbondale where she helped him raise cows. The article printed Gertrude Lindegren's opinion that yeast would be the "food of the future." It was already acting as a cheap, nourishing source of vitamins and proteins in India, Israel and China, where Anheuser-Busch had been sending large quantities as a food source.[77]

Along with their industrial sponsorship, cancer research funding was an important source of support for the Lindegrens' laboratory. The study of yeast for the purpose of elucidating a cellular mechanism implicated in the development of human cancers was in many respects not

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[75] Egyptian Staff, "Lindegren Expounds New Genetic Theory," *The Egyptian*, September 15, 1949, 2. Italics added.
[76] When his lab had been at Washington University in 1947, Lindegren's foreign visitors came from Copenhagen, Stockholm, Paris, and London. In *Missouri Botanical Garden Bulletin*, XXXV, 19-20.
[77] Bradford, "Microbiologist's Wife: Scientist and Homemaker," 5.

unique to the Lindegrens since this possibility had been of interest at least since the late nineteenth century with the rise of germ theory. Pathologists culturing certain malignant tumors had then revealed the presence of living yeasts and suspected them as a cause of human cancers. By 1920, however, the French botanist Alexandre Guilliermond was cautioning that these microbes may have been present merely as adaptive opportunists which "develop simply because they find the organism weak and [find] in the neoplastic tissue a favorable environment." The yeasts' chemical 'ferment' was not as intoxicating as once presumed because most cancer deaths could not be attributed to the action of a secreted toxin.[78] Moreover, cancer deaths were much more common among people over age 40, yet germs infected people of all ages.[79] With greater interest in specific enzymes, connections had been made between organisms on the basis of shared biochemical properties like bios, growth factors, and the vitamins to rule out sources for their differences. By 1932, Kluyver could describe for members of the Cancer Research Laboratories of the University of Pennsylvania School of Medicine the potential utility of unicellular microorganisms to elucidate the metabolism of cancer cells. He proposed that all living organisms shared a metabolic unity and he expressed his hope that, "conversion of a normal tissue cell into a cancer cell [might] ultimately depend on quantitative change in property of one single catalytic agent which determines metabolism."[80] Perhaps this single catalyst could be identified within the microbes.

In the early 1950s, Southern Illinois University was awarded a $10,800 grant from the U.S. Atomic Energy Commission (AEC) to support the Lindegrens' yeast research program in Carbondale. In the immediate aftermath of the Second World War, the possibility of mutator

[78] Guilliermond, *The Yeasts*, 122.
[79] "The Cancer Germ Theory," *Science* 62, no. 1600 (1925): x.
[80] Albert J. Kluyver, "Microbial Metabolism and Its Bearing on the Cancer Problem," *Science* 76, no. 1980 (1932): 527-529.

genes – and mutagenesis – had captured the scientific imagination with fear over the biological consequences of atomic fallout.[81] Although they expected yeast would "help solve the problems of food and nutrition after an atomic bombing," the Lindegrens maintained that their primary interest was always with yeast fundamentals and not with the potential of commercial or medical applications.[82] Their actions suggested otherwise, and they certainly led their funders to believe that yeast research might yield these applications.

The significance of yeast "fundamentals" was not greatly drawn out in the 1940s and 1950s. Only with time would investigators come to assert the representativeness of hereditary mechanisms in the yeasts to human biology and to claim the organism's particular utility as a molecular model.[83] Carl Lindegren did not make such justifications in 1950, nor, indeed, even in the 1960s, but instead found yeast's status as a "living cell" to be reason enough for its applicability to cancer research. In 1950, he told a local reporter that he had disproved a theory then under intensive study by the nation's cancer investigators. By showing that the "cell" did not change its nucleic acid content as it adapted to the use of new sugars, he claimed to have ruled out one theory about cancer's origins.[84] At the start of the 1960s, Lindegren told *Popular Mechanics* that he studied yeast a matter of convenience. The organism's short life-span and rapid reproduction meant that a number of generations could be studied within a short period.

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[81] Toward mid-century, discovery of a link between human health and heredity became an increasingly urgent public matter of concern, historian Nathaniel Comfort has noted, motivated by the specter of atomic warfare. See Comfort, *The Science of Human Perfection: How Genes Became the Heart of American Medicine*, 98, 132. See also Haynes, "My Road to Repair in Yeast: The Importance of Being Ignorant," 146.

[82] Lyons, "Release: Immediate."

[83] This will be explored in greater detail in the subsequent chapters which focus on the emergence of molecular biology and development of yeast as a model eukaryote.

[84] Egyptian Staff, "Southern Scientists Help Simplify Cancer Research," *The Egyptian*, July 13, 1950. See also an early explanation of this theory that "cancer cells may be found to differ in their growth factor requirements from cells of normal origin" in Joshua Lederberg, "A Nutritional Concept of Cancer," *Science* 104, no. 2705 (1946).

The magazine reported that Lindegren could "tell how many generations it will take for the effect of alpha rays, beta rays, gamma rays, x-rays, or ultraviolet rays to prove fatal" within an irradiated cluster of cells, and that, "Such findings are valuable in measuring the hereditary effects on a human population of radioactive fallout from atomic bomb tests and cosmic rays." Moreover, since temperature affected fermentation ability in the yeasts, "extremes of temperature may have a big influence on the spread of cancer" since yeast and human cells shared similar statistical patterns of heredity.[85] By 1966, Lindegren was still drawing his metaphors at the level of the cell and population, and told the local press that the unique anaerobic conditions of yeast growth could be used to elaborate a theory that cancer originated when oxygen-starved cells began to ferment.[86] His generalized view of the yeast cell was not all that different from the nineteenth century claim that yeast fermentation was analogous to blood putrefaction in disease processes. The yeast-human analogies drawn by other investigators in the 1960s and 1970s would grow much more elaborate to justify continued investment in yeast genetic research.

The Politics of a Growing Discipline

In addition to focused yeast programs in Copenhagen and Carbondale, two additional yeast genetics laboratories formed at the end of the 1940s – each stirred by the Lindegrens' claims for a role of the cytoplasm in heredity. Boris Ephrussi had worked in the 1930s on mouse and *Drosophila* genetics with George Beadle at Caltech and in own laboratory at the Rothschild Institute for Physico-Chemical Biology in Paris. During the war, Ephrussi fled the German

[85] "Yeast Yields Secrets," 8.
[86] Daily Egyptian Staff, "Intensive Study of Yeast Linked to Search for Causes of Cancer," *Daily Egyptian*, March 11, 1966, 7.

occupation of France and took a position at Johns Hopkins University where he continued work on *Drosophila* genetics. In 1945, he returned to Paris as the first chair of genetics at the Sorbonne. By 1949, intrigued by the reported cases of adaptive mutations in yeast, he had taken up study of *Saccharomyces cerevisiae* and began to publish his own observations on non-Mendelian heredity.[87]

Ephrussi observed that on rare occasions some yeast colonies grew slowly only to a small size when compared with normal colonies. The occurrence of these small colonies would increase when a mutagen was applied to the growth medium. Once a yeast began to yield small colonies, the trait appeared heritable and irreversible. The yeast never reverted back to produce colonies of the normal size. Ephrussi called this the "petite" mutation and found that it was due to a respiratory deficiency in the yeast which resulted in slower cell growth. He observed that when non-respiring strains were mated with other yeasts, the petite mutation disappeared or was occasionally present among offspring in unexpected statistical proportions.[88] Initial tetrad analyses indicated that more than a dozen recessive genes would have to be involved in the Mendelian inheritance of this trait. Since that seemed highly unlikely given the rate of

[87] Ephrussi is said to have been motivated by one of Winge's early studies which had suggested in 1940 the possibility of cytoplasmic phenomena. See Winge and Laustsen, "On a Cytoplasmatic Effect of Inbreeding in Homozygous Yeast," 17-39; Herschel Roman, "Boris Ephrussi," *Annual Review of Genetics* 14, no. 1 (1980): 447-450; Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, 136. But by the time of Ephrussi's first publications on yeast genetics in 1949, Carl Lindegren had published close to a dozen articles in major scientific journals on related phenomena and was likely a greater motivator given the lively controversy which attended his experimental methods and speculative conclusions. This may have been a difficult inspiration to admit in later decades once so many of the Lindegrens' theories had been challenged.

[88] Later work identified different varieties of the petite mutation, some which conformed to traditional Mendelian heredity and operated by gene control. The suppressive mutation was a later variety that did not result in standard tetrad ratios. See Boris Ephrussi, Hélène de Margerie-Hottinguer, and Herschel Roman, "Suppressiveness: A New Factor in the Genetic Determinism of the Synthesis of Respiratory Enzymes in Yeast," *Proceedings of the National Academy of Sciences of the United States of America* 41, no. 12 (1955): 1065.

spontaneous mutations, Ephrussi hypothesized that these yeast respiratory functions were instead inherited through the cytoplasm.[89]

At the 1951 Cold Spring Harbor Symposium, Ephrussi noted that yeast respiratory enzymes were concentrated in the normal cell not in the nucleus but in what were "probably mitochondria." There was as yet "no evidence at present which permits the identification of these bodies with the cytoplasmic particles postulated on genetic grounds," however.[90] He also considered the possibility that the same mechanism of cytoplasmic mutation might be operating in the cell differentiation of multicellular organisms.[91] He made these claims during the discussion period, but was cautious to publish such speculations.

Like Lindegren, Ephrussi proposed that a hereditary mechanism in the cytoplasm was formed by the genome and reproduced independently of it. Unlike Lindegren, however, for

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[89] Ephrussi described this cytoplasmic inheritance as a form of "particulate" heredity. In Boris Ephrussi and Hélène Hottinguer, "Direct Demonstration of the Mutagenic Action of Euflavine on Baker's Yeast," *Nature* 166, no. 4231 (1950): 956. For this reason, Ephrussi has been credited with having "shaped the transition" from Mendelian to molecular genetics. See Richard M. Burian, Jean Gayon, and Doris T. Zallen, "Boris Ephrussi and the Synthesis of Genetics and Embryology," in *A Conceptual History of Modern Embryology*, ed. Scott F. Gilbert, Developmental Biology (Springer US, 1991), 208; Roberts, "The Inheritance of Enzymatic Characters in Yeasts," 172; Giorgio Bernardi, "The Petite Mutation in Yeast," *Trends in Biochemical Sciences* 4, no. 9 (1979): 197.

[90] "The nature of the gene was the central question" at the 1951 Symposium. In Nathaniel C. Comfort, "Two Genes, No Enzyme: A Second Look at Barbara Mcclintock and the 1951 Cold Spring Harbor Symposium," *Genetics* 140, no. 4 (1995): 1162; Boris Ephrussi and Hélène Hottinguer, "On an Unstable Cell State in Yeast," *Cold Spring Harbor Symposia on Quantitative Biology* 16 (1951): 85. The petite mutation was detected because yeast continued to grow in the absence of full respiration. This ability was later leveraged for classifying drugs according to their anti-mitochondrial activity once the respiratory role of yeast mitochondria was demonstrated.

[91] In the 1960s, Georgii Frantsevich Gause proposed that the mitochondria of the petit mutant could serve as a model for the cancer cell. "In particular, distorted organization of mitochondria in the respiratory-deficient yeast may be instructive as a model for understanding some aspects of molecular organization of tumor mitochondria." In G. F. Gause, "Microbial Models of Tumor Metabolism," in *Advances in Applied Microbiology*, ed. W. Umbreit Wayne (Academic Press, 1968), 88.

reasons later cited by his colleagues as Ephrussi's experimental rigor and strict conformity to genetic dogma in all other respects, Ephrussi was later celebrated for his contributions to yeast genetics.[92] His conservatism in work was no doubt intended to counter accusations of political radicalism in life, and it seems to have helped. His work was extolled as the first of its kind, not only in opening the field of mitochondrial genetics, but also as providing a credible example of adaptive mutation.[93]

Ephrussi's hesitancy to make speculative leaps was questioned and praised simultaneously by his fellow practitioners, who in retrospect failed to note the delicate political context in which he was operating.[94] For one, French institutions were only beginning to

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[92] Ephrussi's accuracy, apparently, made him sensitive to syntax. In September of 1957, Ephrussi notified Roman of an oversight in their 1955 paper on suppressiveness: "I am taking this opportunity to inform you of a most regrettable discovery which may seriously affect both your and my reputations as geneticists... we say: "The occurrence, incompatible with a Mendelian segregation in a diploid, of asci of both 4:0 and 0:4 types… [when what we mean to say is that] 4:0 α 0:4 should not occur in the absence of other ratios." In Boris Ephrussi, General Correspondence, 1941-1989, (September 21, 1957), Box 1, Folder 6, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington. Underscore in original.

[93] When Ephrussi's first yeast publications appeared in 1949, several years after the adaptive fermentation studies by Spiegelman and the Lindegrens, his research has been cited as "the *first rigorous* demonstration of a non-Mendelian determinant in yeast" in S.W. Liebman and F. Sherman, "Cytoplasmic Inheritance," in *Landmark Papers in Yeast Biology*, ed. P. Linder, D. Shore, and M.N. Hall (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 14. Italics added for emphasis. **"**Yeast later became the organism of choice for studies of the mitochondrial genome." In Sapp, *Genesis: The Evolution of Biology*, 166. Following Ephrussi's lead, a strong community of "mitochondriacs" (so-named by multiple participants) had taken up mitochondrial genetics by the late 1960s.

[94] Historians of science have since addressed this oversight. See the discussion of Ephrussi's genetic research against the backdrop of Cold War France in Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, 123-162; John Krige, *American Hegemony and the Postwar Reconstruction of Science in Europe* (MIT Press, 2006), 115-152. Contrast these with the internalist history offered by Roman: "Although he could not have been oblivious… Ephrussi seemingly was reluctant to give a physical reality to his cytoplasmic factor." In Herschel Roman, "Boris Ephrussi and the Early Days of Cytoplasmic Inheritance in *Saccharomyces*," in *Mitochondrial Genes*, ed. P. Slonimski, P. Borst, and G. Attardi (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 1982), 3-4.

recognize and organize genetic research in the early 1950s. Ephrussi was a member of the international genetics community at a time when France was resistant to this on intellectual, social and institutional grounds.[95] Secondly, and with consequence to his research funding, Ephrussi was caught in the position of potentially defending anti-Mendelian views on heredity at the same time the Soviets were elevating such views to scientific orthodoxy through the use of legislation, rhetoric and force. In the early years of the Cold War, the neo-Lamarckian dogma of the Russian botanist Trofim Lysenko appeared as another form of communist aggression to those in the West.[96] The presumed communist leanings of Ephrussi's institution in 1950 cost him an award from the Rockefeller Foundation despite his best efforts to explain to the Americans that Lamarckism had a long and often conservative history in the French context and did not constitute a communist practice by his laboratory within the newly-founded Centre National de la Recherche Scientifique Institute of Genetics at Gif-sur-Yvette.[97]

Adaptive fermentation raised questions about the ability of the environment to induce change in the genotype and phenotype, and yeast served as another proxy site in the Cold War between the Americans and the Soviets. Ephrussi had evidence for phenotypic change, which held that an individual organism could respond rapidly to environmental changes and pass these

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[95] Jean Gayon and Richard Burian have argued that genetics was not very prominent among French biologists until after 1965, and then in part due to Ephrussi's contributions. "French biologists became molecular geneticists not only through their bias towards physiological issues and through their use of micro-organisms… but also because they were motivated by the question of the inheritance of acquired characteristics." Jean Gayon and Richard M. Burian, "National Traditions and the Emergence of Genetics: The French Example," *Nat Rev Genet* 5, no. 2 (2004): 150-156.

[96] François Jacob recalled how genetics "acquired new importance, even prestige, following the incredible Lysenko affair… In the face of this collective lunacy, genetics became a bastion of reason. To do genetics was to say no to intolerance and fanaticism." In Jacob, *The Statue Within: An Autobiography*, 209-210.

[97] Krige, *American Hegemony and the Postwar Reconstruction of Science in Europe*, 134. Ephrussi saw French neo-Lamarckism, not Lysenkoism, as the "real threat to genetics in France." In Sapp, *Genesis: The Evolution of Biology*, 179.

effects to its offspring, but would revert without reinforcement.[98] This was not the more radical position of Lysenko who had argued for permanent changes to the genotype, and an evolution by revolution. In the American view, however, it was still a threat to be contained.[99]

Like Ephrussi, Carl Lindegren was acutely aware of the politics at play, but felt on the whole "it was a shame so many scientists consider science a social activity," as he told a reporter for the *Chicago Tribune* in 1955.[100] Carl Lindegren anticipated that his defense of non-Mendelian heredity in yeast would make him a political target. He had preempted this critique in the 1948 preface of his book, *The Yeast Cell*, with an appeal to Western rationalism:

> Some readers may interpret this as support of Lysenko's theories of heredity. This is by no means the case. Lysenko's views are based on (1) belief in Lamarck's theory of the inheritance of acquired characters and (2) the view that genes and chromosomes have no control over heredity… Current editorial criticism of Lysenko consists largely of attacks on the tenability of his scientific views. I believe this attitude is deplorable. Opposition to Lysenko should not be based on the criticism of his scientific views, weak and naive though they are, but on the fact that he has achieved his prestige by conniving at the murder of his scientific adversaries rather than by argument and discussion and that he acts as an arbitrary dictator over other biologists, suppressing freedom of discussion and research.[101]

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[98] Ephrussi believed that "the phenotype of an organism is always the result of interaction between genotype and environment." Originally, "le phénotype d'un organisme est toujours le résultat des interactions entre génotype et milieu." In Boris Ephrussi and Piotr P. Slonimski, "La Synthèse Adaptive Des Cytochromes Chez La Levure De Boulangerie," *Biochimica et Biophysica Acta* 6, no. 0 (1950): 256. See also Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, 138.

[99] David Joravsky reminds us that Lysenko would not have characterized his own views in this way. "By 1937, Lysenko ceased to speak of genes or genotypes except to deny their existence." In D. Joravsky, *The Lysenko Affair* (University of Chicago Press, 2010), 210. For a study of the American strategy of containment in the early Cold War period see J.L. Gaddis, *Strategies of Containment: A Critical Appraisal of Postwar American National Security Policy* (Oxford University Press, 1982).

[100] Thomas Morrow, "By the Way," *Chicago Daily Tribune*, December 8, 1955, 1-B1.

[101] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, viii-ix.

When his colleagues turned their critique equally to Carl Lindegren's scientific views, he responded in kind, accusing them of acting like Lysenko by no small matter of degree.[102] In his pursuit of yeast cytoplasmic heredity and of "gene conversion" – a claim that would become even more fiercely contested as his book began to circulate – Carl Lindegren felt persecuted on the national and international stage.[103] The attacks grew worse when he failed to reproduce some of his key experiments, and this stain was never lifted from his career. When in 1960, for example, Carl Lindegren was invited to speak alongside George Beadle and the American biologist Tracy Sonneborn to an audience of poultry farmers, agricultural scientists and geneticists on the subject of "the particulate gene," he began his talk by stating that, "We like to think of science as a logical system divorced from personalities because we seek the guidance of a principle rather than a person. This desire supports the illusion that science is the objective structure which every scientist hopes to aggrandize." He continued to lambast the practice of scientific indoctrination that would bias scientists "toward rejection of the new and reaffirmation of the old."[104] During the question and answer period, Sonneborn rejoined with obvious disapproval of the material that had been presented: "Dr. Lindegren has raised the question of

[102] In 1949, Carl Lindegren wrote about the American Genetic Society's formation of a Committee for Scientific Freedom designed to prevent the teaching of Lysenkoism. Noting the irony of the committee's name, and specifically calling out Tracy Sonneborn's participation in it, he wrote, "If deviation assumes serious proportions, scientists are not above suppressing it by direct action." Lindegren, *The Cold War in Biology*, 8, 50. Sapp also identifies this confrontation, and by the 1960s has Carl Lindegren "dismissed to the periphery of American genetics where he criticized what he called the anti-intellectual, atheoretic, and doctrinaire climate of American biology." See Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, 102.

[103] Harvard evolutionary geneticist Richard Lewontin has described the marginalization and delayed acceptance of the Lindegrens' observations, which became "a source of snickering reference in cocktail bars at scientific meetings." In R. C. Lewontin, "Facts and the Factitious in Natural Sciences," *Critical Inquiry* 18, no. 1 (1991): 488.

[104] Carl C. Lindegren, "The Particulate Gene" (paper presented at the Ninth Poultry Breeders' Roundtable, Chicago, Illinois, April 30, 1960), 49.

personalities; and it is important in science. I think this is certainly true to some extent, and has been exemplified here today."[105] He and Beadle proceeded to refute a number of Lindegren's claims.

After his retirement, Carl Lindegren wrote openly about his experiences in the *Cold War in Biology.* He saw as oversimplification the view that American and Russian science was polarized into two clear camps and called for tolerance to ease the tensions of biological controversy. "[A]ctually there are more disagreements and conflicts and a greater variety of attitudes among scientists of the Western World than have been generally recognized," he wrote. He described the power of scientific indoctrination and the self-imposed tendency to conformity, explaining that, "the scientist" who encounters deviant experimental phenomena must fear being wrong or suffering humiliation. "[H]e feels that it would be ridiculous to question the established ideas, or more seriously, it would make him look ridiculous to do so." He described "the sacrifice of logic" by Sonneborn, an "indoctrinated Mendelist," which had allowed him to fit observations of cytoplasmic inheritance to the theory of the gene, and he fired directly at Beadle: "In Beadle's psychological approach to science he can ignore inconsistencies without misgivings… He is not devoted to order because it has beauty; he only wants things to look nice… Beadle has done much good, but like anyone in high position, he has also done much harm."[106]

[105] Ibid., 72.

[106] The text also rallies against what Carl Lindegren identified as the erosion of academic freedom and "creative science" by "capitalist conformity." Without the development of new concepts from "pure" science [his own scare quotes], creative science would disappear from the modern world, as it did from the ancient, leaving "a race of superb technologists" to "build roads and television sets, and automobiles and jet planes with models that will be frozen for a thousand years." Lindegren, *The Cold War in Biology*, vii, 8, 14, 49.

The text also wandered into unfounded speculations on a variety of scientific subjects where Carl Lindegren had not done experimental work. This was nothing new for the man who had once "prophesied the extinction of all of life on the earth at a much earlier date than previously anticipated" due to "the depletion of the carbon dioxide supply in the world."[107] One review of his book pointed out Carl Lindegren's unwelcome iconoclasm to explain the difficulty he had had in finding a publisher.[108] Carl Lindegren began channeling his ruminations into popular publications like "The Saturday Review," where, for example, he applied his experience with cell culture population averages to the "societies" of cells that made up higher organisms, and concluded that the nervous system likely controlled hereditary development by changing cell-type proportions: "no *new kinds of members*… [just] *new kinds of balances.*" He recommended a continued focus on cytoplasmic heredity, and warned against the opposing tendency "to search for the solutions to the problems of life in the analysis of the mechanism controlling the production of an enzyme by a gene." Although this "gene-centrism" of the geneticist and biochemist was a worthy pursuit, he warned, "it would be fatal to lose sight of the higher goals and to assume that the molecular biologist could achieve even a modicum of success without the help of the anatomist, the ecologist, the physiologist, the taxonomist, the cytologist, the immunologist, the psychologist, and, above all, the philosopher."[109] It is likely Carl Lindegren fancied himself as a bit of each of these.

Carl Lindegren was also concerned with obtaining recognition for ideas that had gradually found acceptance over time. In 1964, for example, he wrote to Francis Crick to dispute

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[107] "College Clippings," *The Cowl*, November 6, 1936, 2.
[108] Laura R. Livingston, "The Cold War in Biology," *The Yale Journal of Biology and Medicine* 41, no. 3 (1968): 290.
[109] Carl C. Lindegren, "The Brain in Evolution," *The Saturday Review*, October 5, 1968, 58. Italics in original.

Jacques Monod's priority in identifying a genetic control of enzyme synthesis. Jacques Monod, André Lwoff, and François Jacob were jointly awarded the 1965 Nobel Prize for this work. "[T]here has been hanky-panky here. Monod stated that the first discovery of the gene-controlled adaptive enzymes in bacteria was in his laboratory. This statement with its qualification is precise and correct. But he knew very well that I reported gene-controlled adaptive enzymes in yeast three years earlier."[110] Carl Lindegren left Carbondale in 1964 to direct genetics at the University of Puerto Rico. That winter, he returned to Illinois to begin his retirement.[111] Partial redemption of his research program has since occurred with the rare citation or unintentional endorsement.[112]

In the late 1940s, the Lindegrens' insistence on the importance of cytoplasmic heredity also flew in the face of the first and still most prominent yeast genetics laboratory at Carlsberg in Copenhagen. Carl Lindegren had first met Øjvind Winge in July of 1947, and he was invited to lecture at Carlsberg laboratory several times in the late 1940s. Following one lecture in particular, an observer recalls, Winge objected strongly to the evidentiary basis of Carl Lindegren's "ad hoc theories."[113] These early arguments grew personal and "quite vituperative," especially as a greater number of investigators began to contribute their contradictory findings.[114]

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[110] Carl C. Lindegren, Letter to Dr. F. H. C. Crick, (July 20, 1964), PP/CRI/1/1/12, Francis Harry Compton Crick Papers, Wellcome Library for the History and Understanding of Medicine, Bethesda, MD.

[111] "SIU Professor Writes Genetics Book by Air Mail," *The Edwardsville Intelligencer*, February 1, 1964, 5.

[112] The Lindegrens' findings were later incorporated into orthodox molecular genetics but only then as "historical relics, prefigurations of evidence… playing no role in the establishment of new ideas." In Lewontin, "Facts and the Factitious in Natural Sciences," 488.

[113] Carl Lindegren was one of a number of early yeast geneticists who passed through the physiology laboratory at Carlsberg during this period. Other visitors included Mogens Westergaard, Urs Leupold, Giovanni E. Magni, Herschel Roman, Piotr P. Slonimski, and Boris Ephrussi. In Szybalski, "My Road to Øjvind Winge, the Father of Yeast Genetics," 2.

[114] Roman, "The Early Days of Yeast Genetics: A Personal Narrative," 5.

The confused state of the field caught Ronald Fisher's attention in Cambridge in the early 1950s, and the statistician wrote Winge to praise the Carlsberg scientist's "justly severe criticism on some preposterous work with yeast."[115]

The yeast geneticist Robert Mortimer later suggested that the conflict between Øjvind Winge and Carl Lindegren delayed progress in the field. "Most young investigators started work on bacteria and bacteriophages at that time and, had they considered yeast as an alternative, probably decided against this organism because of the controversy existing in the literature," he wrote.[116] There is equally evidence for the reverse claim, however. For example, for several weeks in the spring of 1947, Carl Lindegren delivered a series of lectures at the University of Washington in Seattle on the work he, Gertrude Lindegren, and Sol Spiegelman had completed.[117] Carl Lindegren had been brought to Seattle on a visiting professorship in botany at the invitation of Herschel Roman who was considering switching from corn into yeast. Corn grew poorly in the Northwest climate, and Roman had recently made up his mind to find another organism.[118] He had invited Carl Lindegren to the department to consider work with yeast. Roman recalled that Carl Lindegren's views during this visit were highly controversial, and a

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[115] Ronald Aylmer Fisher, Sir, Correspondence with Öjvind Winge (Copenhagen), (April 25, 1951), R.A. Fisher Digital Archive, University of Adelaide Library Special Collections, Adelaide, AU. Fisher was likely praising Øjvind Winge, "The Relation between Yeast Cytology and Genetics. A Critique," *Comptes Rendus des Travaux du Laboratoire Carlsberg. Série physiologique* 25, no. 3 (1951): 85.

[116] Robert K. Mortimer, "Some Recollections on Forty Years of Research in Yeast Genetics," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 14-15.

[117] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, vii.

[118] Roman had trained in corn genetics under Lewis Stadler at the University of Missouri, and had intended to practice this at the University of Washington after his appointment in 1942. He was delayed by the war, but following his military service in Texas and Florida with the U.S. Air Force, Roman rented acreage in eastern Washington and maintained a plot of corn at Caltech to grow his crop for a short period before giving up on the idea. In S Gartler and D Stadler, "Herschel L. Roman (1914-1989)," *Genetics* 126, no. 1 (1990): 2.

number of alternative explanations were raised by the scientists in his department to account for Carl Lindegren's data on adaptive fermentation. Carl Lindegren was unyielding, and his "unorthodox interpretations presented a challenge" to geneticists who identified with the mainstream. Roman recalled that wanting to disprove Carl Lindegren's findings after this visit was "largely responsible for my choosing yeast as an experimental organism."[119]

At the end of the 1940s, the Lindegrens had a large stock of yeast strains at Carbondale and had identified genes to control the fermentation of five different sugars and the synthesis of seven B vitamins.[120] They had classified yeast "genetical characters" into five "arbitrary" categories: terminal, quantitative, and biochemical/physiological characters, as well as "lethal" genes and "modifiers." Carl Lindegren had published the first chromosome maps for yeast along with his linkage calculations, and his work was increasingly oriented to questions of cytoplasmic heredity. He had begun to explain the non-Mendelian ratios seen in yeast tetrads no longer in terms of "cytogenes," but now in terms of "gene conversion." This new explanation held that alleles "contaminated" one another during meiosis and converted wild-type to mutant, and vice versa.[121]

Roman saw this unorthodox interpretation from Carl Lindegren as a challenge to explore in his own laboratory. In the late 1940s, Roman established the fourth yeast genetics laboratory in Seattle with Howard Douglas, a colleague in the University of Washington microbiology department who was already conducting physiological studies of yeast and biochemical studies of yeast fermentation. They were aided in this set up by the Lindegrens' former student, Sol

[119] Roman, "The Early Days of Yeast Genetics: A Personal Narrative," 3.
[120] Carl C. Lindegren, "Genetics of the Fungi," *Annu Rev Microbiol* 2 (1 vol.) (1948): 59.
[121] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 11: 11. See also an irreverent characterization of this work by Roberts, "The Inheritance of Enzymatic Characters in Yeasts," 172.

Spiegelman, who offered them advice on equipment purchases and sent the latest reprints on cytoplasmic heredity.[122] The move was a direct contradiction to Carl Lindegren's prediction in 1949 that the great stock of corn and *Drosophila* varieties, along with the simple and widely-known genetic techniques which could be applied to these organisms, meant that "a person who had spent half his working life time on [either] cannot afford to change."[123] This was wishful thinking on Carl Lindegren's part, who at the same time was advertising and sharing his stable mating type strains with any laboratory which asked for them.[124] This included the Seattle researchers whose initial experiments with the strains would be designed to disprove Lindegren's finding of yeast gene conversion.

New Conflicts & Alliances in the Early 1950s

The conflicts over yeast heredity persisted from the late 1940s well into the 1950s, at which point several studies emphasized the importance of shared research materials to genetic practice. Beginning 1948, Øjvind Winge and an American co-investigator at Carlsberg, the microbiologist Catherine Roberts, began to refute many of the Lindegrens' conclusions with respect to non-Mendelian patterns of heredity detected in yeast tetrads and they weighed in on the phenomenon of "long-term adaptation" in the yeasts.[125] The phenotype under study was not

[122] Sol Spiegelman, Series II: Correspondence, 1946-1985, (May 22, 1948), Box 10, Folder 19, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.
[123] Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 12: 11.
[124] Carl C. Lindegren, "Unusual Cultures Available for Distribution," in *Yeasts: A News Letter for Persons Interested in Yeasts*, ed. Leslie R. Hedrick (1950), 6.
[125] Roberts received her doctorate in microbiology at the University of California in 1943. She worked with Winge in Copenhagen from 1946-1961 and was responsible for many of the lab's English publications until quitting this work in genetics to begin a radical rejection and critique of scientific practice beginning in the 1960s. This transformation will be explored in greater detail in the next chapter.

the presence or absence of fermentation, but rather strong or weak fermentation, they claimed. Yeast fermented sugar under a threshold of visibility and this fermentation could be observed even among weak fermenters once they had amassed a sufficiently-high concentration of specific enzymes.[126] Winge and Roberts determined that three different normally-segregating Mendelian genes controlled this enzyme production, as long as one accounted for "crossing-over" – the separation and recombination of "linked" traits along the chromosomes during sexual reproduction.

Carl Lindegren and graduate student Balaji Mundkur disagreed, showing that for certain strains "slow" fermenters underwent mutation and selection. They suggested that this mutation was possibly a "conversion" of one gene to another.[127] Their work had questioned "a long-held genetical tenant: the integrity of the gene as a Mendelian unit." The only way to interpret the "exceptional ratios," they claimed, was on the basis of "gene conversions."[128]

Winge and Roberts' account of "long-term adaptation" had the support of a previous observation of "crossing-over" in *Drosophila*, but the Lindegrens' former graduate student Sol Spiegelman was not satisfied with this interpretation, and he began his own studies on the

[126] Øjvind Winge and Catherine Roberts, *Inheritance of Enzymatic Characters in Yeasts, and the Phenomenon of Long-Term Adaptation* (Hagerup in Komm., 1948). See also Roberts, "The Inheritance of Enzymatic Characters in Yeasts," 170. This idea that the enzyme may be been present in too small an amount to be measured also appears in footnote 7 in Spiegelman's 1944 paper on this subject: Spiegelman, Lindegren, and Hedgecock, "Mechanism of Enzymatic Adaptation in Genetically Controlled Yeast Populations," 23.
[127] Balaji D. Mundkur and Carl C. Lindegren, "An Analysis of the Phenomenon of Long-Term Adaptation to Galactose by Saccharomyces," *American Journal of Botany* 36, no. 10 (1949): 727.
[128] Balaji D. Mundkur, "Evidence Excluding Mutations, Polysomy, and Polyploidy as Possible Causes of Non-Mendelian Segregations in Saccharomyces," *Annals of the Missouri Botanical Garden* 36, no. 3 (1949): 278.

subject.[129] Spiegelman had left St. Louis and taken a job in the Bacteriology Department at the University of Illinois at Urbana-Champaign. He brought with him several of the Lindegrens' yeast strains and requested that others be sent to him by mail. Although the Lindegrens complied with strain requests and sent technical details for their use, they did not engage Spiegelman in the scientific conversations he sought with them following his move to a new university. Multiple times he requested more personal communications and opinions, and offered to engage in collaborative studies as was common between other laboratories, but Carl Lindegren was growing protective of his controversial observations, believing the genetic breakthroughs would eventually be credited to him alone.[130]

Winge and Roberts suggested several problems with Carl Lindegren's hypothesis, "a hitherto unknown method of inheritance."[131] They suggested that a more obvious explanation was for the tetrads to have initially produced eight spores, where four of the spores had died at random to produce four-spored tetrads with odd ratios. This they argued on the basis of finding

[129] Thomas Hunt Morgan and Eleth Cattell, "Data for the Study of Sex-Linked Inheritance in Drosophila," *Journal of Experimental Zoology* 13, no. 1 (1912): 79; Sol Spiegelman, Series II: Correspondence, 1946-1983, (August 13, 1948), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.
[130] See Spiegelman, Series II: Correspondence, 1946-1983, (August 13, 1948), Box 6, Folder 59, Sol Spiegelman collection (MSC 561); Sol Spiegelman, Series II: Correspondence, 1946-1983, (February 28, 1950), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.
[131] Øjvind Winge and Catherine Roberts, "The Polymeric Genes for Maltose Fermentation in Yeasts, and Their Mutability," *Comptes Rendus des Travaux du Laboratoire Carlsberg. Série physiologique* 25 (1950): 35.

several tetrads with five or six spores.[132] Spiegelman wrote Carl Lindegren to say that he was satisfied by this new interpretation out of Copenhagen of the non-Mendelian ratios.[133]

In 1950, yeast enzymatic adaptation was "much talked about" in laboratories from Urbana-Champaign to Paris. Sol Spiegelman was invited to speak at the Pasteur Institute, for example, in the laboratory of microbiologist André Lwoff who was studying how bacteria could inherit and reactivate viruses across generations.[134] Yeast adaptation provided a parallel to the question of how events in the cell might be transmitted as a defined set of environmental responses. In addition to presenting their work, the yeast geneticists were also exchanging advice and materials with other microbial geneticists on this subject. Boris Ephrussi, Sol Spiegelman, and Gertrude Lindegren, for example, all wrote to Guido Pontecorvo at Glagsow University in 1950, to ask for the geneticist's banked strains or opinions given his familiarity with other fungal species.[135] Pontecorvo wrote for permission before passing along yeast strains that had come into

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[132] Øjvind Winge and Catherine Roberts, "Non-Mendelian Segregation from Heterozygotic Yeast Asci," (1950): 157.

[133] Spiegelman, Series II: Correspondence, 1946-1983, (February 28, 1950), Box 6, Folder 59, Sol Spiegelman collection (MSC 561).

[134] Lwoff studied how bacterial cells infected by the phage could sometimes pass the virus to offspring in an inactive form (which he called prophage). After exposing one of these progeny cells to ultraviolet light, Lwoff witnessed reactivation of the virus. He called this "induction of the prophage." In Jacob, *The Statue Within: An Autobiography*, 215, 226. Yeast appeared in these experiments only as an extract - the growth medium for bacteria. In André Lwoff, "The Prophage and I," in *Phage and the Origins of Molecular Biology*, ed. J. Cairns, J.D. Watson and G.S. Stent (New York: Cold Spring Harbor Laboratory of Quantitative Biology, 1966), 94.

[135] Pontecorvo was an early contributor to *Aspergillus* genetics. See, for example, G Pontecorvo et al., "The Genetics of *Aspergillus Nidulans*," *Advances in Genetics*, no. 5 (1953); G.H. Goldman and S.A. Osmani, *The Aspergilli: Genomics, Medical Aspects, Biotechnology, and Research Methods* (CRC Press, 2007), 10. The inspiration leading to Ephrussi's finding of the "petite" mutation has been credited to Pontecorvo. See Bundle of Correspondence between Pontecorvo and Professor Boris Ephrussi Concerning Three Mutant Strains of Yeast Pontecorvo Sent to Ephrussi to Be Used in Experiements for His Metabolic Work, (May-June, 1950), UGC198/193/191/191/192, Guido Pontecorvo Papers, University of Glasgow Archive Services, Glasgow; Bernard L. Cohen, "Guido Pontecorvo ("Ponte"): A Centenary Memoir," *Genetics* 177, no. 3 (2007): 1442.

his collection from another investigator, but he hesitated to exchange strains with the Lindegrens. "We did some work initially with your strains, but found them not to be quite suitable," he told Gertrude Lindegren. And again, in response to her request for another investigator's material, "He is not particularly keen in sending that strain because it has some most interesting biochemical features on which he is working."[136]

As Sol Spiegelman continued his work on yeast adaptation, he put greater distance between himself and the Lindegrens, and he made clear his independence to other scientific associates. His studies indicated a role for the cytoplasm in response to changes in the cellular environment, but he objected to the Lindegrens' "mutation idea."[137] In one publication, he calculated that a mutation could not have occurred in their populations of cells since the rate of population change was statistically predicted to have been faster.[138] He was also troubled by Winge's critique of his early work with the Lindegrens and he worried that the association reflected poorly on him. Tracy Sonneborn assured Spiegelman in 1950, "I am …one of your ardent admirers and have always felt that whatever was lacking in the early work was probably attributable to the Lindegrens."[139] Spiegelman replied to Sonneborn that Carl Lindegren's recent

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[136] Correspondence between Pontecorvo and Dr. Gertrude Lindegren Concerning Lindegren's Request for a Sample of Pontecorvo's Mutant Baker's Yeast to Expermiment On, (October-December, 1950), UGC198/193/191/114, Guido Pontecorvo Papers, University of Glasgow Archive Services, Glasgow; Correspondence between Pontecorvo and Dr. Sol Speigelman Concerning Speigelman's Interest in Engaging with Yeast Genetics and Pontecorvo's Developments with Aspergillus Nidulans, (September-December, 1950), UGC198/193/191/111, Guido Pontecorvo Papers, University of Glasgow Archive Services, Glasgow.

[137] Herschel Roman, Series II: Correspondence, 1946-1985, (October 6, 1950), Box 10, Folder 19, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

[138] Sol Spiegelman, Racquel Rotman Sussman, and E. Pinska, "On the Cytoplasmic Nature of "Long-Term Adaptation" in Yeast," *Proceedings of the National Academy of Sciences of the United States of America* 36, no. 11 (1950): 593.

[139] Tracy M. Sonneborn, Letter to Sol Spiegelman, (November 8, 1950), The Sol Spiegelman Papers, National Library of Medicine, Bethesda, MD.

book had proven "conclusively that they [the Lindegrens] haven't the foggiest notion of what an experiment is and are completely incompetent to carry one through without the closest sort of supervision." He had reached the "bitter conclusion" that yeast genetics would have been better off without his experiments with the Lindegrens since they had "engendered only irrationality and confusion… for heartbreakingly irrelevant reasons of incompetence."[140]

The Lindegrens' mass mating technique had long been subject to the criticism that it failed to prevent continual yeast breeding and thus allowed the overlap of multiple generations to obscure accurate observation. Winge and Roberts had made a recent note of this, and in a footnote of his latest paper Spiegelman questioned Carl Lindegren's apparent sloppy practices – his difficulty repeating experiments and poor use of controls.[141] Spiegelman took special precautions in his own work "[t]o minimize the confusion which Winge and Roberts pointed out."[142]

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[140] Sol Spiegelman, Letter to Tracy M. Sonneborn, (November 15, 1950), The Sol Spiegelman Papers, National Library of Medicine, Bethesda, MD, 5. See also T.D. Brock, *The Emergence of Bacterial Genetics* (Cold Spring Harbor Laboratory Press, 1990).

[141] See footnote 2 in Spiegelman, Sussman, and Pinska, "On the Cytoplasmic Nature of "Long-Term Adaptation" in Yeast," 605; Winge and Roberts, "The Polymeric Genes for Maltose Fermentation in Yeasts, and Their Mutability," 35. Spiegelman also shared his doubts about Lindegren's experimental work with Roman. "Lindegren's pedigrees contained completely impossible segregation such as mating + and – and getting all four negatives out. I am certain now that solution is that he was studying second and possibly even third and fourth cycle sporulation." In Sol Spiegelman, Series II: Correspondence, 1946-1985, (February 8, 1951), Box 10, Folder 19, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD. Lindegren's carelessness had permitted illegitimate "rematings." In Sol Spiegelman, Series II: Correspondence, 1946-1985, (January 18, 1952), Box 10, Folder 19, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

[142] Spiegelman ended his experiments after a period of six days to avoid having multiple cycles of sporulation and recombination obscure his results. The six-day period is not explained, but is a curious choice considering that *Saccharomyces cerevisiae* has a generation time of 80 minutes. See Sol Spiegelman and W. F. Delorenzo, "Substrate Stabilization of Enzyme-Forming Capacity During the Segregation of a Heterozygote," *Proc Natl Acad Sci U S A* 38, no. 7 (1952): 585.

Seattle as "Prayerful Hope"

As the newcomers to the field, Herschel Roman and Howard Douglas followed these investigations with some interest from the University of Washington in Seattle as they slowly brought their genetic stock and equipment up to speed. They moved cautiously at first, sometimes finding that one or another researcher "beats us to the punch" as they worked through the complicated data.[143] They had acquired the Lindegrens' stable haploid mating type strains after Carl Lindegren's visit to Seattle. Such material transfers were typical in this period between the geneticists and other research laboratories as well. After the yeast culture collection at the University of California, Berkeley was transferred to Davis in 1951, for example, Emil Mrak, Herschel Roman, and Sol Spiegelman kept up a ready exchange of strains and new findings.[144]

The Lindegrens had been the first to report yeast mating types in strains which could be bred with one another but not to other cells of the same strain. Winge and Roberts had

[143] Roman, Series II: Correspondence, 1946-1985, (October 6, 1950), Box 10, Folder 19, Sol Spiegelman collection (MSC 561).

[144] See Emil M. Mrak, Series II: Correspondence, 1946-1984, (March 18, 1947), Box 8, Folder 14, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Emil M. Mrak, Series II: Correspondence, 1946-1984, (November 15, 1949), Box 8, Folder 14, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Sol Spiegelman, Series II: Correspondence, 1946-1984, (December 13, 1951), Box 8, Folder 14, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Sol Spiegelman, Series II: Correspondence, 1946-1984, (February 15, 1952), Box 8, Folder 14, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Sol Spiegelman, Series II: Correspondence, 1946-1984, (November 5, 1954), Box 8, Folder 14, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD. Trading strains went on before the move too while Emil Mrak was embroiled in the University's loyalty oath controversy. In March of 1950, Mrak wrote Spiegelman: "we are all up to our necks out here pledging our loyalty, but at the same time fighting an unnecessary oath." In Emil M. Mrak, Series II: Correspondence, 1946-1984, (March 10, 1950), Box 8, Folder 14, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

contradicted this report with the finding that cells of a single strain could also mate and, further, that this ability was under the control of a single gene.[145] The early conflict indicated the importance of sharing experimental material since Winge and Roberts resolved from the contradictory observations that they and the Lindegrens must have been using different strains of *Saccharomyces cerevisiae* which possessed or lacked this gene for diploidization. This helped to explain their divided views on the existence of "illegitimate" hybrids, and paved the way for future research into yeast's ability to undergo mating type switching, involving genetic regulation by "cis" and "trans" factors.[146]

Based on these new material conditions, the Seattle researchers hoped to retest the Lindegrens' hypothesis that instable genes were "converting." As part of their recently NIH-funded "*Saccharomyces* Studies" project in Seattle, Herschel Roman and Howard Douglas gave

[145] They found that when interfertile strains were crossed with intrafertile strains, the tetrads yielded 2 spores of each phenotype once grown up into new cultures. In Øjvind Winge and Catherine Roberts, *A Gene for Diploidization in Yeasts* (Copenhague: Hagerup in Komm., 1949).
[146] After a half century of genetic research on yeast mating patterns, geneticists determined that strains could be intrafertile or interfertile depending on the presence of a gene (*HO*) that allowed for mating type switching. They concluded that Lindegren's strain had undergone a natural, inactivating mutation of *HO* to enable the stable propagation of yeast lines of each mating type. "There was a big schism in the East in the '40s between Lindegren on the one hand and a Danish scientist, Winge … It turns out that… Winge was working with yeast that had a gene called HO, and Lindegren was studying yeast that did not have the HO gene. This locus called the mating type locus immediately switched in the case of Winge's yeast… Lindegren's yeast didn't do that." In Benjamin D. Hall, interview by Erika Langer, February 24, 2014, "Oral History with Ben Hall, Part 2," San Francisco, CA, Life Sciences Foundation. There have been multiple reviews of the subject of yeast mating type determination. See, for example, Kim Nasmyth, "Molecular Genetics of Yeast Mating Type," *Annu Rev Genet* 16 (1982); Ira Herskowitz, Jasper Rine, and Jeffrey Strathern, "Mating-Type Determination and Mating-Type Interconversion in Saccharomyces Cerevisiae," *Cold Spring Harbor Monograph Archive* 21 (1992); James E Haber, "Mating-Type Gene Switching in Saccharomyces Cerevisiae," *Trends in Genetics* 8, no. 12 (1992); Yasuji Oshima, "Homothallism, Mating-Type Switching, and the Controlling Element Model in *Saccharomyces Cerevisiae*," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993). Mating type switching and the common language of fungal sexuality and human gender identity will be explored in a later chapter.

Donald Hawthorne, then an undergraduate at the University of Washington, the task of examining yeast tetrads for gene conversion.[147] Hawthorne recalled finding unusual tetrads on the same day South Korea was invaded. As he was called up to serve in Korea with the U.S. Naval Reserve, Roman promised to publish the findings.[148]

Roman explained the irregular Mendelian ratios that Hawthorne had observed as the consequence of haploids sometimes producing both haploid and diploid cultures. The offspring of such crosses might have even greater numbers of chromosomes and be polyploid (e.g., triploid, tetraploid), resulting in irregular genetic ratios. A study out of the Indian Institute of Science in Bangalore had previously criticized the identification of ploidy without clear cytological evidence of the chromosomes as "arbitrary" and "artificial."[149] While Roman did not have the cytological techniques to give chromosomal counts, he found genetic support for polyploidy "by the evidence at hand," that is, by the same statistical analysis of the tetrads he was trying to prove.[150] The earlier chromosomal critique was never put to Roman since his interpretation offered closure to an old argument. He had not sided with the Lindegrens, nor with Winge, but had located the source of their conceptual differences in different sources of material.

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[147] NIH funded other molecular studies of microbial mutation in the 1950s because of the implied relevance to the medical problem of drug resistance. In Sapp, *Genesis: The Evolution of Biology*, 168.

[148] Donald C. Hawthorne, "Saccharomyces Studies, 1950-1960," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 109-124.

[149] MK Subramaniam, "Haploidy and the Species Concept in Yeasts," *Journal of the Indian Institute of Science*, no. 32 A (1950): 42-43.

[150] Herschel Roman, Donald C. Hawthorne, and Howard C. Douglas, "Polyploidy in Yeast and Its Bearing on the Occurrence of Irregular Genetic Ratios," *Proceedings of the National Academy of Sciences of the United States of America* 37, no. 2 (1951): 82, 83; Herschel Roman, M. M. Phillips, and S. M. Sands, "Studies of Polyploid Saccharomyces. I. Tetraploid Segregation," *Genetics* 40, no. 4 (1955): 546-561.

Carl Lindegren reviewed Roman's manuscript prior to publication and wrote to its author early in 1951 to propose an addendum. While he was convinced by the findings of polyploidy, Carl Lindegren did not think this explanation accounted for all of his irregular ratios. "It is these exceptions which are important. They are the basis for a new concept in genetics. I think it would be unfortunate to give the impression that 'all is well' because I am convinced that 'something is rotten.' This may merely be my personal view, but your paper, as it appears now, would give 'aid and comfort' to the conservatives. I believe it would slow up any change in thinking." He proposed that Roman make clear that gene conversion had not been ruled out conclusively and that further investigations would be necessary to differentiate the phenomenon from polyploidy. "I would not like to have you feel that I wish to influence your conclusions in any way, but I am not convinced that gene conversion… does not occur," he wrote. "Above all please do exactly what you believe is right."[151] Carl Lindegren also suggested that his laboratory and Roman's continue to exchange cultures and findings, and try duplicating experiments.[152] Roman's manuscript suggested that it was the Lindegrens' mass mating method which had enabled "illegitimate" matings to obscure their results. In Lindegren's laboratory, Mundkur retorted separately that "not even the Winge crossing method is immune from this objection, since, one cannot be sure that the single cells used in matings were not themselves of illegitimate origin."[153]

[151] Carl C. Lindegren, General Correspondence, 1941-1989, (January 9, 1951), Box 1, Folder 5, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.
[152] Ibid.
[153] Balaji D. Mundkur, General Correspondence, 1941-1989, (January 9, 1951), Box 1, Folder 5, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington. Mundkur had won a scholarship in Bombay from the Sethna Foundation to study for his doctorate under Carl Lindegren beginning in 1948. See "Indian Student Follows Instructor," *Kentucky New Era*, July 13, 1948.

By the end of January, Spiegelman had learned of Roman's manuscript and was congratulating its author on the findings. "I have heard quite direct rumors that you have settled yeast genetics into a nice, safe and sane rut of respectability by the discovery and use of polyploidy."[154] Roman asked for clarification on the praise, "Do you concur with Carl that we are interfering with original thought in yeast?"[155] Spiegelman assured him, "Originality which bears little relation to reality is not particularly useful in science." The phrase "nice, safe and sane" was "not one of derision but expressed rather a prayerful hope." With the proper experiment, Roman might blow "sky-high" the Lindegrens' past unorthodox hypotheses.[156] Spiegelman certainly wished to forget them. The Lindegrens' finding of yeast gene conversion after it had been declared a defunct explanation of genetic recombination was so controversial that it seemed to threaten not only Spiegelman's reputation by association, but that of the entire American yeast community. Nearly twenty years earlier the German botanist Hans Winkler had been the first to theorize about gene conversion, but the theory of chromosomal rearrangement had triumphed.[157] If gene conversion now existed in the yeasts, it made the organism useless to mainstream genetic research. There would be no way to map such unstable genes.[158]

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[154] Spiegelman, Series II: Correspondence, 1946-1985, (February 8, 1951), Box 10, Folder 19, Sol Spiegelman collection (MSC 561).
[155] Herschel Roman, Series II: Correspondence, 1946-1985, (January 30, 1951), Box 10, Folder 19, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.
[156] Spiegelman, Series II: Correspondence, 1946-1985, (February 8, 1951), Box 10, Folder 19, Sol Spiegelman collection (MSC 561).
[157] Winkler had suggested that gene conversion was responsible for all genetic recombination at a time when the alternative theory of the breaking and rearrangement of chromosomes was being established. See Hans Winkler, *Die Konversion Der Gene* (Jena: G. Fischer, 1930).
[158] For a perspective on how the controversy affected early shaping of the field, see Mortimer, "Some Recollections on Forty Years of Research in Yeast Genetics," 14-15; R. Holliday, "The Early Years of Molecular Biology: Personal Recollections," *Notes and Records of the Royal Society of London* 57, no. 2 (2003): 199.

Roman waited until his manuscript was published to respond to Carl Lindegren. **"**I'm very sorry that I was unable to use the addendum; it turned out to be a digest of a number of important ideas that could best be put into a separate paper from your laboratory," he wrote.[159] The Lindegrens confirmed Roman's explanation of polyploidy in March of 1951, and said that they could not rule out the possibility of gene conversion.[160] Their paper defined with a high level of defensive detail the "safeguards" and "assurance" they had taken against any breeding "accident."[161]

Further investigations enabled Roman to argue that the Mendelian ratios were universally valid. He agreed with Winge and Spiegelman that abnormal tetrads were not respectable but the result of Carl Lindegren's speculative leaps and careless practice. The following year, Donald Hawthorne was admitted to graduate school at the University of Washington, and he resumed his work for Roman to characterize the genetic stock. Along with the Lindegrens' yeasts, Roman had obtained two additional strains from Boris Ephrussi's laboratory during a 1952 sabbatical to Paris. Given the hybrids that could be produced from these few strains, the small yeast collection in Seattle began to grow, headed now in its own direction.[162]

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[159] Herschel Roman, General Correspondence, 1941-1989, (March 28, 1951), Box 1, Folder 5, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.

[160] Roman, who spent a great many years opposing Lindegren's theory, later admitted the 1951 paper was an "important exception to orthodoxy" as the conclusions were eventually vindicated. See Herschel Roman, "Development of Yeast as an Experimental Organism," in *The Molecular Biology of the Yeast Saccharomyces: Life Cycle and Inheritance*, ed. Jeffrey N. Strathern, Elizabeth W. Jones, and James R. Broach (Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press, 1981), 1.

[161] Carl C. Lindegren and Gertrude Lindegren, "Tetraploid *Saccharomyces*," *Journal of General Microbiology* 5, no. 5 (1951): 886.

[162] Hawthorne mapped several yeast genes for fermentation and metal resistance for his dissertation research. His thesis and the resultig publication are: Donald C. Hawthorne, "Chromosome Mapping in Saccharomyces" (PhD diss., University of Washington, 1955);

Physical Allies

Another growing practice of yeast genetics at the start of the 1950s came not from a genetics laboratory but from the Donner Laboratory of Biophysics and Medical Physics at the University of California, Berkeley. There, medical physicist Cornelius Tobias and Raymond Zirkle, visiting professor of radiobiology and biophysics from the University of Chicago, were studying whether the lethal effect of radiation on yeast was due to damage to the nucleus or cytoplasm. To test this, they had obtained cultures of Carl Lindegren's two stable mating type haploid yeasts, as well as Emil Mrak's original diploid. They found that since the haploid and diploid yeasts responded differently, radiation must be affecting hereditary material in the nucleus.[163] They assigned Robert Mortimer, a biophysics graduate student who had come to Berkeley from Canada in 1949, to continue exploring the phenomenon. To do so, he would need yeast genetic techniques then unknown to the Berkeley campus.

Mortimer referred to Carl Lindegren's 1949 book *The Yeast Cell*, but the nearest scientist he could consult about yeast was Edward Tatum, who had returned to Stanford from Yale in 1948. Tatum sent a graduate student over to Berkeley to show Mortimer how to perform yeast tetrad analysis, and after a lengthy preparation of his own dissecting equipment, Mortimer began to radiate his yeast and isolate mutants as the basis of his thesis work.[164]

Donald C. Hawthorne, "The Use of Linear Asci for Chromosome Mapping in Saccharomyces," *Genetics* 40, no. 4 (1955): 511-518.

[163] Raymond E. Zirkle and Cornelius A. Tobias, "Effects of Ploidy and Linear Energy Transfer on Radiobiological Survival Curves," *Archives of Biochemistry and Biophysics* 47, no. 2 (1953): 282-306.

[164] For arranging this, Tobias has been credited with starting yeast research at Berkeley. In Ellie Blakely, Howard Mel, and Robert K. Mortimer, *Cornelius A. Tobias, Biophysics: Berkeley*, ed. University of California History Digital Archives, In Memoriam (Berkeley: University of California, 2000). Mortimer's preparations involved tapering, sharpening and passing current

This was a period in which physicists saw yeast as a convenient tool for measuring and analyzing the quantitative relationships between radiation dose, mutation and death, and when the science of biology was in large part its physics.[165] Over the course of the 1950s, half of all federally-funded genetic research in the U.S. would be supported by the Atomic Energy Commission (AEC) as part of the Cold War build-up of knowledge production in the life and physical sciences.[166] The microbiologist Seymour Pomper had been offered a position conducting yeast radiation studies for the AEC at Oak Ridge National Laboratory in Tennessee after graduating from Yale in 1949. He was the first yeast geneticist at Oak Ridge and resolved to settle the recent confusion over concepts of gene action and interaction, and possible experimental artifacts. His research induced yeast mutations by the use of x-rays, ultraviolet irradiation, nitrogen mustard and other poisons.[167] Pomper left Oak Ridge in 1952 for an eight-month postdoc on yeast gene-controlled enzyme synthesis at Berkeley and then went on to direct Fleischmann Laboratories for Standard Brands.[168]

Mortimer's project at Berkeley on yeast physical genetics had been funded by a state cancer grant to study the "deleterious" effects of radiation. Since 1947, California had appropriated funds for work on "the origin, prevention, and cure of cancer" to the Regents of the

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through a tungsten wire needle for microdissection of the yeast tetrads. In Robert K. Mortimer, Technical Documents, 1950-1999, (undated), Box 1, Folder 5: Logbook #4 Yeast Research, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA. See also Davis, *The Microbial Models of Molecular Biology: From Genes to Genomes*, 70.

[165] Canadian physicist Robert Haynes describes how he "got religion" only much later in the 1950s and early 1960s with the realization that "biology" was more important than the physics of biology. In Haynes, "My Road to Repair in Yeast: The Importance of Being Ignorant," 164.

[166] L.E. Kay, *Who Wrote the Book of Life?: A History of the Genetic Code* (Stanford: Stanford University Press, 2000), 10.

[167] Pomper, "Recent Developments in Yeast Genetics," 17, 20.

[168] In *Research Fellows of the National Cancer Institute*, 658, 82. It was rumored that Pomper mixed all of his old mutants together to produce Fleischmann's yeast found on grocery shelves. In von Borstel, "Taming the Oldest Domesticated Organism," 189.

University of California.[169] Mortimer's research focused on "delay in cell division; a disturbance in chromosome structure, resulting from breaks in chromosomes or chromatids; gene mutations which are most commonly lethal; or a disturbance in cellular physiology such as a change in respiration rate… [or] death."[170] He examined whether yeasts of higher ploidy tended to exhibit greater resistance to radiation exposure, as was predicted, since additional copies of the hereditary material might provide a protective effect. Cornelius Tobias had seen this effect for diploids over haploids in 1952, but it now appeared that he had failed to conclusively establish the borrowed yeast was diploid. Mortimer crossed strains to form yeasts with higher ploidy, including triploids and tetraploids. He found, contrary to expectation, that the yeasts with more copies of each chromosome showed greater sensitivity to the radiation.[171] Mortimer published these results and stayed on as an instructor at Berkeley following his graduation.[172] Further studies established how the mutation could be transmitted across generations.[173]

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[169] California Department of Public Health, *A Chronic Disease Program for California: Report of the California Chronic Disease Investigation* (1949), 182.

[170] Robert K. Mortimer, Technical Documents, 1950-1999, (1953), Box 1, Folder 14: Mortimer Dissertation, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA, 1.

[171] Robert K. Mortimer, "The Relative Radiation Resistance of Haploid, Diploid, Triploid and Tetraploid Yeast Cells," *Atomic Energy Commission Report UCRL* 1922 (1952): 66-78; Robert K. Mortimer, "Cytological and Environmental Factors Related to the Effects of Radiations on Yeast Cells" (PhD diss., University of California, Berkeley, 1953). Tobias' initial claims can be found in Cornelius A. Tobias, "The Dependence of Some Biological Effects of Radiation on the Rate of Energy Loss," in *Symposium on Radiobiology: The Basic Aspects of Radiation Effects on Living Systems*, ed. J.J. Nickson (New York: John Wiley & Sons, 1952), 357-392; Cornelius A. Tobias and B. Stepka, "Mutations to Increased Radiosensitivity in Yeast Cells," *US Atomic Energy Comm. Rept. UCRL-1922* (1952): 40-59.

[172] Mortimer, Technical Documents, 1950-1999, (undated), Box 1, Folder 7: Research #6 [Logbook], Robert K. Mortimer Collection (ARO-5425).

[173] Robert K. Mortimer and Cornelius A. Tobias, "Evidence for X-Ray Induced Recessive Lethal Mutations in Yeast," *Science* 118, no. 3070 (1953): 517-518; Robert K. Mortimer, "Evidence for Two Types of X-Ray-Induced Lethal Damage in Saccharomyces Cerevisiae," *Radiation Research* 2, no. 4 (1955): 361-368; M.E. Owen and Robert K. Mortimer, "Dominant Lethality Induced by X-Rays in Haploid and Diploid Saccharomyces Cerevisiae," (1956); Robert K.

Mortimer's next research project was to study the yeast chromosomes. Since they were small and not available to a cytological approach, he decided to begin a yeast genetic map in the style of *Neurospora*. After a trip to visit Herschel Roman in Seattle, Mortimer learned that Donald Hawthorne, then a postdoc at Caltech, had mapped yeast genes for his dissertation work at the University of Washington. Mortimer arranged a visit to Caltech and proposed that Hawthorne collaborate with him on a map for several yeast nutritional mutants he had isolated. He had hoped to finish the map within a year "but it turned out to be a much bigger job."[174] In retracing and expanding upon the untrusted work that the Lindegrens had started, the two men had much closer ties to Seattle than the investigators in Carbondale who had provided their experimental material.[175] Herschel Roman saw to this personally. Initially, Mortimer failed to keep Roman informed on his progress mapping the yeast chromosomes with Hawthorne, and he was harshly reprimanded. He would never make the same mistake again.[176]

Uncluttering the Historical Stakes

Communication between Sol Spiegelman and the Lindegrens began to unravel in the winter of 1951. The prior summer, they had disagreed about the ability of yeast to oxidize a sugar without being able to ferment it, and Spiegelman offered his strains for Carl Lindegren to

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Mortimer, "Radiobiological and Genetic Studies on a Polyploid Series (Haploid to Hexaploid) of Saccharomyces Cerevisiae," *Radiation research* 9, no. 3 (1958): 312-326. A study out of Ontario at this time found unusual patterns of inheritance induced in irradiated yeast and attributed these to crossing over. See Allen P. James and Brenda Lee-Whiting, "Radiation-Induced Genetic Segregations in Vegetative Cells of Diploid Yeast," *Genetics* 40, no. 6 (1955): 831.

[174] Robert K. Mortimer, "The 2002 George W. Beadle Medal Essay: Why I Developed the Yeast Genetic Map," *Genetics* 164, no. 2 (2003): 424.

[175] Winge, however, may have observed Mortimer's work during a visit to the Berkeley campus over the course of several weeks in November of 1957.

[176] Mortimer, "Some Recollections on Forty Years of Research in Yeast Genetics," 178; Hawthorne, "Saccharomyces Studies, 1950-1960," 118.

reproduce the experiment. He reminded his former mentor to "bear in mind that biological material is relatively complex. Finding a different phenomenon with different material under different circumstances should not surprise us nor should it lead to a set of mutually exclusive contradictory conclusions."[177] The Lindegren laboratory remained in contact that fall and winter, but failed to send their discrepant results and material in turn.[178] After repeated requests, Spiegelman's patience ran out:

> I regret to say we have not received… a comparable account… which has led to the apparent discrepancy. If we are going to straighten this matter out, I think the cooperation should be less one-sided. Unless there is a free flow of information between our laboratories, I don't think it profitable to undertake any cooperative attempt to settle the experimental discrepancy…[179]

He asked one last time for the strain used in the experiments. When it arrived in late March of 1952, he sent it off with his own strain for a third party analysis. The discrepancy came back settled in his favor, but his ties with the Lindegrens were irrevocably damaged.[180]

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[177] See Sol Spiegelman, Series II: Correspondence, 1946-1983, (June 4, 1951), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

[178] Carl C. Lindegren, Series II: Correspondence, 1946-1983, (August 21, 1951), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Balaji D. Mundkur, Series II: Correspondence, 1946-1983, (August 21, 1951), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; A. Leonard Sheffner, Series II: Correspondence, 1946-1983, (December 7, 1951), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

[179] Spiegelman, Series II: Correspondence, 1946-1983, (June 4, 1951), Box 6, Folder 59, Sol Spiegelman collection (MSC 561).

[180] See A. Leonard Sheffner, Series II: Correspondence, 1946-1983, (January 15, 1952), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Sol Spiegelman, Series II: Correspondence, 1946-1983, (April 10, 1952), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Sheffner, Series II: Correspondence, 1946-1983, (January 15, 1952), Box 6, Folder 59, Sol Spiegelman collection (MSC 561); Spiegelman, Series II: Correspondence, 1946-1983, (April 10, 1952), Box 6, Folder 59, Sol Spiegelman collection (MSC 561).

Spiegelman was instead allying himself to Roman in their common cause to use yeast for generalizable knowledge aligned with mainstream genetic practice. In 1951, Spiegelman recommended Roman for a Guggenheim fellowship, claiming, "I can think of no other man who is more likely to unravel the difficulties in this material [yeast] and bring it to a state where he as well as other experimentalists can realize in full the potential value of this material for fundamental investigations into the nature of the gene and of gene action..."[181] Polyploidy had been an important claim, and Spiegelman saw Roman as possessing "a fresh approach uncluttered by subconscious stakes in the historical development of the subject."[182] This next generation of yeast research was not tied to the yeasts' unique agricultural interests. What was fresh in Roman's approach was yeast "fundamentals" to address the universal gene. The "subconscious stakes" of an older generation had shown themselves recently, for example, in the published outbursts by Winge against the Lindegrens. This unfortunate show of emotion seemed almost as detrimental to the field as the Lindegrens' speculations. Roman agreed with Spiegelman that Winge's findings also needed to be questioned on the basis of his "inordinate attachment to the spore-to-spore mating method." They formed a secondary alliance against the "Winge polemic" on long-term adaptation.[183]

In the early 1950s, Roman and Spiegelman accepted polyploidy and mating type mutation as an explanation of the non-Mendelian patterns that the Lindegrens were calling gene conversion. Roman felt that the "the confusion that existed about illegitimate hybridization and

[181] Spiegelman, Series II: Correspondence, 1946-1985, (February 8, 1951), Box 10, Folder 19, Sol Spiegelman collection (MSC 561).
[182] Spiegelman, Series II: Correspondence, 1946-1985, (January 18, 1952), Box 10, Folder 19, Sol Spiegelman collection (MSC 561).
[183] Herschel Roman, Series II: Correspondence, 1946-1985, (April 10, 1952), Box 10, Folder 19, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

about the resulting inviability of spores… was entirely unnecessary and the events can be fully accounted for..."[184] The Lindegrens and Ephrussi both agreed with him, but for different reasons. They suspected some cytoplasmic mutation might account for the odd yeast behavior. At Carlsberg, Winge and Roberts did not observe either phenomenon in their stable, diploid brewer's yeast. Instead, they put forward the theories of crossing-over and the random survival of spores in multi-spore tetrads to account for their observations according to Mendelian patterns of inheritance.[185] In contradictory papers, Carl Lindegren found that mutation and selection in one case accounted for, and in another case did not account for, "the Winge and Roberts' phenomenon" of long-term adaptation.[186]

Given the conceptual differences apparent in the strains of different laboratories, yeasts were circulated with their own kind of intellectual inheritance and spoken of in terms of these laboratory lineages. Their exchange was critical to test alternative explanations. In January of 1953, for example, Spiegelman tried to obtain a yeast strain from the Lindegrens which had shown long-term adaptation, imploring, "I hope you will agree that such a comparative study on different strains is of value, particularly in view of the confusion which has attended the employment of different strains by different laboratories."[187] Carl Lindegren was unmoved and responded that, "my complete personal research program is concentrated exclusively on this project, and I would prefer to hold these strains a little longer until I have polished up some of

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[184] Ibid. See also Herschel Roman and Stanley M Sands, "Heterogeneity of Clones of Saccharomyces Derived from Haploid Ascospores," *Proceedings of the National Academy of Sciences of the United States of America* 39, no. 3 (1953).
[185] Øjvind Winge, "On Interallelic Crossing Over," *Heredity* 9 (1955): 373-384; Roberts, "The Inheritance of Enzymatic Characters in Yeasts," 177.
[186] Claimed in Sol Spiegelman and O. E. Landman, "Genetics of Microorganisms," *Annu Rev Microbiol* 8 (1954): 190-191.
[187] Sol Spiegelman, Series II: Correspondence, 1946-1983, (January 29, 1953), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

the pertinent questions."[188] But his were no longer the questions of yeast genetics, and Carl Lindegren would be left behind.[189]

Changing of the Guard

1955 saw the beginning of a turning point in the controversy over gene conversion when a number of studies began to offer evidence of its occurrence within the microbes. A new yeast study from Carl Lindegren met with relative silence, but after Caltech's Mary Mitchell showed gene conversion in the more established system of *Neurospora* the possibility became more permissible for yeast.[190] Roman thought he had confirmed yeast gene conversion in 1956. He directed Mortimer to prepare a table of his data for use in a presentation at the Cold Spring Harbor Symposium that June which pulled together the past several years of yeast work in Seattle and Berkeley. Roman calculated a more ready reception to this pivotal paper by leaving out the term "gene conversion" in front of his international audience. Instead, he put forward an

[188] Carl C. Lindegren, Series II: Correspondence, 1946-1983, (April 7, 1954), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD; Sol Spiegelman, Series II: Correspondence, 1946-1983, (March 15, 1954), Box 6, Folder 59, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

[189] Occasionally, Carl Lindegren still served as a repository of historic information about the yeasts. Spiegelman, for example, sought to borrow his film, "Life Cycle of a Yeast Cell" for the 1953 Symposium for the British Society of General Microbiology. See Spiegelman, Series II: Correspondence, 1946-1983, (January 29, 1953), Box 6, Folder 59, Sol Spiegelman collection (MSC 561).

[190] Excluding self-citations, Lindegren's 1955 paper was cited 15 times in the 1950s and 6 times in the 1960s; Mitchell's papers were cited a combined total of 55 and 60 times during the same two periods. See Carl C. Lindegren, "Non-Mendelian Segregation in a Single Tetrad of Saccharomyces Ascribed to Gene Conversion," *Science* 121, no. 3147 (1955); Mary B Mitchell, "Aberrant Recombination of Pyridoxine Mutants of Neurospora," *Proceedings of the National Academy of Sciences of the United States of America* 41, no. 4 (1955); Mary B Mitchell, "Further Evidence of Aberrant Recombination in Neurospora," *Proceedings of the National Academy of Sciences of the United States of America* 41, no. 11 (1955).

unnamed description of the phenomena as recombination between elements of the gene ("inter-allelic" rather than mutational as Lindegren had proposed: "degrading the dominant to recessive status"). He opened his results to expert debate and consensus.[191] Roman had been greatly looking forward to the Symposium as an opportunity to introduce Seattle yeast genetics to the wider community.[192] As he wiped the Lindegrens' name from their cause of gene conversion, the phenomena became acceptable as a biological oddity characterizing just several microorganisms. Øjvind Winge retired that same year, and Seattle was positioned as the new American center of yeast genetic research.[193] While the University of Washington lacked the reputation of Europe's longstanding research institutes and private laboratories, it would overtake them in the 1960s as the world's center of yeast genetics in part because of Roman's strategic relationship building in the practice of a new science. While Roman's study is remembered as being well-received at the 1956 meeting because it used "rigorous controls that were so much more convincing than Lindegren's experiments," his consensus-building approach propelled him into a leadership role in the next generation of yeast genetics concerned foremost with the multidisciplinary studies of the gene and not the organism.[194]

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[191] He preferred not to imply a mechanism for the mutation. See Herschel Roman, *Studies of Gene Mutation in Saccharomyces*, vol. 21, Cold Spring Harbor Symposia on Quantitative Biology (Cold Spring Harbor Laboratory Press, 1956), 175-185; Herschel Roman, "Gene Conversion and Crossing-Over," *Environmental Mutagenesis* 7, no. 6 (1985): 923; Gartler and Stadler, "Herschel L. Roman (1914-1989)," 2.

[192] Herschel Roman, Letter to C. Leo Hitchcock, (1956), Box 1, Folder 1-6, Herschel Roman papers (#2955-82-9), University of Washington Libraries Special Collections, Seattle, Washington.

[193] Roman wrote that his "unequivocal demonstration that gene conversion really existed, and neither was due to faulty observation nor could be explained as the result of more orthodox causes [like polyploidy], gave yeast a certain respectability among geneticists." In Roman, "The Early Days of Yeast Genetics: A Personal Narrative," 7. See also the news of Winge's retirement in "Professor Øjvind Winge," *Hereditas* 42, no. 1-2 (1956): iii.

[194] This "rigor" is reported by Rowland Davis, former Caltech postdoc and student of Mary Mitchell, in Davis, *The Microbial Models of Molecular Biology: From Genes to Genomes*, 70.

During the discussion period following Roman's talk, Carl Lindegren commented that for too long Roman had been blinded to the possibility of gene conversion given "his fixed ideas (1) that the gene is a stable entity and (2) that genic variation can only arise from longitudinal discontinuity along the chromosome." Since these ideas were "rapidly disappearing," they would have to reevaluate old assumptions," he claimed.[195] Only later as Roman began to receive multiple acknowledgements of his study as the convincing proof for yeast gene conversion did Carl Lindegren raised the question of priority, and then only in the semi-obscure Swiss journal *Experientia*.[196] His claim was a senseless argument by 1958. Roman's gene conversion provided evidence of a generalizable theory of gene action, while Carl Lindegren's gene conversion was an observation specific to yeast.[197]

The Department in Seattle

In the early postwar years, Roman and Douglas's laboratory at the University of Washington formed a hub for the exchange of genetic concepts and techniques, and Roman was intentional about these interactions. Seattle became the site of frequent genetic seminars and sabbatical visits from various yeast workers, including geneticists, microbiologists, ecologists

[195] Roman, *Studies of Gene Mutation in Saccharomyces*, 21, 183. This eventually transpired, although few heard Lindegren's point at that time.
[196] Roman's 1956 study was cited by others 16 times in the 1950s, and 51 times in the 1960s. In 1958, Carl Lindegren advocated that credit for gene conversion go to Winkler's study of 1930, and his own studies in yeast. In Carl C. Lindegren, "Priority in Gene-Conversion," *Experientia* 14, no. 12 (1958): 444-445.
[197] The generalized theory developed in *Saccharomyces cerevisiae* continues to characterize much of the contemporary understanding of the mechanisms of homologous recombination (the exchange or transfer of information between DNA sequences of perfect or near-perfect homology). Based on yeast studies, "Two general classes of recombination events have been identified… crossing-over and gene conversion." See Lorraine Symington, "Homologous Recombination," in *Landmark Papers in Yeast Biology*, ed. P. Linder, D. Shore and M.N. Hall (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 33.

and taxonomists. After her tenure at the Centraalbureau voor Schimmelcultures, for example, Delft microbiologist Jacomina Lodder spent time in Roman's laboratory learning new methods in yeast genetics which helped support a revised taxonomy of the yeasts.[198] The University of Washington yeast geneticists also frequently traveled to pick up new techniques. Roman visited Ephrussi's laboratory in 1956, and he returned to France on a Fulbright to spend time at the Pasteur Institute as well.[199]

Roman had ambitions to expand genetics beyond the university's current program in the medical school. He received support from the anatomy department and other faculty in botany for a program not tied to existing departmental lines. Early in 1958, he submitted a proposal to the acting dean of the graduate school for a committee that could supervise master's and doctoral training in genetics.[200] The administration responded favorably.[201] They sought examples from other universities and deemed the basic genetics program at the University of Wisconsin-Madison to be a good model. In addition to agriculturally-important organisms, the Wisconsin geneticists, who until quite recently had included Nobel laureate Joshua Lederberg, were also studying bacterial genetics. This included bacterial cell-to-cell sexual reproduction, genetic recombination and viral infection, all of which located bacteria in a "definite place in the scheme

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[198] See Kreger-van Rij, "In Memoriam Dr. Jacomina Lodder," ii.

[199] Boris Ephrussi, General Correspondence, 1941-1989, (June 29, 1955), Box 1, Folder 6, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington. Ephrussi moved much of his laboratory south of Paris to Gif-sur-Yvette in 1956. In Davis, *The Microbial Models of Molecular Biology: From Genes to Genomes*, 72. He would leave yeast genetics two years later in 1958, after being passed over for the Nobel Prize. In Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, 202.

[200] H. Stanley Bennett, W.U. Genetics Dept, (October 22, 1958), Box 6, Folder 1, Herschel Roman papers (#2955-001), University of Washington Libraries Special Collections, Seattle, WA.

[201] Robert H. Williams, W.U. Genetics Dept, (October 24, 1958), Box 6, Folder 1, Herschel Roman papers (#2955-001), University of Washington Libraries Special Collections, Seattle, WA.

of terrestrial life" but did not necessarily have immediate practical intent.[202] It was a program about shared fundamentals.

Based on the Wisconsin model, the Board of Regents of the University of Washington approved a new department of genetics in Seattle with Roman as chair, effective July 1, 1959. The department's mission would be to provide advanced training to undergraduates in biology, medicine, and other fields dealing with human variation, such as anthropology, psychology, and sociology. It would train professionals and specialists in genetics (later conferring graduate degrees), and engage in research. The development was thought to signal an acknowledgement by the administration of genetics' importance to both medicine and general biology.[203] The NIH had recently recognized the same by making available basic research and training funds in genetics, a fact which Roman had pitched to the administration.[204]

That fall, six faculty members, including Herschel Roman, Howard Douglas, and Donald Hawthorne (who had finished his postdoc at Caltech and recently been hired to the botany department in Seattle) moved into the newly-established genetics department. They introduced "physical" genetics to the curriculum at that time to explore the hereditary effects of radiation. According to Roman, physical genetics supplied a "modern approach to the nature and properties

[202] Wisconsin's had been the first university genetics department within the U.S. W.U. Genetics Dept, (November 11, 1958), Box 6, Folder 1, Herschel Roman papers (#2955-001), University of Washington Libraries Special Collections, Seattle, WA. Lederberg, meanwhile, left the genetics faculty in 1957 to establish a medical genetics department at Madison. He was awarded the Nobel for his work on bacterial genetics the following year and moved to Stanford in 1959. In Lederberg, "Joshua Lederberg - Biographical."

[203] University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066), University of Washington Libraries Special Collections, Seattle, Washington.

[204] Herschel Roman, W.U. Genetics Dept, (June 23, 1959), Box 6, Folder 1, Herschel Roman papers (#2955-001), University of Washington Libraries Special Collections, Seattle, WA.

of the hereditary substance."[205] It enabled new funding sources and multidisciplinary collaborations within a community of established scientists, including stronger ties with the Donner Laboratory of Biophysics and Medical Physics at Lawrence Berkeley Laboratory.

Robert Mortimer was on the genetics faculty at Berkeley in 1959, and continued to run yeast experiments in the Donner Laboratory. Once the Seattle department was up and running, he arranged to visit Donald Hawthorne. Mortimer had a new technique to routinize the rapid dissection of asci using the digestive use of snails to break down the yeast cell wall and speed access to the spores, and the two began a study of 70 genes in yeast using tetrad and linkage analyses to build out their map of the chromosomes.[206] By 1960, they had mapped 26 genes to 10 yeast chromosomes.[207] Their publication that year has been praised for reinvigorating the field after a long, perplexing introduction by Øjvind Winge and the Lindegrens.[208] A map of the chromosomes signaled that yeast was well-known, reliable territory for molecular prospecting. The organism had already been made to follow Mendelian rules, but now it became a stable, standard reference for molecular work.[209]

Mortimer continued his efforts on the yeast genetic map for the next four decades. In the early years, he and Hawthorne had justified the collaborative project as developing "to the fullest

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[205] Ibid.
[206] Mortimer, "Some Recollections on Forty Years of Research in Yeast Genetics," 180.
[207] Donald C. Hawthorne and Robert K. Mortimer, "Chromosome Mapping in Saccharomyces: Centromere-Linked Genes," *Genetics* 45, no. 8 (1960): 1108. Roman and Douglas had identified at least five linkage groups by 1953. See Herschel Roman, Series II: Correspondence, 1946-1985, (October 1, 1953), Box 10, Folder 19, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.
[208] Mortimer, "The 2002 George W. Beadle Medal Essay: Why I Developed the Yeast Genetic Map." Such claims reflect how scientists define the field of yeast genetics. See another claim for Winge's primary significance. See "Professor Ojvind Winge: A Profile," *The New Scientist* 8, no. 196 (1960): 463.
[209] More will be said in the next chapter on the transition in molecular biology from organizing *genes* along the chromosomes to the ordering of *molecules* within the gene.

the potentialities of yeast as a genetic organism."[210] It was a goal with great longevity. In 1995, one year before completion of the *Saccharomyces cerevisiae* genome, Mortimer turned the project over to Stanford University's David Botstein for publication of the twelfth edition of the map.[211]

Seattle had had a reputation for excellent yeast research since the 1956 Cold Spring Harbor meeting, and the new department attracted postdocs from the University of London, Asahi Brewery Company in Japan, and the University of California at Berkeley.[212] In its first year of operation, the department also brought in "fourteen persons of national and international repute for seminars and consultations."[213] One of these visitors was Brooklyn College Associate Professor Seymour Fogel, who had known Roman during graduate school at the University of Missouri and who had also studied corn genetics with Lewis Stadler. When Fogel's corn plot was paved over at Brooklyn College, Roman was sympathetic to the plight and invited Fogel to come learn yeast genetics at the University of Washington. Fogel arrived on a U.S. Public Health traineeship. As federal funders expanded their support for research on basic principles tied to general biology and loosely tied to health and medical interests, yeast researchers were less reliant on local industrial or agricultural sponsors. Fogel became a "devout" admirer of Roman,

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[210] This undated justification was likely from 1966. In Mortimer, Technical Documents, 1950-1999, (undated), Box 1, Folder 15: Correspondence 1967-1968, Robert K. Mortimer Collection (ARO-5425).

[211] Mortimer, "The 2002 George W. Beadle Medal Essay: Why I Developed the Yeast Genetic Map," 424.

[212] Herschel Roman, Annual Report No. 1, July 1, 1959 to June 30, 1960, (November 21, 1960), Folder 95-208, UW Genetics Department Records (#VF2395), University of Washington Libraries Special Collections, Seattle, Washington; University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066); David Wilkie, "Early Recollections of Fungal Genetics and the Cytoplasmic Inheritance Controversy," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 261.

[213] Roman, Annual Report No. 1, July 1, 1959 to June 30, 1960, (November 21, 1960), Folder 95-208, UW Genetics Department Records (#VF2395).

later singing with his students the "Gregorian Genetic Chant" in Roman's honor, and hanging a sign on his door that read "Roman is Never Wrong."[214]

Fogel's view of Roman may have been inflated by his encounter with expanding postwar opportunities for basic research in genetics. Indeed, this picture of Roman's character greatly contrasts with the experience of University of Washington graduate Rita Colwell, who completed her PhD in marine biology in Seattle in 1961 and later went on to serve as director of the National Science Foundation (NSF). Colwell had initially hoped to study microbiology at the University of Washington, but she switched out of the department to escape the apparent tension between Herschel Roman and Howard Douglas. Later she recalled, "Herschel Roman was in the department of Genetics on the main campus, and Howard Douglas was slaving. He had a degree in Enology, from UC Davis and he was in the medical school. I went up to see Herschel Roman, and as it turned out Herschel Roman was a very unpleasant, very arrogant person who didn't like women..."[215] Colwell's opinion of Roman is contrasted, however, by that of yeast geneticist Elizabeth Jones, who was the first student to graduate from the new genetics doctoral program in 1964. Jones experienced Roman's attitude toward women in science very differently. She had joined his laboratory specifically to escape the discrimination she encountered in chemistry, a discipline she characterized as being "completely hostile to the presence of women" at that time.

[214] Rochelle Easton Esposito, "Humble Beginnings," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 422; Michael S. Esposito, Michael Freeling, and Philip Spieth, *Seymour Fogel, Genetics: Berkeley*, ed. University of California History Digital Archives, In Memoriam (Berkeley: University of California, 1994).

[215] Colwell believed that Howard Douglas and Herschel Roman hated each other. In G. Wientjes, *Creative Genius in Technology: Mentor Principles from Life Stories of Geniuses and Visionaries of the Singularity* (North America: Lulu Enterprises Incorporated, 2011), 204.

Roman, Jones said, “introduced me to research and provided unfailing encouragement as I joined this most perfect profession.”[216]

Yeast geneticists have celebrated Roman as the early figurehead of their discipline and he has been remembered for establishing yeast science as compatible with broader genetics practice.[217] Roman was founding editor of the *Annual Review of Genetics* and saw that fungal genetics received special attention in the 1967 inaugural issue.[218] The following year he served as president of the Genetics Society of America. Yeast’s significance to the larger discipline only continued to grow from that point. In the 1970s, it became a running joke at yeast meetings to refer to Roman as the field’s “pope,” the implication being that he had once presided over extension of the new genetic dogma into yeast.[219]

A Material Compromise

The second generation of yeast geneticists spent much of the early 1950s retracing their predecessors’ steps to identify points of departure in the experimental material. A similar problem had impacted the group of phage workers at Cold Spring Harbor Laboratory under the direction of German physicist Max Delbrück, and in the mid-1940s Delbrück had resolved the

[216] Elizabeth W. Jones, "Genetic Roots," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 339.
[217] Roman’s colleagues and trainees acknowledged his leadership throughout Hall and Linder, *The Early Days of Yeast Genetics*.
[218] S Emerson, "Fungal Genetics," *Annual Review of Genetics* 1, no. 1 (1967): 201.
[219] “Pope” was a title bestowed on Roman by Giovanni Magni at the yeast geneticists’ 1972 meeting in Italy. For Magni, the yeast community was a “true church” whose saints were Winge and Lindegren. Any researcher over the age of 40 was declared a cardinal. See Gartler and Stadler, "Herschel L. Roman (1914-1989)."; von Borstel, "Taming the Oldest Domesticated Organism," 194.

conflict by singling out for exclusive experimental use a bacterial host and seven “well-behaved” phage to improve the comparability and replicability of the group’s findings.[220]

With its various regional centers in the 1940s and early 1950s, there was no such unilateral decision-making in the disordered field of yeast genetics. After years of controversy, the apparent resolution by consensus had underscored the importance of sharing and specifying genetic stock. Roman’s explanation of gene conversion had elevated yeast’s status as a potentially useful experimental organism for genetics but if it was now to provide generalizable knowledge in biology, the field would have to ensure the comparability of experiments across various laboratories. The new practice needed, not the experimental organism, but the experimental “system,” bounded and well-characterized.[221]

The standard laboratory yeast strain was developed just prior to the June 1956 Cold Spring Harbor Symposium, and like all good hybrids at the end of the industrial yeast breeding era, it recombined the preferred traits of its parents to produce a superior organism. The yeast’s parents in this case were all of the early laboratories of yeast genetics. Later, a story out of Southern Illinois University claimed that each new "recruit" to yeast genetics had gotten their start using the Lindegrens’ strains. Indeed, Carl and Gertrude Lindegren had sent Emil Mrak’s diploid yeast and the two stable mating type haploids derived from it to Herschel Roman at the University of Washington, Seymour Pomper at Yale, Edward Tatum at Stanford, Cornelius Tobias at the University of Berkeley, as well as private companies like Standard Brands and

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[220] “The Phage Treaty” of 1944 helped to establish these rules. See Anderson, "Electron Microscopy of the Phages," 73. See also Creager, *The Life of a Virus: Tobacco Mosaic Virus as an Experimental Model, 1930-1965*, 208.

[221] Hans-Jörg Rheinberger has characterized experimental systems in the science as “device[s] to materialize questions.” In Hans-Jörg Rheinberger, "Experiment, Difference, and Writing: I. Tracing Protein Synthesis," *Studies in History and Philosophy of Science Part A* 23, no. 2 (1992): 309. See also Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube*.

Monsanto Chemical.[222] When Mortimer inherited these strains from Tobias in the early 1950s, he listed in his laboratory notebook the various problems he might try with the yeasts. These included testing inheritance of radiation sensitivity or resistance, and comparing yeast to other fungi. Mortimer was still looking for a reliable means of examining spores at that time, but by March of 1951, he noted that Mrak's diploid showed remarkable radiation resistance.[223] Mortimer was also using the Lindegrens' stable mating type strains to produce hybrids which carried as many of the known yeast genes as possible. In late March of 1956, he crossed two strains differing for ten phenotypes, including mating type, and different nutrients necessary for survival. He analyzed these tetrads and landed on spore S288C, which when grown into a haploid culture exhibited all possible phenotypes in a single strain.[224]

S288C had a minimal number of nutritional requirements and could grow on a variety of culture media. This meant that the mutants derived from it could be readily identified by new nutritional needs.[225] S288C was non-clumpy so that its cells dispersed in liquid culture for ease of mass mating and isolation. It had high spore viability and rare mating-type switching to allow

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[222] Bill Lyons, "Release: Immediate," news release, (Carbondale, Illinois: Southern Illinois University Information Service), August 2, 1963; Lindegren, *The Yeast Cell: Its Genetics and Cytology*, Chapter 19: 13; John G. Kleyn, "Research in Yeasts: Monsanto Chemical Company, St. Louis, Missouri," in *Yeasts: A News Letter for Persons Interested in Yeasts*, ed. E.M. Mrak (1952), 2-3.

[223] Robert K. Mortimer, Technical Documents, 1950-1999, (June 19, 1950), Box 1: Yeast Project 5-2 Logbook, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA, 79; Robert K. Mortimer, Technical Documents, 1950-1999, (March 21, 1951), Box 1: Yeast Project 5-2 Logbook, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA, 68.

[224] He dissected and scored the asci S280 to S297, and found two strains with minimal nutritional requirements which dispersed well in water "but apparently S288C was the better of the two." In Mortimer, "Some Recollections on Forty Years of Research in Yeast Genetics," 176.

[225] Ruth S. Lerner Robert K. Mortimer, and June K. Barr, *Ultraviolet-Induced Biochemical Mutants of Saccharomyces Cerevisiae*, trans. Radiation Laboratory, Biology and Medicine (Berkeley, California: University of California, 1957), 3.

generation of both **a** and **α** mating type strains for use in yeast gene mapping. It was self-sterile to allow for controlled crosses to prevent illegitimate breeding.[226] In short, it offered the hard-won conclusions of every major controversy and well-established practice over the previous twenty-one years of yeast genetics and was thus an ideal "wild-type" system with which to begin deriving mutants in future studies of the gene.

Following publication of the first yeast chromosomal map in 1960, Mortimer began receiving many inquiries for the mutants he and Hawthorne had analyzed. The mutants derived from S288C and were maintained by annual transfer onto fresh media in a collection at Berkeley.[227] Mortimer introduced this resource in Carbondale in 1961 at the First International Conference in Yeast Genetics. Held in a setting meant to honor the Lindegrens' contributions, the meeting was called to set genetic nomenclature rules for the field.[228] It was attended by

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[226] Robert K. Mortimer, Technical Documents, 1950-1999, (1956), Box 1, Folder 10: Research #15 Logbook, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA; Robert K. Mortimer, Technical Documents, 1950-1999, (July 24, 1956), Box 1, Folder 11: Research #16 [Logbook], Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[227] Robert K. Mortimer, Technical Documents, 1950-1999, (October 23, 1967), Box 1, Folder 15: Correspondence 1967-1968, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA. Mortimer described the procedure for reviving yeast strains from the Berkeley collection, which had been shipped on sterile filter paper in a suspension of evaporated milk. See Mortimer, Technical Documents, 1950-1999, (undated), Box 1, Folder 19, Robert K. Mortimer Collection (ARO-5425). This was a slight modification of the method used by Jørgensen at the turn of the twentieth century involving a travelling can closed with a cotton-wool filter. "Such cultures were sent out from the author's laboratory in 1885 for the first time to breweries in tropical counties, and the experiment was completely successful. It is therefore possible to supply breweries, distilleries, &c., in all parts of the world with absolutely pure cultures." Jørgensen and Grey, *Practical Management of Pure Yeast: The Application and Examination of Brewery, Distillery, and Wine, Yeasts*, 41.

[228] These designations had long been recognized as a problem. In one instance, Roman had written to Spiegelman, "the stock that you call 276-X is actually 27L-X. The "X" is Roman numeral 10." In Roman, Series II: Correspondence, 1946-1985, (April 10, 1952), Box 10, Folder 19, Sol Spiegelman collection (MSC 561). In another, Spiegelman wrote to Roman, "with

eleven people, and Roman was conspicuously absent. Mortimer, then Assistant Dean of the University of California, Berkeley College of Letters and Sciences, provided an introduction to what would later become Yeast Genetic Stock Center at Berkeley, and offered to make his strains available to anyone in the community for the price of shipping.[229]

Informal operation of the stock center during the 1960s resulted in the wide distribution of S288C as the standard "wild type" *Saccharomyces cerevisiae*, along with guidance on strain nomenclature and usage.[230] Mortimer fulfilled requests for reprints and circulated the contact information of other investigators.[231] The stock center produced a regular catalog and by 1967, it

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reference to Lindegren's observations, I am afraid that there has been some confusion which stems from my not having been very clear in my early letter. The plus and minus signs which I employed did not refer to mating type but rather to fermenting characters." In Spiegelman, Series II: Correspondence, 1946-1985, (January 18, 1952), Box 10, Folder 19, Sol Spiegelman collection (MSC 561).

[229] Robert Sanders has credited Mortimer for upholding an existing "culture of sharing" in the yeast genetics community. In Robert Sanders, "Memorial for Late Yeast Expert Robert Mortimer," news release, (Berkeley, CA: UC Regents), October 23, 2007. See also the discussion about yeast culture collections in the previous chapter.

[230] Mortimer's letters to enquiring researchers named strain S288C the standard "wild-type." See, for example, Mortimer, Technical Documents, 1950-1999, (March 1, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425); Mortimer, Technical Documents, 1950-1999, (October 23, 1967), Box 1, Folder 15: Correspondence 1967-1968, Robert K. Mortimer Collection (ARO-5425). Microbiologists and biophysicists were also active in helping to standardize the genetic nomenclature. In January of 1970, for example, the *Yeast News Letter* out of Davis informed readers that it was including in the mailing a supplemental issue from the *Microbial Genetics Bulletin*, purchased for them as a courtesy by Dr. R. C. von Borstel of the Oak Ridge National Laboratory. "This supplement proposes a uniform genetic nomenclature for yeast, and include a compilation of the presently known products of a large number of genes of Saccharomyces. Since genetics studies of yeast are progressing rapidly, it is very desirable that some standard nomenclature be used, and the editors therefore urge all readers of YEAST to follow the recommendations in their future communications." In Herman J. Phaff, "Special Note," in *Yeast: A News Letter for Persons Interested in Yeast*, ed. Herman J. Phaff (1970), 3.

[231] See, for example, Technical Documents, 1950-1999, (February 17, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA; Gerald Fink, Technical Documents, 1950-1999, (April 3, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence

was fulfilling close to 50 requests per year with multiple strains per investigator.[232] It was setting standards for the field and had become a central node in the yeast geneticists' international network of exchange.[233]

Mortimer was a member of the Genetics Society Committee on the Maintenance of Genetic Stocks, which in the mid-1960s was concerned with the loss of stock "by accident, retirement, death, grant termination, alienation of the investigator's affection, and the like." California's new governor, Ronald Reagan, had "struck with predictable fury" to jar the foundations of the university, and was pushing for budget cuts. There was not yet a panicked departure of faculty, Mortimer noted in February of 1967, "but if things continue there could be."[234] Moreover, "hippies and diggers" were facing off with the university's "serious scientists" all over campus and it seemed that something would soon erupt.[235] The Committee was considering how to minimize such dangers to its research resources at multiple sites throughout

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Berkeley National Laboratory Archives and Records, Berkeley, CA; Raúl N. Ondarza, Technical Documents, 1950-1999, (May 19, 1967), Box 1, Folder 15: Correspondence 1967-1968, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA. He was also receiving offers for book deals on the yeasts. John Staples, Technical Documents, 1950-1999, (September 28, 1967), Box 1, Folder 15: Correspondence 1967-1968, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[232] Mortimer, Technical Documents, 1950-1999, (March 1, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425).

[233] On the use of standards in biology see Adrian Mackenzie et al., "Classifying, Constructing, and Identifying Life: Standards as Transformations of "the Biological"," *Science, Technology & Human Values* (2013): 1-2. See also Timmermans and Berg's study of medical protocols that proposed an interactive effect of standards with "already existing interests, associations, and practices." This, the authors argued, produces a "local universality" which is essential for standards to operate. Stefan Timmermans and Marc Berg, "Standardization in Action: Achieving Local Universality through Medical Protocols," *Social studies of science* 27, no. 2 (1997): 287.

[234] Mortimer, Technical Documents, 1950-1999, (October 23, 1967), Box 1, Folder 15: Correspondence 1967-1968, Robert K. Mortimer Collection (ARO-5425).

[235] This culture clash was observed by a visiting foreign scientist. In ibid.; R. C. von Borstel, Technical Documents, 1950-1999, (June 15, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

the U.S., and in March of that year, it was deciding whether to consolidate stock "in dependable hands" or let "natural selection" run its course.[236]

Mortimer began to pursue formal funding support for the Berkeley stock center. He argued that unlike the Davis collection and American Type Culture Collection (ATCC), which maintained a variety of species for the purpose of deriving taxonomy, the Berkeley collection offered full "genetic coverage" of the prime industrial organism *Saccharomyces cerevisiae*. NSF granted partial funding for the center in 1971, and from that point forward Mortimer collected statistics on all of the published studies utilizing his strains.[237] By the mid-1970s, the stock center was supporting a curator to manage the 500 strains in its collection. It distributed an average of 127 strains per month.[238] NSF funding reached $114,262 in 1978, at a time when *Saccharomyces cerevisiae* was being "heavily utilized" in studies of enzyme regulation, cell cycle regulation, genetic suppression and genetic recombination.[239] Mortimer argued in NSF renewal applications that he wanted to avoid charging users for access to these strains so as not to "diminish the overall scientific character of the enterprise."[240] Toward the end of the decade, the information generated about the standard reference using cloning and recombinant techniques was "overwhelming," and the stock center was said to serve a critical "informational clearing

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[236] Technical Documents, 1950-1999, (March 9, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.
[237] Mortimer, Technical Documents, 1950-1999, (undated), Box 1, Folder 19, Robert K. Mortimer Collection (ARO-5425).
[238] Robert K. Mortimer, Technical Documents, 1950-1999, (May 1, 1976), Box 1, Folder 21: 189, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.
[239] Robert K. Mortimer, Technical Documents, 1950-1999, (1978), Box 2, Folder 1, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.
[240] Robert K. Mortimer, Technical Documents, 1950-1999, (1977), Box 2, Folder 1, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

house."[241] By 1979, the mailing list for its catalog had reached 500 yeast workers, one-third of whom were from outside the U.S.[242] NSF could not sustain this international network and in 1982 recommended that Mortimer begin charging $10 per strain or $50 for industrial users. He complained about the drop in requests and increased administrative burden.[243] Later, under sponsorship from NIH, the center continued to maintain this fee-based model.

In 1986, Mortimer and colleague John Johnston submitted a pedigree of S288C for publication in *Genetics*. In a "Genealogy of Principal Strains of the Yeast Genetic Stock Center," they traced the strain's descent out of various laboratories. Eighty-eight percent of S288C's gene pool was shared with Emil Mrak's diploid yeast which had been collected from a rotting fig orchard in 1938. This finding suggested that a majority of the wild-type genome was "natural," thus legitimizing extrapolation from this laboratory yeast to other organisms.[244] In 1980, Davis yeast microbiologist Herman Phaff had reported that stable haploid *Saccharomyces cerevisiae*, such as the Lindegren's mating type strains, did not occur in nature.[245] Mortimer, too, distinguished the evolving "natural" strains used in winemaking, and occasionally in baking,

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[241] R. C. von Borstel, Technical Documents, 1950-1999, (1978), Box 2; Folder 1, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA; Mortimer, Technical Documents, 1950-1999, (1977), Box 2, Folder 1, Robert K. Mortimer Collection (ARO-5425).

[242] Robert K. Mortimer, Technical Documents, 1950-1999, (1979), Box 2, Folder 1, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[243] Robert K. Mortimer, Technical Documents, 1950-1999, (1982), Box 2, Folder 1, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[244] Eleven years later, the strain's genome had grown more artificial, and Mortimer lowered his initial estimate of the proportion attributable to Mrak's strain to 85%. In Mortimer, Technical Documents, 1950-1999, (November 13, 1997), Box 5, Folder 16, Robert K. Mortimer Collection (ARO-5425).

[245] *Saccharomyces* were more typically haploids that underwent mating type switching. See von Wettstein, *Molecular Genetics in Yeast: Proceedings of the Alfred Benzon Symposium 16, Copenhagen 15-19, June 1980*, 425-426.

from the commercial strains used by brewers and distillers since the latter, it seemed to him, were not in the evolutionary pool but had been selected and maintained in industrial processes.[246] The diploid ancestor of S288C, however, was like the wine yeasts, "wild," and had therefore been subjected to natural selection.[247] The remaining portion of the S288C genome, "with the omission of many intervening crosses," came from breeding experiments with the Lindegrens' two stable mating type haploids, as well as a hybrid that Donald Hawthorne had derived from still other crosses in the laboratories of Mrak, Tatum, Pomper, the Lindegrens, Roman and Douglas, Ephrussi, and an American commercial yeast used in the long-term adaptation study by Winge and Roberts.[248] Experimental contributions to S288C had been predominantly American and from the universities, but the strain represented European and commercial contributions as well. When Roman reviewed the paper, he found it to be of obvious historical interest. For him, the strain's large number of contributors worked retrospectively to justify its selection and prioritization. He also suggested that knowledge of the strain's origins could be compared against future evolution of the S288C genome.[249] In the 1990s, the distinction between natural and artificial trait variation in yeast was challenged by the decades of S288C's use in the laboratory, and it was argued that "*S. cerevisiae* is essentially a human artefact, maintained in

[246] Mortimer, Technical Documents, 1950-1999, (November 13, 1997), Box 5, Folder 16, Robert K. Mortimer Collection (ARO-5425).
[247] The laboratory and wine yeasts "originated from the same place," according to Mortimer. In Mortimer, Technical Documents, 1950-1999, (1997), Box 5, Folder 19, Robert K. Mortimer Collection (ARO-5425).
[248] Mortimer and Johnston, "Genealogy of Principal Strains of the Yeast Genetic Stock Center."; Donald C. Hawthorne, "The Genetics of Galactose Fermentation in Saccharomyces Hybrids," *CR Trav. Lab. Carlsberg., Ser. Physiol* 26 (1956).
[249] He was concerned with future "dissimilarities that are found experimentally." See Herschel Roman, General Correspondence, 1941-1989, (August 29, 1985), Box 1, Folder 7, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.

domestication."[250] Despite this artificiality, S288C was a natural choice for a standard at mid-century because it included many of the ideals and compromises of the first generation of yeast geneticists. If it had become subsequently "artificial" that was only because it was so widely used.[251]

Following his retirement in 1991, Mortimer went to Florence to study genetics of the wine yeasts. NIH funding for the Berkeley stock center was set to end in September of 1997, and he realized that he should find a new home for his collection which now numbered in the thousands. S288C had been the first eukaryote to have its genome sequenced and published in October of 1996, a project Mortimer had helped lead.[252] He had several options for relocating the yeasts, including Germany, where Karl Dieter Entian was maintaining a collection of single gene disruptions for the European Yeast Genome Sequencing Project. Mortimer had also been contacted by the American Type Culture Collection (ATCC), an organization which he had once opposed "in general" on the grounds that private collections could have "tragic consequences for

[250] This was in part what Mortimer had been trying to address with the 1986 paper. A record of the strain's genealogy would help to assess whether the variation it exhibited was present in the initial breeding stocks or if it had been introduced subsequently in the laboratory. Mortimer and Johnston, "Genealogy of Principal Strains of the Yeast Genetic Stock Center," 35. Quote from John F.T. Spencer and Dorothy M. Spencer, *Yeast Technology*, 31-32. More recently, "evo-devo" scientists have advocated for the introduction of new species to the laboratory since standardized model organisms have become "routinized and genetically entrenched" non-natural examples. See Gerd B. Müller, "Six Memos for Evo-Devo," in *From Embryology to Evo-Devo: A History of Developmental Evolution*, ed. M.D. Laubichler and J. Maienschein (Cambridge: MIT Press), 508-509.

[251] Recently, even geneticists have argued for the contingency of their variables. "In nature, there is no wild type, rather, all phenotypes are quantitative traits… beyond some arbitrarily defined point along a spectrum." They note that the same is true of "disease." In John L. Hartman, Barbara Garvik, and Lee Hartwell, "Principles for the Buffering of Genetic Variation," *Science* 291, no. 5506 (2001): 1001-1004.

[252] From 1984 to 1987, Mortimer assumed the acting directorship for the Human Genome Project at Lawrence Berkeley National Laboratory. See Goffeau et al., "Life with 6000 Genes," 546-567; Stacia R. Engel et al., "The Reference Genome Sequence of Saccharomyces Cerevisiae: Then and Now," *G3: Genes|Genomes|Genetics* 4, no. 3 (2014): 389-398.

future research with this organism."[253] The ATCC now appealed to him as "a creditable place in the USA" which would be able to access NIH grant support if need be, as long as they agreed to a number of conditions for strain maintenance. They did, and Mortimer turned over the strains with a note of nostalgia for the center which had done much to develop yeast genetics from the 1960s.[254] In 2016, according to ATCC's website, frozen ampules of S288C are available for $185 (nonprofit) to $222 (for profit) per order.[255]

The collection of S288C mutants survived many changes in the decades since it had first been established. As practices changed, new justifications were given to rationalize use of a standard. In 1975, for example, amidst growing interest in yeast gene expression studies, the yeast geneticist John Pringle recommended use of the S288C "family of strains" to standardize the "genetic background" against which a given mutation might be expressed. S288C and its mutants could be obtained from the Berkeley collection, he noted, or - since these had already been so widely-disseminated - another yeast worker could provide them as well.[256] Only with the

[253] Robert K. Mortimer, Technical Documents, 1950-1999, (1984), Box 3, Folder 8, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[254] His conditions for the ATCC were: employment of a qualified yeast geneticist, reliable storage, reference to the strains' original designations, separation of the Berkeley collection within their catalog, availability of the catalog on the internet, and the elimination of any Berkeley strains which had been deposited at ATCC by others. In Mortimer, Technical Documents, 1950-1999, (1997), Box 5, Folder 19, Robert K. Mortimer Collection (ARO-5425); S. C. Jong, Technical Documents, 1950-1999, (1997), Box 5, Folder 19, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA; Carol Mimura, Technical Documents, 1950-1999, (1997), Box 5, Folder 19, Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[255] American Type Culture Collection, "*Saccharomyces Cerevisiae* Meyen Ex E.C. Hansen (A.T.C.C.® 204508™)," accessed June 6, 2016, http://www.atcc.org/Products/All/204508.aspx.

[256] Pringle had done a genetics postdoc in Seattle and in 1975 was doing a second postdoc at the Swiss Federal Institute of Technology. John R. Pringle, "Induction, Selection, and Experimental Uses of Temperature-Sensitive and Other Conditional Mutants of Yeast," in *Methods in Cell*

completion of the S288C genome sequencing project did the Berkeley collection close, its mutants replaced by a new bioinformatic standard within emergent postgenomic practices.[257] In the 2000s, the utility of "genetic backgrounds" and "standard genomes" has been called into question for model organisms like S288C.[258] While the species, *Saccharomyces cerevisiae*, with "its large number of mainly small chromosomes (n=16) appears to be an exception amongst the yeasts," S288C appears to be an even greater extreme.[259] One recent study characterized it as a "highly atypical representative of the species."[260] Identification of a number of "heterogeneities" and "detrimental" molecules in this strain pose a problem for its general representativeness and have underscored the challenges of working from any specific genome toward universal principles.[261]

Conclusion

Biology: Yeast Cells, ed. David M. Prescott (San Francisco, CA: Academic Press, Inc., 1975), 238, 251.

[257] Sabina Leonelli and Rachel Ankeny have described the need among several model organism communities for a more formalized and centralized system of specimens in the 1990s. They found that existing stock centers were overwhelmed by the growth of model organism communities during this period into "large conglomerate of researchers with no direct geographical, personal or disciplinary ties." In Leonelli and Ankeny, "Re-Thinking Organisms: The Impact of Databases on Model Organism Biology," 33.

[258] Sabina Leonelli and Rachel Ankeny have also noted this shift, writing that, "model organism research hinges on developing a detailed genetic account of the organism; this characteristic is not an ''in principle'' requirement, but rather one derived from the historical context in which this type of research developed." See Leonelli and Ankeny, "What Makes a Model Organism?," 210-211.

[259] John F.T. Spencer and Dorothy M. Spencer, *Yeast Technology*, 31-32.

[260] Jonas Warringer et al., "Trait Variation in Yeast Is Defined by Population History," *PLoS Genetics* 7, no. 6 (2011): 10.

[261] See, for example, M Gaisne et al., "A 'Natural' Mutation in *Saccharomyces Cerevisiae* Strains Derived from S288c Affects the Complex Regulatory Gene Hap1 (Cyp1)," *Current Genetics* 36, no. 4 (1999): 195-200.

The standard yeast laboratory strain shaped genetics at mid-century as both an object of scientific knowledge and the cultivation of a set of practices. If, as two biologists once wrote, "Mendel used peas. Morgan used *Drosophila*. Delbrück used T4 phages," then an entire yeast genetics community used S288C, for it was the significance of the new community that was established as the result of the strain's breeding and distribution.[262] Robert Mortimer's development of S288C in 1956 signaled the beginning of an agreement among yeast geneticists, not only to the use of shared materials and methods, but to a common purpose found in a shared research agenda, shared theoretical concepts and nomenclature, and a shared sense of their disciplinary history and cultural identity. It was these factors that enabled the perceived successes of model organism research during the same period in which the Yeast Genetic Stock Center operated.[263]

The year 1956 also saw a closure to the gene conversion controversy and the emergence of the University of Washington in Seattle as a strong center of yeast genetics training and research. By the end of the decade, the new genetics department there would garner federal support and international recognition under the direction of Herschel Roman. This would further enable a collaborative, multidisciplinary research practice in pursuit of yeast "fundamentals." The next chapter will examine the justifications given for their practices and the consequences of their approach.

The interests of an older generation of yeast geneticists were passing at mid-century. The industrial foundations and siloed questions of the Winge and Lindegren laboratories limited their investigations to the organism rather than to the gene, or more specifically, to knowledge of

[262] Elizabeth A Kellogg and H Bradley Shaffer, "Model Organisms in Evolutionary Studies," *Systematic Biology* (1993): 409-414.
[263] The next chapter will examine in greater detail the emergence of yeast molecular models.

yeast through genetics rather than knowledge of the genes through yeast. During the 1930s, 1940s, and 1950s, chemists, microbiologists, geneticists, and physicists found a common agenda in establishing the nature of the gene. The early yeast investigators had faced off during these years about experimental breeding approaches, species definitions, and the effects of adaptation and natural selection in yeast evolution. They were contesting the nature of yeast genes but they were also contesting the nature of yeast genetic practice. Would the field fulfill its promise to industry in the production of superior yeasts, or would it break with established practices and received knowledge in order to prevent the settling molecular dogma? Neither, it turned out, would be the future of yeast genetics.

Chapter 3

From Experimental System to Model Eukaryote Organism

Yeast genetics, which had been the esoteric specialty of a small number of laboratories in the 1940s and 1950s, was still a minor contributor to general knowledge about genetic mechanisms at the beginning of the 1960s.[1] Herschel Roman had made yeast a relevant "experimental system" for molecular genetics at the 1956 Cold Spring Harbor Symposium with the closure of the gene conversion controversy, but yeast had nothing like the popularity of *Escherichia coli* (*E. coli)* bacteria at this time. After its establishment in 1959, the genetics department at the University of Washington in Seattle began to act as a hub of exchange between a number of yeast researchers from other disciplines who began to appropriate questions, concepts, and techniques from one another.

This chapter follows the Seattle researchers and their associates as they built up the practice of yeast molecular genetics and navigated the development in the early 1960s of a bacterial model of genetic regulation which appeared to describe the general transfer of hereditary information. Many molecular biologists abandoned the use of bacterial systems at that time, feeling that the limits of microbial genetics had been reached. They began instead to study

[1] Of the early yeast genetics laboratories, Carl and Gertrude Lindegren were still at work in Carbondale, Illinois in 1956. Øjvind Winge retired that year from Carlsberg. See "Professor Øjvind Winge," iii. Boris Ephrussi's yeast research program moved from Paris in 1956 to Gif-sur-Yvette, where the French National Center for Scientific Research (CNRS) had established a new genetics laboratory. In Richard Burian and Jean Gayon, "Genetics after World War II: The Laboratories at Gif," *Cahiers pour l'Histoire du CNRS* 7 (1990); Davis, *The Microbial Models of Molecular Biology: From Genes to Genomes*, 72; Gottfried Schatz, "From "Granules" to Organelles: How Yeast Mitochondria Became Respectable," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 242.

multi-cellular organisms as the next stage of their science.[2] Yeast research provided an important exception. When a study out of Yale indicated a fundamental distinction between yeast and bacterial genetic organization, yeast geneticists began to construct an independent research trajectory for their organism. Over the course of the decade, faculty and trainees at the University of Washington in Seattle began to unify genetic, evolutionary and developmental descriptions of both the organism and the cell in molecular terms. These developments elevated yeast to occupy a special position in molecular research as a model organism for eukaryotic biology. Yeast molecular geneticists leveraged both the specificity of the biochemists and the homology of the microbiologists to make this possible.

Biochemistry of Heredity

In 1959, the Dutch biochemist Albert Jan Kluyver, who had once declared the "unity of biochemistry," stopped to reflect on a guiding principle for study of the microbes.[3] He recalled what the German physiologist Max Rubner had written about the yeasts responsible for alcoholic fermentation in 1913. Rubner had found that despite species' variations, their general physiology was reflective of "the common picture of the whole."[4] To Kluyver, the past several decades had

[2] Michel Morange has claimed that the new regulatory models made molecular biologists confident enough to turn their efforts towards the study of complex organisms and their development. In Morange, "The Transformation of Molecular Biology on Contact with Higher Organisms, 1960-1980: From a Molecular Description to a Molecular Explanation," 370.
[3] Given his general bacteriological work on bacterial growth factors and the vitamins at the Pasteur Institute, André Lwoff has been credited with asserting the biochemical unity of living things in the 1930s. The first chapter of this dissertation offered several earlier and parallel examples out of yeast science. See the claim for Lwoff, that he, "Not quite singlehandedly… established microorganisms as biochemical entities" in Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, 351, 610. See also the declaration from Kluyver and Donker, "Die Einheit in Der Biochemie," 134-190.
[4] Originally, "Die allgemeine Physiologie stellt sich durch die Vergieichung der Naturerscheinungen verschiedener Spezies die Aufgabe, zu gemeinsamen Grundsätzen über die

confirmed the truth of this remark. He asked, "Does one not, time and again, observe that the investigators of higher forms of life deign to descend to studies with one-celled organisms such as bacteria, yeasts, algae, etc., in order there to seek and frequently also to find the answers to their problems?"[5]

The yeasts had repeatedly shown biochemical principles that not only appeared to have generalizable relevance, but had actually defined that relevance for other organisms. This had been true in the early decades of the twentieth century with the findings on bios, growth factors, and the vitamins, as well as in the late nineteenth century with the emergence of enzymatic specificity as a chemical basis for heredity. In the years that followed, the proteins had been accepted then dismissed as the true bearers of heredity, and by 1960, deoxyribonucleic acid (DNA) had been linked to both unity and specificity in biology. Yeast had played a significant role in these biochemical investigations.

For a time, desoxyribonucleic acid, which had been derived from calf thymus, was thought to be characteristic of all animals, while ribonucleic acid, found in "the yeast plant," was known as yeast nucleic acid and thought to be characteristic of all plants.[6] These two kinds of nucleic acid - one in animals and another in plants - had been identified by the 1920s, although the function of each was unknown.[7] In the 1930s, the nucleic acids were distinguished for containing unique chemical molecules and there was increasing evidence that both types were

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Erscheinungen des Lehens zu gelangen. Was lebt, — ist Eins, daher muß trotz der Varianten, welche die einzelnen Spezies vorstellen, in ihrem Leben das gemeinsame Bild des Ganzen sich widerspiegeln." In Max Rubner, *Die Ernährungsphysiologie Der Hefezelle Bei Alkoholischer Gärung* (Leipzig: Verlag von Veit & Comp., 1913), 1.

[5] Kluyver and Kamp, *Albert Jan Kluyver: His Life and Work*, 330.

[6] The early term desoxyribonucleic acid was used interchangeably with deoxyribonucleic acid (or DNA).

[7] See Mortimer, "Some Recollections on Forty Years of Research in Yeast Genetics," 174; Portugal and Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*, 63, 85-86.

universally present in all organisms.[8] Desoxyribonucleic acid appeared in large amounts within the chromosomes, but the reason for this was unknown in the 1930s since the hereditary material was held to consist of protein.[9] In 1944, a bacterial study out of the New York Rockefeller Institute suggested that genes might be made of desoxyribonucleic acid instead of protein and encouraged the continued exploration of the biochemistry of heredity.[10] That same year, physicist Erwin Schrödinger drew upon Max Delbrück's atomic model of heredity to ask the question *What is Life?* and contended that "what we actually see under the microscope as the chromosome… [contains] some kind of code-script [for] the entire pattern of the individual's future development and of its functioning in the mature state."[11] By the end of that decade, a biochemical study of yeast and other species offered the "first example of a comparative study… of both types of nucleic acid derived from the same cell." According to the study's authors, Columbia University biochemists Ernst Vischer, Stephen Zamenhof, and Erwin Chargaff, the ratios of nucleic acid constituents across species revealed "certain striking, but perhaps

[8] The unique RNA base uracil, which differed from the DNA base thymine, had been reported in yeast as early as 1901. See Alberto Ascoli, "Ueber Ein Neues Spaltungsprodukt Des Hefenucleins," *Hoppe-Seyler´s Zeitschrift für physiologische Chemie Hoppe-Seyler´s Zeitschrift für physiologische Chemie* 31, no. 1-2 (1901): 161-214.

[9] It was the proteinacious gene, located on the chromosome, which the physicist Max Delbrück asserted in 1935 consisted of a physical "assemblage of atoms." The original German appears as Timoféeff-Ressovsky, Zimmer, and Delbrück, "ÜBer Die Natur Der Genmutation Und Der Genstruktur," 189-245. See the note on Delbrück's use of the word "Atomverband" in a preface to the English translation. In Phillip R. Sloan and Brandon Fogel, eds., *Creating a Physical Biology: The Three-Man Paper and Early Molecular Biology* (Chicago, Illinois: University of Chicago Press, 2011), 217.

[10] Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III," *The Journal of experimental medicine* 79, no. 2 (1944): 137-158.

[11] According to Schrödinger, "A well-ordered association of atoms, endowed with sufficient resistivity to keep its order permanently, appears to be the only conceivable material structure that offers a variety of possible ('isomeric') arrangements… within a small spatial boundary." In Schrödinger, *What Is Life?: The Physical Aspect of the Living Cell*, 21, 61-62.

meaningless, regularities."[12] Chargaff followed up in 1951 with an explanation for the regularity he had seen across organisms, and suggested that nucleic acid constituents were proportional.[13] Two years later, American biologist James Watson and English physicist Francis Crick used this finding in the development of a helical model of deoxyribonucleic acid with paired bases.[14] According to Watson and Crick, the model had genetic implications because it defined mutation as a physical change in the sequence of bases.[15] The double helix offered a structural symbol with which to make sense of the recent changes to the explanation of biological continuity and change. The sequential order of molecules within the nucleic acids was what gave them functional meaning. Thus, as a summary representation of the principles to date, their model was quickly "rather generally accepted" among yeast microbiologists.[16] After the elucidation of DNA structure, molecular biologists increasingly prioritized genes, chromosomes, and nucleic acids as their research subjects, and demoted proteins as the downstream consequence of hereditary processes. Additional studies would be designed to sort out the order of hereditary operations relating these substances to one another.

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[12] Ernst Vischer, Stephen Zamenhof, and Erwin Chargaff, "Microbial Nucleic Acids: The Desoxypentose Nucleic Acids of Avian Tubercle Bacilli and Yeast," *Journal of Biological Chemistry* 177, no. 1 (1949): 436-437.

[13] In a publication on salmon sperm nucleic acids, Chargaff along with biochemistry trainees Rakoma Lipshitz, Charlotte Green, and Marion Hodes questioned whether the equivalences across species might be "an expression of certain structural principles." See Erwin Chargaff et al., "The Composition of the Deoxyribonucleic Acid of Salmon Sperm," *J. Biol. Chem* 192, no. 1 (1951): 229.

[14] James D Watson and Francis HC Crick, "Molecular Structure of Nucleic Acids," *Nature* 171, no. 4356 (1953): 737-738; Portugal and Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*, 201-202.

[15] James D. Watson and Francis H. C. Crick, "Genetical Implications of the Structure of Deoxyribonucleic Acid," *Nature* 171, no. 4361 (1953): 964-967. Watson and Crick, together with Maurice Wilkins were awarded the 1962 Nobel Prize in Physiology or Medicine for this work on the discoveries of the hereditary function and molecular structure of nucleic acids. See Francis Crick, "Nobel Lecture: On the Genetic Code," in *Nobel Lectures, Physiology or Medicine 1942-1962* (Amsterdam: Elsevier Publishing Company, 1962).

[16] Spiegelman and Landman, "Genetics of Microorganisms," 216.

Yeast had been helpful in several biochemical investigations of the heredity material, but the organism was not yet developed as a source for generalizable genetic investigations at mid-century. The American yeast geneticists Carl and Gertrude Lindegren insisted on the uniqueness of yeast inheritance. Over the following decades, the relationships developed through the genetics department at the University of Washington in Seattle to microbiologists, biochemists, and biophysicists investigating yeast molecular processes enabled a collective prioritization of the organism for generalizable study. The practice of relating yeast genes to other biochemical and physiological processes of the organism in terms of molecular structures and functions came to be understood as yeast molecular biology.

Generalizing Genetic Mechanisms

Despite the generalizability of yeast biochemistry, yeast prior to 1956 was not trusted as a source of universal genetic principles. After breaking his association with the yeast geneticists Carl and Gertrude Lindegren, for example, microbiologist Sol Spiegelman together with a colleague in the department of bacteriology at the University of Illinois, in Urbana, had reviewed the range of experimental phenomena that could be observed in yeast genetics depending on one's selection of material. Despite the apparent inconstancy of yeast behavior, they believed that yeast studies ought to generalize about "fundamental" biology. "From its inception microbial genetics has held out the hope of providing information relevant to the problem of gene function in terms of mechanisms interpretable at the enzymatic and biochemical level," the authors wrote in 1954. The studies they reviewed showed a "wide range in autonomy of the systems determining the expression of phenotype," and these genetic findings did not always

agree. Geneticists, however, were expected to "ultimately find explanation in a unified theory of gene function."[17]

This was two years before Herschel Roman offered closure to the gene conversion controversy in yeast, and geneticists did not yet have a standard experimental material from which to observe genetic principles that might have relevance to other organisms. Biological findings in yeast often required confirmation in another more established organism. In a 1955 paper delivered at a symposium of the U.S. National Research Council and Armed Forces Quartermaster Food and Container Institute, for example, Spiegelman contemplated that either DNA or RNA must be responsible for protein synthesis, given evidence from yeast and other organisms.[18] The following year the answer appeared to be DNA when a study of sickle-cell anemia showed a genetic mutation in humans altered the biochemical structure of the hemoglobin protein.[19] Spiegelman had been invited to the 1955 symposium to speak on "Yeast, Its Characteristics, Growth and Function in Baked Products" to evaluate yeasts' leavening abilities and thermostability when dehydrated.[20] Since active dry yeast was a critical ingredient in the Army's baking operations, the Institute had a specific interest in yeast storage under

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[17] Ibid., 195.

[18] Sol Spiegelman, Series V: Professional Activities, 1945-1982 / Meetings, Symposia, Conferences, 1945-1981, (June 22, 1955), Box 66, Folder 38, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD. Herschel Roman had written Spiegelman about the research of the Quartermaster in 1951, noting to his delight that they supported studies on yeast adaptation. "This is an unexpected, very pleasant surprise; I didn't think that government laboratories permitted as much flexibility," he wrote. In Roman, Series II: Correspondence, 1946-1985, (January 30, 1951), Box 10, Folder 19, Sol Spiegelman collection (MSC 561).

[19] V.M. Ingram, "A Specific Chemical Difference between the Globins of Normal Human and Sickle-Cell Anæmia Hæmoglobin," *Nature* 178, no. 4537 (1956): 792-794; R.P. Wagner and H.K. Mitchell, *Genetics and Metabolism* (New York: J. Wiley, 1964), 12.

[20] Chas McWilliams, Series V: Professional Activities, 1945-1982 / Meetings, Symposia, Conferences, 1945-1981, (March 23, 1955), Box 66, Folder 38, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD.

elevated temperatures.[21] The research had been funded by the U.S. Office of Naval Research, Standard Brands' Fleischmann Laboratories, and the U.S. Public Health Service Cancer Institute – the latter since the enzymatic processes which had relevance for yeast storage and baked products were also believed to have relevance for human cancer. Although yeast's genetic principles were not generalizable for theory-making, the organism still attracted cancer research funding on the basis of shared biochemistry of the cell. These conclusions could not be overextended, however, and wherever findings proved not replicable in other organisms, they became unique to yeast. For example, when it was shown that the amount of nitrogen in yeast differed from that in bacteria, it was hypothesized that nitrogen was required uniquely for yeast enzymatic synthesis.[22]

After 1956 yeast appeared more acceptable for use in generalizing hereditary mechanisms and was considered to be not all that different from other fungi or bacteria. That the nucleic acids appeared in the cells of all organisms meant that they could be studied in a variety of contexts by whatever conditions proved most conducive to the investigation. Yeast was commonly a source of experimental confirmation. In a study out of Stanford University in 1957,

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[21] W. George Parks, Series V: Professional Activities, 1945-1982 / Meetings, Symposia, Conferences, 1945-1981, (May 31, 1955), Box 66, Folder 38, Sol Spiegelman collection (MSC 561), National Library of Medicine History of Medicine Division Modern Manuscripts Collection, Bethesda, MD. Yeast temperature sensitivity and the engineering of high temperature-tolerant strains have again come under study, more recently as a response to rising global temperatures and predicted climate change. See a description of this work in D. Barry Starr, "If Yeast Can't Stand the Heat, Our World May Be in Trouble," accessed October 23, 2015, yeastgenome.org. In terms of the elevated temperatures which many have been of interest in 1955, the U.S. was conducting military operations off the coast of mainland China, and had begun sending advisors into the tropical climate of South Vietnam in 1954. See Richard F. Grimmett, "Instances of Use of United States Armed Forces Abroad, 1798 - 2004," ed. Defense Foreign Affairs, and Trade Division (Washington, D.C.: Congressional Research Service, Library of Congress, 2004); Michael Green, *Armoured Warfare in the Vietnam War: Rare Photographs from Wartime Archives* (Pen & Sword Books Limited, 2014), 11.

[22] Spiegelman, Series V: Professional Activities, 1945-1982 / Meetings, Symposia, Conferences, 1945-1981, (June 22, 1955), Box 66, Folder 38, Sol Spiegelman collection (MSC 561).

for example, the biochemist Fu-Chuan Chao described the RNA content of yeast protein synthesizing ribosomes as characteristic "perhaps in all living cells" due to similar observations in *Neurospora* and mammalian tissues.[23]

The following year at a meeting of the Society for Experimental Biology in London, the English physicist Francis Crick offered a picture of the gene as an informational molecule and explained that "once 'information' has passed into protein it cannot get out again."[24] In this "central dogma" of molecular biology, Crick related molecular sequence to biological specificity. Once this molecular and sequential "information" was ciphered, it was believed that all specificity – and species – followed from it. Crick's talk was a call for the organism to come second to what was now "central" in biology.[25] Organisms were readily interchangeable because pursuit of a universal genetic code supported the use of generalizations from any experimental system that could yield them.

In 1960, newly-synthesized yeast RNA was found to match the base ratios of yeast DNA and was held to indicate that, in general, RNA might help to transfer nuclear information prior to

[23] Fu-Chuan Chao, "Dissociation of Macromolecular Ribonucleoprotein of Yeast," *Archives of biochemistry and biophysics* 70, no. 2 (1957): 426.
[24] In F. H. C. Crick, "On Protein Synthesis," *Symp. Soc. Exp. Biol.* 12 (1958): 153. In an article later revisiting the central dogma, Crick again negatively defined the transfer of hereditary information in terms of the direction it could *not* flow: "sequential information… cannot be transferred from protein to either protein or nucleic acid." In Francis Crick, "Central Dogma of Molecular Biology," *Nature* 227, no. 5258 (1970): 561.
[25] Hannah Landecker has written about the rise and fall and reappearance of the cell as the central biological actor of the twentieth century. As DNA came to the fore, the cell, its species of origin, its noncoding constituents, and nuances of behavior, became less relevant and even uninteresting. Of its recent reappearance in biology, Landecker writes, "After decades of attention to other biological entities, particularly The Gene, such a return to the livelier, complex, and indeed entirely more personable entity of the cell seems refreshing." In Landecker, *Culturing Life: How Cells Became Technologies*, 6.

protein synthesis.[26] That year, at the University of Illinois, Sol Spiegelman, together with a new instructor of physiological chemistry, Benjamin Hall, developed a procedure for DNA-RNA hybridization with *E. coli*-T2 phage and hypothesized that a template supported the transfer of information from DNA into RNA.[27] This was the first step of the central dogma, and it offered sequentially-ordered molecules as the mechanism for biological specificity. On the basis of this work, Herschel Roman recruited Hall to the genetics faculty at the University of Washington in Seattle, at first to continue working on bacterial systems.

Seattle yeast geneticist Donald Hawthorne continued collaborating with Berkeley biophysicist Robert Mortimer at this time, after their publication of the first yeast genetic map in 1960. Early in the decade, their studies used yeast in a confirmatory role to generalize what had been seen in other well-established organisms of experimental genetics. In 1963, for example, they demonstrated that like *Drosophila*, *Neurospora*, and *E. coli*, the yeast *Saccharomyces cerevisiae* contained super-suppressor genes that could "suppress the mutant phenotype" and "restore the normal character" at multiple gene loci.[28] Roman recalled that the Seattle-Berkeley experiments "were taken as an illustration of the universality of the genetic code."[29] Their findings also reflected the standardization of their experimental material since Hawthorne and

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[26] Martynas Yčas and W. S. Vincent, "A Ribonucleic Acid Fraction from Yeast Related in Composition to Desoxyribonucleic Acid," *Proceedings of the National Academy of Sciences of the United States of America* 46, no. 6 (1960). See also Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, 436, 442.

[27] This tool became embedded in later practices and technologies of molecular biology including Southern blotting, DNA microarrays, and genome sequencing. The hypothesized "template" was later identified as messenger RNA. See Susie Fisher, "Not Just "a Clever Way to Detect Whether DNA Really Made RNA"1: The invention of DNA–RNA Hybridization and Its Outcome," *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 53 (2015): 40, 46, 47.

[28] D. C. Hawthorne and R. K. Mortimer, "Super-Suppressors in Yeast," *Genetics* 48, no. 4 (1963): 617-620.

[29] Roman, "Development of Yeast as an Experimental Organism," 6.

Mortimer had been identifying yeast mutants which behaved like the wild-type. The closer a hybridized yeast could emulate the standard strain S288C by suppressing its abnormal loss of nutrition requirements, the more genetic control elements there appeared to be in yeast for restoring wild-type character. Wild-type was of course neither "normal" nor "wild," and had not originated with "nature's" desire to minimize strains' nutritional needs. These had been engineering choices later naturalized in the production of the standard strain, and Mortimer had been the very person responsible for its development. But as yeast increasingly paralleled the findings of other organisms with a focus on the specific activity of super-suppressor genes rather than their implications, "nature's" desire to compensate for the apparently non-adaptive aberrations was readily reinforced.

At the University of Washington in Seattle, the separation of trainees into medical and nonmedical genetics was an "arbitrary" designation at the start of the 1960s. According to genetics department chair Herschel Roman, the different training programs corresponded only to the use of different experimental material.[30] This sentiment reflected a belief in the biochemical unity of life and that biological fundamentals derived from various experimental systems would eventually yield applications for human diseases. As the world's leading center of yeast genetics training during this period, yeast had particular significance in Seattle but other training programs sought to integrate bacterial fundamentals and higher organism genetics. Both human and microbial genetics were part of the general coursework in Seattle. While the yeast course, "Biology 552" was one of the first courses of its kind in the country "to acquaint students with the ideas and techniques of microbial genetics," the course "Problems in Human Genetics" was

[30] W.U. Genetics Dept, (February 1, 1961), Box 6, Folder 6, Herschel Roman papers (#2955-001), University of Washington Libraries Special Collections, Seattle, WA.

introduced in 1962.[31] One major "problem" in human genetics was lack of experimental access to the human chromosomes, which were "often neglected or inadequately covered," according to Alfred Sturtevant and George Beadle. They were drawing a comparison to their work on *Drosophila* chromosomes some thirty years earlier, but they noted that microbial genetics and DNA now often took precedence.[32] This was the period in which the University of Washington changed the title of its "Biochemical Genetics" course title to "Gene Action," making it at once more focused on the generalizable gene and its function, rather than an experimental method applied to particular species.[33] DNA and RNA were fast becoming the "dominant interest of biological science."[34] Roman believed that the yeast chromosomal mapping research might reveal general mechanisms with implications for human variation. Since human geneticists could not subject their organism to the same mutation and breeding experiments as they could other species, the department trained them in social science perspectives on the variation observed for populations. Students in microbial genetics completed coursework in botany, zoology, anatomy, mathematics, physics, biology, chemistry, biochemistry, and microbiology, while their counterparts in human genetics received additional training in anthropology, as well as in physiology, pathology, pharmacology, medicine and public health.[35]

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[31] Roman, W.U. Genetics Dept, (June 23, 1959), Box 6, Folder 1, Herschel Roman papers (#2955-001); W.U. Genetics Dept, (May, 1970), Box 6, Folder 1, Herschel Roman papers (#2955-001), University of Washington Libraries Special Collections, Seattle, WA.
[32] A. H. Sturtevant and George Wells Beadle, *An Introduction to Genetics* (Philadelphia: W.B. Saunders Co., 1962), 10. Beadle's more recent contributions in *Neurospora* had contributed to this elevation of bacterial systems in biochemical genetics.
[33] W.U. Genetics Dept, (May, 1970), Box 6, Folder 1, Herschel Roman papers (#2955-001).
[34] As described in Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."
[35] Roman, W.U. Genetics Dept, (June 23, 1959), Box 6, Folder 1, Herschel Roman papers (#2955-001). "Population Genetics" was added as a course in 1966. See W.U. Genetics Dept, (May, 1970), Box 6, Folder 1, Herschel Roman papers (#2955-001).

The conceptual integration of microbial and human genetics looked convincingly promising to the National Institutes of Health (NIH), and Roman continued to secure access to human health-related funding for work in yeast in the early 1960s.[36] This was a different rationale than the shared biochemistry and physiology of the cell which yeast researchers such as Carl Lindegren and Robert Mortimer had used to obtain cancer funding from other sources. NIH's support for fundamental research was grounded at that time in the notion of "molecular disease."[37] In 1963, the year that Roman began a four-year term as chair of the NIH Genetics Training Committee, his university was awarded a $2.5 million Health Research Facilities Grant from the NIH for the construction of Biochemistry and Genetics facility.[38] NIH funding for his own yeast research continued to be renewed for more than thirty years.[39]

Development of a Molecular Taxonomy

Just prior to the elucidation of the DNA structure, Delft microbiologists Jacomina Lodder and Nelly Jeanne Wilhelmina Kreger-van Rij had revised their biochemical yeast taxonomy of the late 1930s by adding metabolic tests for species identification.[40] When the revised

[36] Roman's *Saccharomyces* studies with Howard Douglas and Donald Hawthorne had been funded by NIH from the early 1950s. In Hawthorne, "Saccharomyces Studies, 1950-1960," 109-124. Jan Sapp has suggested that NIH funded microbial mutation research in this early period to address the problem of antibiotic resistance. See Sapp, *Genesis: The Evolution of Biology*, 168.
[37] Sickle cell anemia had provided this template. See L. Pauling, H. A. Itano, and et al., "Sickle Cell Anemia a Molecular Disease," *Science* 110, no. 2865 (1949): 543-548.
[38] W.U. Genetics Dept, (1969), Box 6, Folder 1, Herschel Roman papers (#2955-001), University of Washington Libraries Special Collections, Seattle, WA; Herschel Roman, Annual Report No. 4, July 1, 1962 to June 30, 1963, (July 16, 1963), Folder 95-208, UW Genetics Department Records (#VF2395), University of Washington Libraries Special Collections, Seattle, Washington.
[39] Grant Files, (October/November, 1984), Box 4, Folder 5, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.
[40] Lodder and Kreger-van Rij, *The Yeasts: A Taxonomic Study*. This text remains in print as a three-volume series. The fully-revised fifth edition was published in 2011.

classificatory scheme was published in 1952, it was widely adopted although with some criticism. These complaints reveal some of the competing interests for species' definitions in a moment which lacked an established molecular order.[41]

Fleischmann Laboratories found fault with the revised taxonomy's limited use of growth factor requirements as a means of differentiating industrial strains. These criteria would have been useful in their development of vitamin-enriched products.[42] U.S. Department of Agriculture (USDA) chemist Lynferd Wickerham hoped to "correct" the taxonomy by referencing phylogenetic classificatory criteria. Wickerham had recently begun a yeast collection for the USDA Northern Regional Research Laboratory in Illinois, and he criticized Lodder and Kreger-van Rij's taxonomy on the basis that only the "true relationships" found in nature could yield new industrial uses for wild yeasts. He placed several yeast species in "evolutionary sequence" by comparing the cell-type distribution of their various cultures. He presumed that diploid cultures, such as those found predominantly in the breweries, were the "most recent" evolutionarily while haploid cultures were the "most ancient."[43] This presumption could be

[41] Soraya de Chadarevian has critiqued histories of molecular biology which would locate the field's origins in elucidation of the structure of DNA. In Soraya de Chadarevian, *Designs for Life: Molecular Biology after World War II* (New York: Cambridge University Press, 2002), 165-170. For some examples of how the early historiography of molecular biology has defined its subject see Allen, *Life Science in the Twentieth Century*, 148; Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, 30, 47, 70, 202; Judson, "Reflections on the Historiography of Molecular Biology," 376; Olby, *The Path to the Double Helix: The Discovery of DNA*, 439-440. Here I refer to the double helix model not as *cause* for a molecular taxonomy of the yeasts, but rather as a point of reference - a "cultural icon" as de Chadarevian puts it - for the specificity sought for the yeasts in the latter part of the 1950s and 1960s.

[42] Alfred S. Schultz, "The Yeasts: A Taxonomic Study. Review.," *Science* 117, no. 3035 (1953): 237.

[43] Wickerham's phylogenetic criteria arranged species "in the order of increasing numbers of the diploid cells and of decreasing numbers of the haploid cells which exist together in growing cultures." In Wickerham, *Taxonomy of Yeasts*, i. His review of Lodder's taxonomic text can be found in L. J. Wickerham, "Recent Advances in the Taxonomy of Yeasts," *Annual Review of Microbiology* 6, no. 1 (1952): 330.

based on “unnatural” intervention of the yeast industrialists, disrupting “nature’s” ancient preferences for selection with their own.

These criticisms of the 1952 yeast taxonomy reflected a preference for chemical and phylogenetic criteria to differentiate industrially-useful species. Lodder traveled to the U.S. for three months in 1956 to study with Wickerham in Illinois. She made a favorable impression on him, but according to a Delft colleague, she later became “reluctant to express an opinion [o]n phylogenetic theories.”[44] Instead, biological specificity in the yeasts would come to be defined in the order of molecules. Lodder planned to spend a week in July on the University of California, Davis campus with food technologist and former Delft trainee Herman Phaff, whose division maintained its own collection of the yeasts along with many industrial contacts.[45] She also went to study with Herschel Roman at the University of Washington in Seattle to learn what yeast genetics could offer her taxonomic studies of the organism. She returned to Delft to apply the genetic approaches she had learned to the study of new yeast species. When the next edition of the taxonomy was released in 1970 with the help of thirteen contributors under Lodder’s editorship, it merged older species categories to describe 349 yeast species by their “DNA base composition.”[46] This measure was valued for its descriptive accuracy but proved difficult to

[44] Wickerham claimed to have been impressed by Lodder’s “very pleasant ways,” “ready grasp of our concepts and procedures” and “clear, analytical consideration” of genetic problems. To mark the end of her visit, Wickerham arranged to celebrate “Lodder Day” – a full day of talks and demonstrations on yeast taxonomy followed by films and slides of Holland. In *Yeasts: A News Letter for Persons Interested in Yeast*, ed. Herman J. Phaff, vol. V (1956), 12. Wickerham later became an author for the second edition of the yeast taxonomy text which Lodder was editing. He planned a trip to Europe in the summer of 1966 to meet with the other authors. See "Mycologists Travelling Abroad," in *Mycological Society of America Newsletter*, ed. Richard P. Korf and Apolinar Sánchez (1966), 21. See also Kreger-van Rij, "In Memoriam Dr. Jacomina Lodder," iii.

[45] *Yeasts: A News Letter for Persons Interested in Yeast*, V, 15.

[46] Jacomina Lodder, *The Yeasts: A Taxonomic Study* (North-Holland Pub. Co., 1970), 7; Marc-André Lachance, "Yeast Biodiversity: How Many and How Much?," in *Biodiversity and*

implement for routine practice in the 1970s.[47] By that point, the criteria for species' differences had become as much about shared evolution between groups of organisms as it was about the specificity which distinguished them.

The yeast ecologist Herman Phaff complained about the molecular displacement of organismal biology at the University of California at Davis at the end of the 1960s. This transformation had meant the end of his yeast course in the Food Science Department and its transfer to Bacteriology in 1969 as a relic of basic microbiology. The transition away from whole-organism biology was a trend that continued at other universities as well.[48] Three years earlier, Phaff had written with his fellow yeast microbiologists in Food Science, then-university chancellor Emil Mrak and Martin Miller that, "most biologists and biochemists have little familiarity with the vast array of yeast species known today and with their fascinating diversity in metabolic, biochemical, nutritional, and genetic properties."[49] By the end of the decade it was

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Ecophysiology of Yeasts (Springer, 2006), 4; Herman J. Phaff, "New Books," in *Yeast: A News Letter for Persons Interested in Yeast*, ed. Herman J. Phaff (International Commission on Yeast and Yeast-like Microorganisms of the International Association of Microbiological Societies (IAMS), 1974), 75. The Yeast News Letter had undergone a subtle name change since its founding in 1950 as "Yeasts: A News Letter for Persons Interested in Yeasts." During that decade, under ecologist Herman Phaff's editorship at the University of California, Davis, the title became "Yeast: A News Letter for Persons Interested in Yeast", reflecting increasing consolidation in the field. The secondary title changed in September of 1953, and the header changed in May 1958 - slipped back into plural for two editions - and then remaining "Yeast" permanently from November of 1959.

[47] J. M. Belin, "Identification of Yeasts and Yeastlike Fungi. I. Taxonomy and Characteristics of New Species Described since 1973," *Canadian Journal of Microbiology* 27, no. 12 (1981): 1235.

[48] In 1995, Phaff predicted, "because of the rapidly growing interest in the broad aspects of biodiversity, one may hope that the teaching of organismic microbiology will make a come-back at universities." In Phaff, "Life with Yeasts During Retirement," 432; Phaff, "My Life with Yeasts," 20.

[49] Phaff, Miller, and Mrak, *The Life of Yeasts: Their Nature, Activity, Ecology, and Relation to Mankind*, v. This critique has continued to the contemporary use of high-throughput screening technologies used to sort microorganisms for new industrial uses.

clear that the determination of species' relationships by these criteria appeared less significant than the relationships between molecules which had come to define species.[50]

Homology in Microbiology

The years between the mid-1950s and 1970 which witnessed a revised molecular taxonomy of the yeasts were filled equally with the reverse influence of general microbiology upon genetic practice. In particular, yeast geneticists came to adopt the microbiologist's evolutionary homology. In 1955, Albert Jan Kluyver's student, the Delft microbiologist Cornelis van Niel thought that:

> [T]he microbiologist can take heart from the knowledge that the material he deals with represents life in a relatively simple form and can often be investigated under conditions far more favourable than those needed for similar studies on higher plants and animals, while yet the fundamental principles he may discover by his efforts will be applicable to all living organisms.[51]

The following year, an end to the gene conversion controversy in yeast, consolidation of yeast genetics training in Seattle, and the development of a shared experimental material with a precise genetic background – "well-defined" but also well-negotiated – meant that the organism could be used to derive fundamental principles that were hereditary as well as chemical. Molecular principles could be extrapolated from yeast to all organisms.

The Darwinian theory of natural selection had posited a common evolutionary ancestor for all of life, and, since at some point in both individual development and species evolution

[50] The molecular taxonomy resulted in its own set of classificatory uncertainties. In 1979, for example, Ruhr University Bochum scientists Ulf Stahl and Karl Esser recommended continued physiological testing for species diagnosis since single biochemical gene mutations might appear as different species but did not justify this status. In U Stahl and K Esser, "Inconsistency in the Species Concept for Yeasts Due to Mutations During Vegetative Growth," *European Journal of Applied Microbiology and Biotechnology* 8, no. 4 (1979): 271.

[51] C. B. Van Niel, "Natural Selection in the Microbial World: The Second Marjory Stephenson Memorial Lecture," *Microbiology* 13, no. 2 (1955): 216. van Niel had moved to the U.S. in 1928 to continue general studies of bacteria for Stanford University's Hopkins Marine Station.

every organism originated as a simple, single cell, shared structures and functions found in the cells of complex organisms could be termed "homologies." The concept of biological homology had predated even Charles Darwin's investigations, however, and was a term used in the 1840s to describe the perceived structural similarities between organisms.[52] Darwin had used homological evidence of this sort to argue for his theory of common descent. In a reversal of this logic, the acceptance of Darwinian theory entailed the acceptance of common descent as an explanation for newly observed biological homologies. Homology had proven Darwinian theory, but Darwinian theory came to explain homology.[53] Following Darwin, biologists such as England's Thomas Henry Huxley began to describe a shared physical substance that could undergo transformations into "humanity" and that formed the basis of life even for the yeasts.[54]

Microbes were unique for their ability to allow simultaneous experimental access into the organism *in vivo*, and into the cell *in vitro*. They could be studied on the organism level, as dynamic whole-systems, or as single cells, representing the basic units of life. Delft botanist

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[52] Richard Owen's text from this period reads: "In extending our Anatomical comparisons, we cannot fail to be struck with the close general resemblance of the structure of the lower animal with that of Man: almost every part of the Human frame has its homologue in some inferior animal… [Rather than seeking unity from biological organization, we] must go further, and in a different direction, to gain a view of the beautiful and fruitful physiological principle of the relation of each adaptation to its appropriate function, and if we would avoid the danger of mistaking analogy for homology or identity, and of attributing to inadequate hypothetical secondary causes the manifestations of Design, of supreme Wisdom and Beneficence, which the various forms of the Animal Creation offer to our contemplation." In Richard Owen, *Lectures on the Comparative Anatomy and Physiology of the Vertebrate Animals*, vol. II, Hunterian Lectures (London: Longman, Brown, Green, & Longmans, 1846), 2, 146.

[53] "The acceptance of evolution led to the idea that homology should be defined by common ancestry, and to the confusion between definition and explanation." In A. L. Panchen, "Homology--History of a Concept," *Novartis Found Symp* 222 (1999): 5-23. The fact that homologies are both theoretical and "robust descriptive phenomena" poses no threat to the legitimacy of Darwinian theory since "scientific work is at least as much about creating new phenomena as it is about creating theories that explain phenomena." In Paul E. Griffiths, "The Phenomena of Homology," *Biology & Philosophy* 22, no. 5 (2007): 643-658.

[54] See Huxley, *On the Physical Basis of Life*, 14; Huxley, "Yeast," 23-36.

Martinus Beijerinck had recognized this explicitly, and of his early studies of microbial ecology Beijerinck had claimed that, "the individual microbe can be compared to the whole individual of the higher organism, or to a single tissue-cell of it, - both comparisons are correct."[55]

By the late 1950s, biologists discovered new opportunities for disciplinary synthesis by building consensus through this duel role of the microbes. Homologies identified at either level of organization could be justified as common to higher organisms by virtue of their common descent. These comparisons became central to generalizing molecular mechanisms from yeast biology. The practice was reinforced by the genetic standardization of experimental organisms which ensured the stability of these comparisons.

Anthropomorphizing the Organism

Yeast microbiologists since the start of the twentieth century had drawn connections between the yeasts and humans using biological homologies of the cell. They had extrapolated ideas from human culture to yeast culture and built on a long history of anthropomorphizing the organism. This practice continued over the course of the 1960s, adapting to a new definition of homology.

As early as 1680, the Dutch microscopist Antoni van Leeuwenhoek had described the globules making up a nonliving residue, yeast, in the dregs of his beer as being the same size, shape, and stickiness as those globules found in human blood.[56] The human body offered a

[55] Beijerinck, "On Different Forms of Hereditary Variation of Microbes," 365. As discussed in the first chapter of this dissertation, Beijerinck drew upon the statistical, chemical, and biological sciences in his experiments with microbial populations. He believed that the single-celled microbes permitted a clearer perspective on biological variation than did multi-cellular organisms.

[56] Leeuwenhoek, *The Collected Letters of Antoni Van Leeuwenhoek, Vol. III: 1679-1682*. For more on Leeuwenhoek see Howard Gest, "The Discovery of Microorganisms by Robert Hooke

common reference for the diffuse network of philosopher-correspondents of the Royal Society of London. More than a hundred years later, the French chemist Antoine-Laurent de Lavoisier characterized yeast fermentation as an "intestine motion" involving "disengagement of gas," thus animating the process for an inanimate ingredient in the process.[57] Nineteenth century chemists scoffed at yeast's purported biological nature by satirizing the creature with anatomical features of the higher organisms – a mouth, bladder, and anus – even as the ferment of alcohol was thought to function *like* the ferment of the blood held to cause human disease.[58] Later in the century, cookbooks held that the "blood temperature" of the good housewife was the measure of yeast's proper development, while newspapers joked that, "When the bakers rise they follow the example of their yeast."[59]

Humans have also regularly guided interpretation of fungal phenomena at the population level.[60] At the turn of the twentieth century, the "purest varieties" of yeast were analogized to multiple diligent human workers in a living factory, including:

> …the artisan who executes his work of chemist, the producer who delivers to the man the substance elaborated, the mason who draws from the environing medium the materials… necessary for the making of the product. The wisdom of the patron is also shown in the development of resources; he reproduces himself, continuing his work in a posterity which is reinforced ceaselessly. And this little creature who builds his factory, repairs it, enlarges it, defends it, who united the roles of creator, worker, economist, and who provides for its future, this

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and Antoni Van Leeuwenhoek, Fellows of the Royal Society," *Notes Rec R Soc Lond* 58, no. 2 (2004): 194; Brian J. Ford, *The Leeuwenhoek Legacy* (Bristol: Biopress, 1991), 170.

[57] Lavoisier, *Elements of Chemistry*, 135.

[58] "Das Enträthselte Geheimnis Der Geistigen Gährung," 101.

[59] Yeast should be prepared at "blood temperature" for bread-making and the mark of a good housewife was to be a good baker. In Maria Parloa, *Miss Parloa's New Cook Book: A Guide to Marketing and Cooking* (New York: C. T. Dillingham, 1880), 381-382. See also "Chronicle Cullings," *The San Francisco Chronicle*, June 29, 1886, 2.

[60] Sabine Maasen, Everett Mendelsohn, and Peter Weingart have suggested that "metaphor circulation" may help to explain the co-evolution of scientific theories and political worldviews in S. Maasen, E. Mendelsohn, and P. Weingart, *Biology as Society, Society as Biology: Metaphors* (Springer Netherlands, 2001), 8.

> microscopic capitalist, crowns the student's astonishment by combining the worker with the building: since he himself is the factory.[61]

Like the productive cell, yeast reproduction was also analogized. In 1908, sporulation appeared to be "neither more nor less than the giving birth (by micro-organisms belonging to the vegetable kingdom) to their kind in their complete form just as an animal gives birth to its young." The formation of a film on the surface of fermenting beer was known as a "mother" whose womb-like protection of the sterile wort required the proper conditions of time, temperature, access to filtered air, and the purity of the yeast which brewers had seeded into the broth.[62] Germ theory brought humans and microbes into even closer association. To some, the bacteriological doctrine suggested that, "A man is only what his microbes make him. With a normal proportion of symbiotic bacteria he is the good citizen; with an excess of inimical bacteria he may become… the criminal essayist or novelist. When he speaks, it is not he, but the microbe, that is speaking." In fact, yeast could injure human protoplasm "to the point where the entire aggregation of cells (the man) feels in his subconscious mind that he (that is, his cells) is worthless."[63] Both the human organism and the cells which comprised it had to contend with the sociality of the microbe.[64]

Other social analogs in the yeasts have included the concepts of "races," "sexes," and heteronormative "legitimate" mating.[65] Carl Lindegren found it convenient to describe the four

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[61] Krecker, "World's Smallest Factory Strange and Mysterious."
[62] Johnson, *The Student's Manual of Yeast Culture*, 96, 103-104.
[63] Robert T. Morris, *Microbes and Men*, To-Morrow's Topics Series (Garden City, New York: Doubleday Page & Company, 1915), 5, 90.
[64] This is not unlike contemporary research on the human microbiome. See a brief historical discussion in Jonathan Eisen, "Rediscovering Some Critical Terms of Use in Microbial Discussions: #Microbiomania and #Microbophobia," accessed June 7, 2016, phylogenomics.blogspot.com.
[65] See Chapter 1 for the argument that even as a "species" concept was substituted for race geographic definitions continued to operate in yeast taxonomy after 1930, for example, by

spores of yeast tetrad analysis as the homologues of sperm.[66] Generations of yeast have been referred to in the familial terms of “grandparents,” “parent,” “mothers,” “mom,” “daughters,” “sisters,” “cousins,” and “twins.” Its mating behavior has been evaluated as “promiscuous,” and its fecundity as “respectable.”[67] Such appropriations of human culture and value judgments were readily naturalized into yeast biology.

In the Donner Laboratory of Biophysics and Medical Physics at Berkeley, Robert Mortimer and John Johnston believed they had found in yeast an insight into cell mortality in 1959. After showing that mother and daughter yeast cells differed with respect to the total number of cell divisions they could undergo before they could no longer divide, they concluded that different generations of cells had different replicative capacities. They termed the fertile period during which yeast replicated its “life span,” thus appropriating gendered ideas about reproductive value from human culture to the yeast cell. The “life span” of non-replicating yeast could be much longer, and some yeast cells had been known to survive without cell division up to four-and-a-half decades in storage.[68] Their demonstration of generational differences was thought to be potentially generalizable to the “mortality” of other cell populations which had stopped replicating.[69]

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relating yeast biochemistry to ecological rather than national origins. See Chapter 2 for a description of early genetic studies of yeast sexuality.

[66] Lindegren and Lindegren, "Tetraploid *Saccharomyces*," 886.

[67] Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 12, Yeast Collection, Cold Spring Harbor Laboratory Archives, New York; Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 8, Yeast Collection, Cold Spring Harbor Laboratory Archives, New York.

[68] See Winge and Hjort, "On Some Saccharomycetes and Other Fungi Still Alive in the Pure Culture of Emil Chr. Hansen and Alb. Klöcker," 58.

[69] Robert K. Mortimer and J. R. Johnston, "Life Span of Individual Yeast Cells," *Nature* 183, no. 4677 (1959): 1751. Yeast continues to serve as a model for genetic studies of aging in other organisms. See, for example, Matt Kaeberlein, Christopher R. Burtner, and Brian K. Kennedy, "Recent Developments in Yeast Aging," *PLoS Genetics* 3, no. 5 (2007): e84; Valter D Longo

In the 1960s, the shared properties of "life," "species," "the cell," and "the organism" in miniature continued to serve as regular analogies to the human experience but another basis of comparison, the genetic mechanism, began to specify molecular homology across different levels of microbial explanation, between both cell and organism.

Different Fundamental Organization

In 1960, researchers at the Pasteur Institute reported that the bacteria *E. coli* possessed self-regulating genes which turned on and off the transfer of information from genes to proteins. French biochemical geneticists François Jacob and Jacques Monod named these functional units "operons" and thought that they provided evidence that bacterial systems could be used to study higher organism cell regulation and differentiation.[70] They warned that eventually differentiation would have to be studied in differentiated cells, but in the meantime the experiments to understand how genetic information was used selectively could only be performed on single cells. "This is our excuse for using microbial systems as models for the interpretation of differentiation," they wrote in 1961.[71]

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and Paola Fabrizio, "Chronological Aging in Saccharomyces Cerevisiae," in *Aging Research in Yeast* (Springer, 2012), 101-121; Chong He and Brian K Kennedy, "Aging in the Single-Celled Eukaryote, S. Cerevisiae," *Stem Cell Aging: Mechanisms, Consequences, Rejuvenation* (2015): 19.

[70] François Jacob and Jacques Monod, "Genetic Regulatory Mechanisms in the Synthesis of Proteins," *Journal of Molecular Biology* 3, no. 3 (1961): 352. Their first report of the "operon" appeared as F. Jacob et al., "[Operon: A Group of Genes with the Expression Coordinated by an Operator]," *Comptes rendus hebdomadaires des séances de l'Académie des sciences* 250 (1960): 1727-1729. Historian Jan Sapp has described how Jacob and Monod drew from electronic and cybernetic analogies such as "communication networks, circuitry, feedback loops, and information" to explain cell regulation. In Sapp, *Genesis: The Evolution of Biology*, 198.

[71] Monod and Jacob, "General Conclusions: Teleonomic Mechanisms in Cellular Metabolism, Growth, and Differentiation," 400.

The operon finding especially interested American yeast geneticist Carl Lindegren because it suggested that the phenomena of enzymatic adaptation, which he had studied in yeast, was one of regulated gene expression rather than environmentally-induced mutation. He claimed to have recognized this before Monod.[72] The bacterial control elements also impressed other yeast geneticists, who found themselves "mesmerized by the beauty of the operon model" and assumed that yeast mutations worked similarly to eliminate one enzymatic activity at a time.[73] Yale graduate student Gerald Fink recalled becoming "obsessed over every new paper on regulation" with his genetics lab mates and wanting to determine "whether anything like the bacterial operons existed in eukaryotes."[74]

The term "eukaryote" was a recent development out of cell biology to categorize all organisms containing a nuclear membrane. In 1962, the Canadian microbiologist Roger Yate Stanier and his former mentor, Cornelis van Niel (himself a student of Albert Jan Kluyver in Delft), proposed to classify organisms like *E. coli*, which lacked a nucleus, as "prokaryotes," while organisms like humans, whose cells contained nuclei were "eukaryotes."[75] Over the second half of the twentieth century, the simple distinction of organisms as either plant or animal underwent revision into three, four, five or six different kingdoms. While these later classificatory changes were frequently contested, they largely retained the prokaryotic-eukaryotic

[72] As described in Chapter 2, Lindegren wrote Francis Crick to protest. He argued, "I think that the substitution of [Monod's term] 'operator' for [my term] 'activator' is a matter of deep concern for all those interested in scholarliness." In Lindegren, Letter to Dr. F. H. C. Crick, (July 20, 1964), PP/CRI/1/1/12, Francis Harry Compton Crick Papers.
[73] Jones, "Genetic Roots," 342.
[74] Gerald Fink, "Getting Along with a Little Help from My Friends," *Journal of Biological Chemistry* 284, no. 36 (2009): 23886.
[75] See R. Y. Stanier and C. B. Van Niel, "The Concept of a Bacterium," *Arch Mikrobiol* 42 (1962): 17-35. Jan Sapp has examined Stanier and van Niel's reintroduction of the terms "prokaryote" and "eukaryote" to biology in Jan Sapp, "The Prokaryote-Eukaryote Dichotomy: Meanings and Mythology," *Microbiology and Molecular Biology Reviews* 69, no. 2 (2005): 294.

distinction.[76] In 1964, American biologist Robert Wagner and biochemist Herschel Mitchell used this classificatory system to determine that yeast fungi were eukaryotic because they possessed "true" nuclei and "discernible chromosomes." The yeasts underwent a "comparable or identical" meiosis to plants and animals, but unlike "higher" life forms, the yeasts had "apparently degenerated" to single-celled organisms which enabled them to reproduce both sexually and asexually. Since the most widely used laboratory yeast, *Saccharomyces cerevisiae*, had two stable mating types, Wagner and Mitchell reported, "the end results" of this yeast's life cycle made it a eukaryote therefore "comparable" to higher forms.[77]

The yeast geneticist and former Oak Ridge scientist R.C. "Jack" von Borstel recalled that it was clear by the second international yeast meeting in Gif-sur-Yvette, France, in 1963 that "yeast was headed for a great future as the transfer organism of prokaryotic discoveries into eukaryotic systems."[78] The increment of complexity represented by the nucleus appeared to be surmountable in the repetition of bacterial findings in yeast, and opened a path for recognition and further development of organism as one of secondary confirmation. The yeast genetics "club" began to coalesce at that meeting, recalled another participant.[79] Almost immediately, however, the universality of the genetic code would be called into question.

At Yale, Gerald Fink's graduate research examined the question of operons in the eukaryotes by looking at microbial biosynthesis of histidine. In 1964, he reported that "genetic regions" of yeast and *Neurospora* contained homologies of "the same functional complexity,"

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[76] See Joel B. Hagen, "Five Kingdoms, More or Less: Robert Whittaker and the Broad Classification of Organisms," *BioScience* 62, no. 1 (2012): 67.
[77] Their discussion of the eukaryotes does not appear in the 1955 edition of their text, but appears in the second edition from 1964. See Wagner and Mitchell, *Genetics and Metabolism*, 137, 144.
[78] von Borstel, "Taming the Oldest Domesticated Organism," 194.
[79] Brian Cox, "Psi Phenomena in Yeast," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 219.

but that these simple eukaryotes coordinated their gene functions differently in this process than the prokaryotic *Salmonella* system. Based on this comparison of the three microbes, it appeared the operon theory was limited to prokaryotes.[80] The eukaryotes might not only regulate their genes differently, but possess different fundamental organization. Whereas in the previous decade such a finding of difference would have made yeast unreliable as a subject of genetic research, now it was evolutionarily justified on the basis of the eukaryotic distinction. Yeast provided an important comparison to other experimental organisms on evolutionary grounds because if the same biological mechanism could be found at work in distantly-related species, it was likely to be found as well in any other organism sharing a common ancestor.

Evolutionary Mechanisms

From the early 1960s, molecular genetics posed a challenge to evolutionary biologists, many of whom sought to retain their traditional unit of analysis as the organism or population.[81] Rather than for this group to adopt molecular genetics as a method of evolutionary research in the yeasts, it was the yeast geneticists who stumbled into evolutionary implications. The desire to contribute to the universal genetic code in the mid-1960s prompted a molecular ordering of species relationships and transformed the possibilities for evolutionary research.

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[80] Gerald Fink, "Gene-Enzyme Relations in Histidine Biosynthesis in Yeast," *Science* 146, no. 3643 (1964): 526-527. This was further resolved with the development of yeast transformation at Cornell University in 1978 by Fink, Albert Hinnen and James Hicks allowing Fink to clone the *HIS4* gene. The uninterrupted reading frame yeast did not have a bacterium-like operon for histidine biosynthesis and likely had no operons at all. Fink recalled that, “The “operon or not” question motivated my attempt to devise a transformation system for cloning specific DNAs in yeast.” In Fink, "Getting Along with a Little Help from My Friends," 23887.

[81] Dobzhansky protested “the bandwagon effect” of molecular genetics and claimed that the 11th International Congress of Genetics showed that “active and intellectually stimulating research is going on in organismic as well as molecular genetics.” In Theodosius Dobzhansky, "Evolutionary and Population Genetics," *Science* 142, no. 3596 (1963): 1131.

In 1965, geneticist James Watson tried to make sense of what he called extreme differences between the higher plants and animals in the ratios of their DNA molecules (the sum of the adenine plus thymine bases to the sum of the guanine plus cytosine bases or "A+T/G+C"). Despite having similar percentages of the four main bases, the wide spread of base-ratios ordered humans just below locusts and closer to chickens than horses or trout. "This fact tells us that variation in the *sequences* of the bases is, by itself, sufficient to produce the gene differences between plants and animals," Watson wrote.[82] Species relationships could be found in sequence.

One attempt to decode these relationships came from the finding of cytochrome c sequence homology by yeast geneticist Fred Sherman. Sherman had trained in biophysics at the University of California, Berkeley with Robert Mortimer during the period when Mortimer was deriving mutants for a yeast genetic map using the recently-standardized "wild-type" strain S288C. At the end of the 1950s, Sherman left Berkeley to complete a postdoc in genetics investigating yeast recombination under Herschel Roman at the University of Washington in Seattle. He rounded out his tour of the major yeast genetics laboratories with a second postdoc in Boris Ephrussi's laboratory in Gif-sur-Yvette beginning in 1960, and went on to join the biochemistry faculty at the University of Rochester Medical School. By 1964, Sherman was looking for a change in the amino acid sequence of yeast cytochrome c that would help him understand the gene by way of protein. He believed that this gene-protein relationship would help him to crack the genetic code. At the time, there were only three other proteins known in bacteria and the phage which could be subject to mutational analysis. While "any system exhibiting genetic control of cytochrome c would be of considerable interest," Sherman knew

[82] Watson, *Molecular Biology of the Gene*, 265-266.

that the yeast protein sequence was small and easy to isolate.[83] "[T]he idea, which wasn't completely true but nevertheless the best at that time, is you would try to find a specific mutagen that acted with a certain base."[84] Gene structure could be inferred from the pattern of amino acid replacements.[85]

While he was looking to contribute to a universal code using the methods of molecular genetics, Sherman's work on yeast biology provided a new form of evidence for the study of evolution. In 1965, the associate director of the newly established National Biomedical Research Foundation, American physical chemist Margaret Dayoff, was exploring the use of computer algorithms to compare known protein sequences across species. Dayoff believed that molecular alignment of sequences indicated homology between organisms. The cytochrome c amino acid sequence, for example, could be used to reconstruct ancestral relationships between species

[83] See Fred Sherman, "My Life with Cytochrome *C*," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 347-348; Fred Sherman, "Mutants of Yeast Deficient in Cytochrome C," *Genetics* 49, no. 1 (1964): 39. The protein sequence of cytochrome c had been identified in yeast by Japanese scientists at the Osaka University Institute for Protein Research. See Kozo Narita et al., "The Complete Amino Acid Sequence in Baker's Yeast Cytochrome C," *Biochimica et Biophysica Acta* 77 (1963): 688-690. For an account of the identification of the cytochrome c protein in baker's yeast in 1925, see D. Keilin, *The History of Cell Respiration and Cytochrome* (Cambridge: Cambridge University Press, 1966), 140.

[84] Fred Sherman, interview by Mila Pollok, March 6, 2004, "Oral History Interview," New York, Cold Spring Harbor Laboratory Archives.

[85] Sherman's long-time teaching partner at Cold Spring Harbor Laboratory, yeast geneticist Gerry Fink, later bestowed upon Sherman the title of the first yeast molecular biologist for this work, claiming that, "For more than a decade, Fred's *cyc1* gene provided the picture of the eukaryotic genome. And Fred's work and findings attracted hordes of new scientists to work on yeast." In Gerald Fink, *Tribute to Fred Sherman*, 2014, University of Rochester Medical Center Department of Biochemistry & Biophysics (B&B), 14:30. For the next twenty years, CYC1 and the cytochrome c protein enabled genetic investigations of diverse biological problems, and was used to study translation, mutagenesis, and recombination as general processes. See Sherman, "Oral History Interview."; Susan W. Liebman and James E. Haber, "Fred Sherman (1932–2013)," *Science* 342, no. 6162 (2013): 1059. The use of CYC1 in yeast recombination research is examined in greater detail in the final chapter.

under this new style of molecular (and computational) evolutionary research.[86] When a follow up study compared the molecular phylogenetic tree constructed by cytochrome c to phylogenies established by morphological comparisons, it found them to be similar.[87] Molecular phylogeny could be used to map evolutionary descent of specific sequences. By 1968, Sherman believed that yeast cytochrome c afforded an excellent example of the gene-protein relationship in a eukaryotic organism.[88] In 1971, he claimed that evolutionary evidence supported the extrapolation from yeast to a universal genetic code, writing, "The amino acid sequences of the cytochromes *c* from more than 30 species are sufficiently alike and their differences are of such nature that their evolution from a common ancestral form appears firmly established."[89] Later in the decade, he and others would clone cytochrome c as one of the first genes to be sequenced

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[86] Margaret O. Dayhoff et al., *Atlas of Protein Sequence and Structure 1965* (Silver Spring, MD: National Biomedical Research Foundation, 1965); Joel B. Hagen, "Naturalists, Molecular Biologists, and the Challenges of Molecular Evolution," *Journal of the History of Biology* 32, no. 2 (1999): 326-327; Sapp, "The Prokaryote-Eukaryote Dichotomy: Meanings and Mythology," 300.

[87] See W. M. Fitch and E. Margoliash, "Construction of Phylogenetic Trees," *Science* 155, no. 3760 (1967): 279. Historian Joel Hagen has described how Fitch and Margoliash discarded close to 40 trees to arrive at this result. See Joel B. Hagen, "The Origins of Bioinformatics," *Nat Rev Genet* 1, no. 3 (2000): 235.

[88] Fred Sherman et al., "The Mutational Alteration of the Primary Structure of Yeast Iso-1-Cytochrome C," *Journal of Biological Chemistry* 243, no. 20 (1968): 5446.

[89] Fred Sherman and John W Stewart, "Genetics and Biosynthesis of Cytochrome," *Annual review of genetics* 5, no. 1 (1971): 257. The comparative biochemistry of yeast and human protein function was "like studying the history of specific genes" because "the amount of variation per unit of geological time" could be estimated in molecular evolutionary history, according to microbial geneticist Salvador Luria. In February of 1976, he reported to the American Association for the Advancement of Science that the rate of evolution calculated from these data "fit quite well with the classification proposed by taxonomists [and] the time scale of paleontologists" unlike the naïve calculations of 10 years earlier. While in the 1960s, mutations observed by the geneticist in the genetic script or chromosomes came to be seen as neither "frequent enough nor varied enough to reassure the evolutionist that they know the whole story of genetic variation", later molecular biologists found new kinds of variation to "speed up evolution by generating a greater variety of changes" and "a greater range of genotypes for natural selection to act upon." In Salvador E. Luria, Aaas [American Associaiton for the Advancement of Science] Talk, (February, 1976), QLBBHR, Profiles in Science: The Salvador E. Luria Papers, National Library of Medicine, Bethesda, MD.

through the use of frameshift mutations to help infer sequence pattern.[90] Yeast molecular biology was eukaryotic, generalizable, and accessible.

Likeness between organisms was defined by common descent as homology, but by the end of the 1960s, there began to be some confusion about the meaning of this term. A new word, orthology, appeared at the start of the 1970s.[91] At that time, some argued that the confusion lay in the need to specify the "level" of homology (e.g., genic, structural, functional or behavioral) or to clearly differentiate between distinct molecular pathways of descent.[92] Molecular orthology provided an adaptation of the early structural definition of homology because it was no longer limited to species' characters. Common ancestry supported evolutionary gene conservation requiring comparisons not of characters, but of heritable instructions, at the level of the

[90] Sherman was then competing with Benjamin Hall's laboratory at the University of Washington in Seattle, and Hall became the first to clone the yeast CYC1 gene. Sherman, "Oral History Interview." See also J.W. Stewart and F. Sherman, "Yeast Frameshift Mutations Identified by Sequence Changes in Iso-1-Cytochrome C," *Molecular and environmental aspects of mutagenesis* (1974): 102-127; D. L. Montgomery et al., "Identification and Isolation of the Yeast Cytochrome C Gene," *Cell* 14, no. 3 (1978): 673-680; John I Stiles et al., "DNA Sequence of a Mutation in the Leader Region of the Yeast Iso-1-Cytochrome C mRNA," *Cell* 25, no. 1 (1981): 277-284.

[91] "Where the homology is the result of speciation so that the history of the gene reflects the history of the species… the genes should be called *orthologous*." In W. M. Fitch, "Distinguishing Homologous from Analogous Proteins," *Syst Zool* 19, no. 2 (1970): 99-113. Oxford Dictionaries date the second biological definition of "orthology" to the 1970s; the first definition of the word, "Correct, approved, or traditional use of language", dates to the early 17th century. In "Orthology," in *Oxford Dictionaries* (www.oxforddictionaries.com: Oxford University Press, 2015).

[92] The problem of "levels of homology" is described in W. J. Dickinson, "Molecules and Morphology: Where's the Homology?," *Trends Genet* 11, no. 4 (1995): 119-121. There is also an ongoing attempt to specify different modes of sequence conservation. "Orthology and paralogy differ in that one proceeds from speciation and the other from gene duplication… the terms originated within the evolutionary biology community and strictly refer to sequence divergence associated with either speciation or gene duplication, respectively, and do not have either implicit or explicit functional implications." In Roy A. Jensen, "Orthologs and Paralogs - We Need to Get It Right," *Genome Biology* 2, no. 8 (2001): 2.

genome.[93] Orthology compared sets of molecular sequence data believed to have descended from the same ancestral sequence.[94] The shared mechanisms behind biological phenomena were not "laws," in the sense that heredity, evolution and development were universal characteristics of life. They were rather the systems exhibiting these laws in contextually specific ways.[95] Generalization of the dogma thus required comparisons across specific biological contexts. In this way helpful "experimental systems" would become "model organisms" because they provided specific diagnostic tests of general mechanistic explanations.[96]

By the mid-1960s, the genetic code that specified how encoded genetic information was translated into protein was believed to be fully deciphered. Yeast RNA had served as the

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[93] In recent years it has become evident that molecular homologies may not be compatible with homology at other levels of biological organization since "a structure that is homologous across species can develop based on nonhomologous genes and/or developmental processes, and vice-versa." In Ingo Brigandt and Paul E. Griffiths, "The Importance of Homology for Biology and Philosophy," *Biology & Philosophy* 22, no. 5 (2007): 3.

[94] At the turn of the twenty-first century, Walter Fitch tried to correct common misuse terms, reminding biologists, "The definition of homology is about characters." In W. M. Fitch, "Homology a Personal View on Some of the Problems," *Trends Genet* 16, no. 5 (2000): 227-231. Others had recognized that the older morphological meaning of homology was distinct from molecular biology's quantitative sequence comparisons. See Maurice Wegnez, "Letter to the Editor," *Cell* 51, no. 4: 516. Some argued explicitly that the term homology should evolve to embrace these new meanings, although the confusion has remained. See C Patterson, "Homology in Classical and Molecular Biology," *Molecular Biology and Evolution* 5, no. 6 (1988): 603-625.

[95] William Bechtel and Adele Abrahamsen have claimed that "models of mechanisms are developed for specific exemplars and are not represented in terms of universally quantified statements. Generalization involves investigating both the similarity of new exemplars to those already studied and the variations between them." In William Bechtel and Adele Abrahamsen, "Explanation: A Mechanist Alternative," *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 36, no. 2 (2005): 421.

[96] Molecular biologist Rowland Davis has distinguished between *model organisms*, which serve as communal resources whose biology is understood and generalizable at many different levels, and *model systems*, which are organisms with particular experimental advantages used to study specific research problems without the need for genetic rationales. Model systems have none of the phenotypic genetic analysis performed on model organisms. See Davis, *The Microbial Models of Molecular Biology: From Genes to Genomes*, 255. While this definition differentiates model organisms from experimental systems on the basis of "genetic rationales", characterizations, and analyses, the difference can be further historicized by the shifts *within genetics* that produced modeling as a specific test to further contextualize general principles.

experimental template for protein synthesis, and the findings were believed to hold for all organisms at all levels of complexity.[97] According to the American biochemist Marshall Nirenberg, the translation from nucleic acid to protein relied on the specification of molecules whose "position [is] relative to the previous molecule selected, and the time of the event relative to the previous event." In his 1968 Nobel lecture for this work, Nirenberg explained, "The nucleic acid therefore functions both as a template for other molecules and as a biological clock."[98] This mechanistic and process emphasis in biology would soon find developmental implications even in the single-celled microbes. By the end of the 1960s, the biological code was being touted as "virtually universal," which meant that it offered "no comparative data which might tell us something of its evolution."[99] The code did, however, offer comparative data to trace organisms' evolution.

General and Specific

Despite classification of the yeasts as eukaryotic like higher plants and animals in the middle of the decade, *Saccharomyces cerevisiae* was still a genetically-simple system which might suggest but not predict the hereditary processes of complex organisms. The oddity of yeast gene conversion, which had been debated so contentiously by Herschel Roman and Carl Lindegren in the 1950s, was revisited in the early 1960s in light of a range of experimental

[97] See Sapp, *Genesis: The Evolution of Biology*, 196.
[98] Nirenberg shared the 1968 Nobel Prize in Physiology or Medicine with Har Gobind Khorana and Robert W. Holley for their contributions to breaking the genetic code. His Nobel lecture is Marshall W. Nirenberg, "The Genetic Code (1968)," in *Nobel Lectures: Physiology and Medicine, 1963-1970* (New York: American Elsevier, 1973), 372.
[99] M. Yčas, *The Biological Code* (New York: John Wiley, 1969), 260.

evidence in other fungi.[100] Roman had accounted for gene conversion as a type of genetic recombination rather than a new mutation as Lindegren had proposed. While this aligned more readily with established ideas, it still was not clear how widely the phenomenon extended.

While on leave in Seattle from his position at the John Innes Horticultural Institution in Hertfordshire, the British molecular biologist Robin Holliday sought to account for irregular genetic segregation in the fungi.[101] During a postdoctoral year with Roman in 1962-1963, Holliday proposed a model which could account for the distribution of phenotypes after fungal meiosis. He thought that two simultaneous breaks in the DNA double helix allowed for the rearrangement and exchange of molecules along the chromosomes. Strands of the structure separated and recombined simultaneously and mismatched bases were repaired. Initially, Holliday did not propose that the gene conversion model would hold for all organisms. When writing up his results in 1964, he claimed that "whatever basic mechanism is operating, the details… may not be the same in different organisms; therefore it does not seem profitable… to make the model more specific by very detailed analysis of particular data from one organism or one locus." The model was suggestive of general features of a decontextualized DNA mechanism as part of the universal genetic code, and although it had been constructed in the fungi, it appeared to be compatible with observations in a range of organisms, perhaps even maize and *Drosophila*. "Although the model proposed is a *general* rather than a *specific* one…" Holliday wrote, "it is hoped that the introduction of a model with this complexity will help to

[100] See a discussion of these debates in the previous chapter. Some samples of their work include Carl C. Lindegren, "Gene Conversion in Saccharomyces," *J. Genet* 51 (1953): 625-637; Lindegren, "Non-Mendelian Segregation in a Single Tetrad of Saccharomyces Ascribed to Gene Conversion," 605-607; Roman, *Studies of Gene Mutation in Saccharomyces*, 21, 175-185.
[101] Roman, Annual Report No. 4, July 1, 1962 to June 30, 1963, (July 16, 1963), Folder 95-208, UW Genetics Department Records (#VF2395).

stimulate specific experiments, and that these will provide *definitive* information" above and beyond the simple fungi.[102]

Holliday was still qualifying his conclusions in 1968 with a focus on the utility of the fungi for isolating mutants to test the mechanism of recombination, but he had begun to elaborate the connections to lower and higher organisms, suggesting that it would be work in fungi that would continue to refine the model for generalized understanding.[103] He was wrong about the role of fungi since Harvard biochemists David Dressler and Hunt Potter later used the *E. coli* toxin colicin El to confirm his genetic model experimentally, but the physical evidence they offered in 1976 did substantiate Holliday's claims more broadly. The scientists noted that Holliday's model, which "initially proposed to account for the highly ordered events that are involved in recombination between eukaryotic chromosomes at meiosis, also appears applicable to the potentially less demanding requirements of prokaryotic recombination."[104] In other words, Holliday's fungal model of recombination had become eukaryotic *and* it held for all organisms.[105] This transition occurred in the late 1960s and early 1970s across the problems of molecular genetics as a result of the contributions from several disciplines.[106]

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[102] Robin Holliday, "A Mechanism for Gene Conversion in Fungi," *Genetics Research* 5, no. 02 (1964): 291-292, 305. Italics added.
[103] Robin Holliday, "Genetic Recombination in Fungi," in *Replication and Recombination of Genetic Material*, ed. William James Peacock and Richard Donald Brock (Canverra, Australia: Australian Academy of Science, 1968), 172.
[104] Huntington Potter and David Dressler, "On the Mechanism of Genetic Recombination: Electron Microscopic Observation of Recombination Intermediates," *Proceedings of the National Academy of Sciences* 73, no. 9 (1976): 3004.
[105] Given this hindsight, the model, which is today known as the "Holliday Junction", has been called the most influential early model of recombination. In Symington, "Homologous Recombination," 34.
[106] Another problem already cited was gene regulation. In 1972, an anonymous journal correspondent claimed that, "Research on gene regulation in fungi is important… [I]t will provide information as to whether or not the control mechanisms in eukaryotes and prokaryotes are similar." In "Gene Regulation," *Nat New Biol* 236, no. 68 (1972): 194.

Biochemical Specificity in the Eukaryotes

In the second half of the 1960s, biochemical studies conducted in Seattle supported the observed morphological differences between prokaryotes and eukaryotes. The laboratories of Benjamin Hall and William Rutter were instrumental in producing this biochemical evidence. Hall had come to the University of Washington from the University of Illinois chemistry department. He arrived in Seattle in August of 1963 to join Herschel Roman's genetics department, which had recently been granted federal and state funds to construct a new building and was then still "very much a start-up operation."[107] One year earlier, while the World's Fair had been in town, Hall had interviewed and turned down a job in chemistry at University of Washington, but when genetics offered him the job as associate professor, he saw the new genetics-biochemistry building as a promising sign. Hall had been recruited on the basis of his recent success with Sol Spiegelman on DNA-RNA hybridization, and he signed on to serve as a charter member in the development of molecular biology at the University. Initially, he

[107] Hall received a Bachelor's in Chemistry from the University of Kansas in 1954. He went to study Biophysical Chemistry at Harvard, where, to his great disappointment, he was asked to work on RNA. At that time, Hall recalled, RNA had "barely been heard of" and molecular biology "didn't really exist", but this would become his path out of chemistry. Hall later considered it, "the luckiest thing that ever happened to me." Hall completed his doctorate at Harvard in 1958, the same year that Francis Crick explained the sequential flow of genetic information as molecular biology's central dogma. On the recommendation of his committee member, James Watson, Hall obtained a junior faculty position at the University of Illinois as an Assistant Professor of Chemistry from 1959 until he left for the University of Washington in 1963. It was there that he met Rutter. In Benjamin D. Hall, interview by Allen Gross, December 10, 2009, "A Conversation with Industry Pioneer Dr. Benjamin Hall," Leawood, KS, EFL Associates, Inc., 6.

specialized in teaching and research on the chemistry of genetically-important macromolecules.[108]

The biochemist William Rutter was also recruited from the chemistry faculty at the University of Illinois to Herschel Roman's genetics department. He had been offered a joint appointment in biochemistry, and the move had interested him because both departments in Seattle interacted with the University of Washington medical school. Rutter's interests had been growing increasingly biological and clinical. Early in his career, Rutter had investigated the selective synthesis of digestive enzymes and hormones like insulin in cells of the mouse pancreas. These unique products were specific to different cells, suggesting that the cells had undergone controlled differentiation to enable their different functioning. Rutter had taken up the problem in Seattle with biochemical investigations of the molecular mechanisms behind differential growth and development in simple systems like yeast since the use of a mammalian system such as the pancreas "seemed impossible at that time."[109] He worked with Seattle graduate student Robert Roeder to search for a genetic mechanism of transcription in the eukaryotes to understand how the genes directed different functions for different cells.

Given the speculation that RNA synthesized under different conditions, Roeder had agreed that looking to implicate an enzyme might be a reasonable approach for his dissertation research. At Rutter's suggestion, he had settled on studying RNA polymerase, an enzyme which had been discovered in extracts of mammalian cells and purified in different species of bacteria. Polymerase appeared to be involved in the transcription of genetic messages by nucleic acid

[108] Roman, Annual Report No. 4, July 1, 1962 to June 30, 1963, (July 16, 1963), Folder 95-208, UW Genetics Department Records (#VF2395).
[109] Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

base-pairing, and the synthesis of RNA molecules from DNA.[110] While it was suspected that multiple polymerases might be involved in the specific transcription of eukaryotic RNA, giving some basis to the differentiation of their cells, the nuclei of higher organisms made this challenging to investigate. As his graduate research, Roeder studied yeast, sea urchin embryo and rat liver nuclei and found that three eukaryotic polymerases were involved in transcription.[111] He submitted this finding to the journal *Nature* in 1969, and was rejected on the grounds that the topic was not of general interest.[112] Rutter intervened on Roeder's behalf and convinced the journal to publish the article. It came out mere weeks before Pierre Chambon's laboratory in Strasbourg published a similar discovery of multiple eukaryote RNA polymerases in calf thymus.[113] Eukaryotic polymerases intrigued, if not yet a general audience, then at least an international one.

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[110] C. C. Widnell and J. R. Tata, "Evidence for Two DNA-Dependent RNA Polymerase Activities in Isolated Rat-Liver Nuclei," *Biochim Biophys Acta* 87 (1964): 531-533; A. O. Pogo, Littau, V. C., Allfrey, V. G., and Mirsky, A. E., "Modification of Ribonuclic Acid Synthesis in Nuclei Isolated from Normal and Regenerating Liver: Some Effects of Salt and Specific Divalent Cations," *Proc Natl Acad Sci U S A* 57, no. 3 (1967): 743; G. P. Tocchini-Valentini, P. Marino, and A. J. Colvill, "Mutant of E. Coli Containing an Altered DNA-Dependent RNA Polymerase," *Nature* 220, no. 5164 (1968): 275-276; R. R. Burgess et al., "Factor Stimulating Transcription by RNA Polymerase," *Nature* 221, no. 5175 (1969): 43-46; E. Di Mauro et al., "Rifampicin Sensitivity of the Components of DNA-Dependent RNA Polymerase," *Nature* 222, no. 5193 (1969): 533-537.

[111] R. G. Roeder, interview by James Darnell, 2003, "Albert Lasker Basic Medical Research Award," New York, Lasker Foundation Video Library. Some years later, Rutter reflected on Roeder's polymerase work, "it was obvious that one place to learn about specific gene expression from a mechanistic point of view was to start with the enzymes that transcribe the genes. The enzymes had to act specifically… [and] had to signal, "transcribe *this* gene." Studying transcription was an approach to understanding specific gene expression," he recalled. In Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

[112] Robert G. Roeder, "First Person: Robert G. Roeder," *The Scientist*, September 22, 2003.

[113] R. G. and Rutter Roeder, W. J., "Multiple Forms of DNA-Dependent RNA Polymerase in Eukaryotic Organisms," *Nature* 224, no. 5216 (1969): 234-237; C. Kedinger et al., "Alpha-Amanitin: A Specific Inhibitor of One of Two DNA-Pendent RNA Polymerase Activities from Calf Thymus," *Biochem Biophys Res Commun* 38, no. 1 (1970): 165-171.

Chambon later recalled his satisfaction over the eukaryotic RNA polymerase discovery. Multiple polymerases in eukaryotes began to explain how the complexity of sophisticated animals like humans had "evolved and made us possible." Their very plurality seemed an advance over the single polymerase found in bacteria. These and follow up studies by both groups to characterize the distinct structure of the polymerases bolstered the supposition of a consistent molecular mechanism for transcription across organisms of varying levels of complexity.[114] In theory, this provided a point of enzymatic intervention into the general transcriptional machinery of eukaryotes. In practice, however, this was not much more than an idea that enzymatic transcription was related to gene expression and cell differentiation. Reflecting on the experimental limits of the work, Chambon commented that, "We were in some ways stuck at the beginning of the [19]70s." At that time, biochemists could not reach "the base level" of the DNA structure to characterize where in the genome the transcribed copy was coming from.[115] Their work did however lend support to the idea that yeast might be a "true" eukaryote.

Seattle geneticist Benjamin Hall later described how researchers wanting to work in higher organism genetics at that time could move in one of two directions – mammalian cells,

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[114] In Pierre Chambon, interview by Richard Axel, 2004, "Albert Lasker Basic Medical Research Award," New York, Lasker Foundation Video Library, minute 5:25. For the follow up studies referred to, see RF Weaver, SP Blatti, and WJ Rutter, "Molecular Structures of DNA-Dependent RNA Polymerases (II) from Calf Thymus and Rat Liver," *Proceedings of the National Academy of Sciences* 68, no. 12 (1971): 2994-2999; C Kedinger, P Nuret, and P Chambon, "Structural Evidence for Two A-Amanitin Sensitive RNA Polymerases in Calf Thymus," *FEBS letters* 15, no. 3 (1971): 169-174.

[115] Chambon, "Albert Lasker Basic Medical Research Award," minutes 6:06, 10:14. Roeder and Rutter further studied transcription in bacteria and phage and found that they could use polymerases to affect gene expression but they too could not yet ascribe any molecular meaning to the transcribed DNA. The fifth chapter of this dissertation follows Hall, Rutter, and other investigators from the late 1970s as this work was transformed by the new tools of genetic engineering.

such as liver cells, which lacked the ease of microbial genetics, or yeast as a microbial eukaryotic system. Few chose the latter. According to Hall, when a group in Vancouver, British Columbia, found that yeast cells lacked the chromosomal protein histone H1, for example, they determined that yeast was not a "real" eukaryotic organism. "That was basically mistaken, but there were people of that persuasion. They said, 'If you want to understand mammalian cells, you have to study mammalian cells.'"[116] But with limited experimental access to higher organism chromosomes, such possibilities were limited.[117] Cell biologists, too, initially dismissed yeast as a model for complex organisms like mammals.[118]

Like many chemical converts to molecular genetics in the 1960s, Hall's early research interests in the department focused on *E. coli* and the phage. During a 1968-1969 sabbatical in Geneva, he continued to work in *E. coli*. He talked to his former mentor James Watson that year about the possibility of going into yeast, and Watson encouraged him to do so. Years later, Hall would reflect on this transition, saying, "I thought [that in yeast rather than in bacteria] there was

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[116] Hall, "Oral History with Ben Hall, Part 2." A number of studies looked at these claims about higher eukaryote histones in the yeast and fungi. See, for example, TJ Leighton et al., "Absence of Histones from the Chromosomal Proteins of Fungi," *Proceedings of the National Academy of Sciences* 68, no. 3 (1971): 677-680; D Lohr and KE Van Holde, "Yeast Chromatin Subunit Structure," *Science* 188, no. 4184 (1975): 165-166; Terrance Leighton et al., "The Similarities of Ribosomal and Basic Chromosomal Proteins from Fungi," *Biochimica et Biophysica Acta (BBA) - Nucleic Acids and Protein Synthesis* 432, no. 3 (1976): 381-394.

[117] At a 1972 meeting of the American Chemical Society in Seattle, the University of Washington biochemist Brian McCarthy planned to discuss the poor understanding of gene expression control in mammals despite the rather detailed understanding in simple organisms. See "Mccarthy to Speak in May," *Puget Sound Chemist* 33, no. 4 (1972): 9.

[118] In 1974, Randy Schekman, who had trained in biochemistry and begun postdoc in biology, attended a meeting of the Cell Biology Society where yeast was not represented. At that time, "The yeast people would have gone to more of a molecular biology meeting," he recalled. Schekman later became a Nobel and Lasker laureate for his generalizable work on the regulation of protein transport and secretion in yeast. See Randy Wayne Schekman, interview by Sally Smith Hughes, 2015, "Randy Wayne Schekman: Cell Biologist and UC Berkeley Nobel Laureate," Berkeley, CA, Oral History Center, The Bancroft Library, University of California, Berkeley, 41.

more for the explorer because we didn't really have a clue about how genes expressed in higher organisms."[119] Hall shared the view of his departmental colleagues that yeast would be a good experimental system to model higher organism genetics because it was a single-celled eukaryote open to microbial genetics and so many of its mutants had been characterized. When he returned to Seattle in 1969, Hall set out to characterize the biological function of the three eukaryotic RNA polymerases in yeast.[120] This was his entry into yeast research, and he was "working toward being able to transcribe genes in a test tube [to] study the process of transcription," independent of any organism.[121] In 1973, Hall described his research for the department noting that, "Yeast cells share some, but not all of the biochemical complexities of nuclear organization present in higher eukaryotes." He listed three RNA polymerases among the evidence in yeast's favor.[122]

Developmental Controls

[119] Hall, "Oral History with Ben Hall, Part 2."
[120] Roeder's dissertation work had identified polymerase enzymatic activities in yeast nuclear material, but when Roeder had tested these on yeast mutants, none appeared to show defect. See Robert Gayle Roeder, "Multiple RNA Polymerases and RNA Synthesis in Eukaryotic Systems" (PhD diss., 1969); R. G. Roeder, "Lasker Basic Medical Research Award. The Eukaryotic Transcriptional Machinery: Complexities and Mechanisms Unforeseen," *Nature Medicine* 9, no. 10 (2003): 1239-1244. Hall's laboratory performed a functional genetic analysis by selecting for drug-resistant yeast mutants with inhibitors of RNA polymerase. See R. Adman, L. D. Schultz, and B. D. Hall, "Transcription in Yeast: Separation and Properties of Multiple Fna Polymerases," *Proc Natl Acad Sci U S A* 69, no. 7 (1972): 1702. They found a protein that stimulated the RNA polymerases. See Ernesto Di Mauro, Cornelis P Hollenberg, and Benjamin D Hall, "Transcription in Yeast: A Factor That Stimulates Yeast RNA Polymerases," *Proceedings of the National Academy of Sciences* 69, no. 10 (1972): 2818-2822.
[121] See Hall, "Oral History with Ben Hall, Part 2." Hall echoed Roeder, who had used nearly the same words to describe his desired use of polymerase as an "opportunity to reconstruct a specific transcription event in a test tube." In Roeder, "Albert Lasker Basic Medical Research Award," minute 12:58.
[122] University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066).

Molecular genetics had provided new insights into yeast evolutionary biology but was slower to take hold in yeast developmental biology.[123] At first glance, yeast was an unlikely fit for studies of cellular differentiation which interested developmental biologists. A single cell was not an obvious choice for investigating the cooperation of many, diverse cell types in the higher organisms. Indeed, the Russo-French geneticist Boris Ephrussi quit his investigations of yeast at the start of the 1960s to study higher organism development using fused somatic (i.e. non-reproductive) mammalian cell lines. By "mating" the cells of mice, rats and humans, Ephrussi and colleagues thought that they might reproduce the biochemical methods of microbial genetics on a cellular hybrid of higher organisms. They were seeking direct access to higher organism gene expression, cellular differentiation, and the developmental controls behind cancer by imitating the microbes.[124]

A large number of geneticists left the study of prokaryotic bacterial biology over the course of the 1960s and moved into the "higher" eukaryotes in what has been called the

[123] Robert Meunier has argued that molecular biology adopted the questions of other disciplines in order to justify its existence after the operations of the genetic code had been "solved." Higher organism development offered embryological and neurophysiological puzzles. Molecular biologists needed experts in these fields to help define relevant phenotypes that were accessible to them at other levels of organismal complexity. See Meunier, "Stages in the Development of a Model Organism as a Platform for Mechanistic Models in Developmental Biology: Zebrafish, 1970–2000," 525.

[124] In her history of tissue culture, Hannah Landecker writes that "in the 1960s a practice alternately called "cell fusion," "cell hybridization," and "somatic cell mating" emerged… this episode of novel merging of cells resulted from an attempt to physically reshape the biological matter of higher organisms, particularly that of humans, to be more like their simpler models. The earliest experiments in cell fusion were directed at making complex somatic cells live, behave, and exchange genetic material as bacteria did." In Landecker, *Culturing Life: How Cells Became Technologies*, 181. Later recombinant DNA studies bore certain similarities to Ephrussi's interspecific transplantation technique. See D.T. Zallen and R.M. Burian, "On the Beginnings of Somatic Cell Hybridization: Boris Ephrussi and Chromosome Transplantation," *Genetics* 132, no. 1 (1992): 6.

"eukaryotic turn."[125] They quit working with *E. coli* and the phage and sought to develop new experimental systems in multi-cellular organisms. "[M]olecular genetics, pursued to ever lower levels of organization, inevitably does away with itself," wrote the former phage geneticist Seymour Benzer in 1971, while reflecting on his experiences of the prior decade. "More recently, a number of molecular biologists have turned their sights in the opposite direction, ie, up to higher integrative levels, to explore the relatively distant horizons of development, the nervous system, and behavior."[126] These complex systems included Sydney Brenner's choice of the nematode worm *Caenorhabditis elegans*, François Jacob's shift to the mouse, Seymour Benzer's search for behavioral mutants of *Drosophila*, Gunther Stent's use of the leech, and George Streisinger's studies of the zebrafish.[127]

Seattle's yeast program provided a further alternative. In one sense the intersection of molecular genetics with problems of developmental biology continued a very long tradition of analogizing biological subjects to more complex bodies and experiences. In another sense the mid-1960s witnessed the start of a new project to specify these similarities in the same molecular

[125] Jeanette Simmonds has called this eukaryotic turn, "a virtual Diaspora" in Jeanette Simmonds, *Community Matters: A History of Biological Nitrogen Fixation and Nodulation Research, 1965 to 1995* (Rensselaer Polytechnic Institute, 2007), 81.
[126] S. Benzer, "From the Gene to Behavior," *JAMA* 218, no. 7 (1971): 1015.
[127] For a sample of Brenner's work with the worm see S. Brenner, "The Genetics of Behaviour," *Br Med Bull* 29, no. 3 (1973): 269-271. See also de Chadarevian, "Of Worms and Programmes: Caenorhabditis Elegans and the Study of Development," 81-105. On Jacob and the mouse, see F. Jacob, *Of Flies, Mice, and Men* (Harvard University Press, 1998). See also Michel Morange, "François Jacob's Lab in the Seventies: The T-Complex and the Mouse Developmental Genetic Program," *History and Philosophy of the Life Sciences* 22, no. 3 (2000): 397-411. For an example of Benzer's work on the fly, see Seymour Benzer, "Behavioral Mutants of Drosophila Isolated by Countercurrent Distribution," *Proceedings of the National Academy of Sciences of the United States of America* 58, no. 3 (1967): 1112-1119. On Stent and the leech, see Gunther Stent, "Gunther Stent," in *The History of Neuroscience in Autobiography*, ed. Larry R. Squire (San Diego, California: Academic Press, 1998), 396-422. On Streisinger and the zebrafish, see David Jonah Grunwald and Judith S Eisen, "Headwaters of the Zebrafish—Emergence of a New Model Vertebrate," *Nature Reviews Genetics* 3, no. 9 (2002): 717-724.

terms as the systems' complexity. Shared molecular sequences were not analogous – they were identical. Molecularly-defined experimental systems could thus be anthropomorphized as "model organisms" in the place of direct access to higher organism biology.

Prior to the convergence of yeast molecular genetics and developmental biology at the end of the 1960s, Carlsberg laboratory's Øjvind Winge had provided "the first, and for a long period of time, the only attempt to extend the realms of cytogenetics from the level of organisms to the level of tissues" by visualizing complex tissues as genetically heterogeneous cell populations comparable to yeast cells in culture.[128] In 1961, Berkeley medical physicist Cornelius Tobias had written that yeast could be useful for investigating "many of the functions cells are capable of, in a general sense" with relevance to the higher organisms since "a colony of yeast cells, when grown on agar gel, exhibits certain primitive features of differentiation, has characteristic shape, and its cells are in different states of proliferation depending on the cell's position in the colony."[129]

Then there had been hope that all of life's processes could be read at the molecular level and would unify the biological sciences. In the early 1960s, microbes looked particularly useful

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[128] Over the course of his career, Winge had studied linkage and non-Mendelian inheritance in yeast, and made other practical applications of genetics in plants, poultry, dogs, horses, cattle, forest trees and humans. See "Professor Øjvind Winge," iii. Although he retired from directorship at Carlsberg, Winge continued his genetic research until 1963. In Westergaard, "Øjvind Winge. 1886-1964," 358. Carl Lindegren had continued to speculate in these terms toward the end of the decade, about the "societies" of cells that made up higher organisms. See Lindegren, "The Brain in Evolution," 58.

[129] Cornelius A. Tobias, "Quantitative Approaches to the Cell Division Process," in *Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability*, ed. Jerzy Neyman (Berkeley, California: University of California Press, 1961), 376. Tobias was at that time a professor of Medical Physics in the Donner Laboratory of the University of California at Berkeley and vice chair of Medical Physics for the Department of Physics at Berkeley. See Cornelius A. Tobias, interview by Prita Pillai and Anna Berge, January 16, 1995, "Human Radiation Studies: Remembering the Early Years," Eugene, Oregon, United States Department of Energy (DOE).

for generalizations since the cell - any cell - contained all the complexity of molecular interest. In 1963, LIFE magazine reported that, “A cell is not an individual, but a community - a highly organized community in which a vast and diverse population of molecules go about their business.”[130] Readers of the magazine learned that simple genetic systems like yeast would simplify the search for molecular mechanisms because, it was presumed, higher organisms would “generally have a great deal more DNA.”[131] The public also learned that the molecules of yeast could eventually help to explain human neurobiology and developmental processes as complex as aging. For example, when LIFE magazine reported that researchers had dosed elderly subject with yeast RNA and seen an improvement in their failing memories, RNA became in 1963, possibly “the very stuff that memory is made of.” At least, yeast RNA was “tied up in some way” with the process of human aging, the article explained.[132] Molecular biology would eventually have to explain development over the individual life course, and microbes might serve as a simple point of entry to human processes.

The University of Washington genetics department was well-positioned to argue for yeast’s transference role at the nexus of the past, present, and future of molecular biology.[133] From the second half of the 1960s, this group began a successful campaign to establish yeast as the premier experimental eukaryote with relevance to higher organism biology, and young,

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[130] Alicia Hills and Albert Rosenfield, "DNA: Key to All Life," *LIFE Magazine*, October 4, 1963, 77-78.
[131] D. Wilkie, *The Cytoplasm in Heredity* (Methuen, 1964), 5.
[132] Hills and Rosenfield, "DNA: Key to All Life," 82. There have since been a number of studies using yeast as a model for cellular aging. See, for example, Elizabeth H Blackburn, Carol W Greider, and Jack W Szostak, "Telomeres and Telomerase: The Path from Maize, Tetrahymena and Yeast to Human Cancer and Aging," *Nature Medicine* 12, no. 10 (2006): 1133-1138.
[133] Molecular biologists often made claims on the past and future as a way of securing their status in the present. See for example, Francis Crick’s introduction to the 1966 Cold Spring Harbor Symposium, Francis HC Crick, "The Genetic Code—Yesterday, Today, and Tomorrow" (paper presented at the Cold Spring Harbor Symposia on Quantitative Biology, 1966), 3-9.

creative researchers passing through Seattle began to take up the refrain. They were attracted to Roman's department because of its spacious facilities, its cooperative intellectual atmosphere, and the "avant-garde" eukaryotic focus.[134] With ready access to a large amount of experimental material, tools, equipment, and interdisciplinary expertise, yeast could be put to work immediately. The molecular genetics were well-established, and the leading investigators were welcoming compared to competitive programs like that of Caltech where *Neurospora* work was being done.[135] It would be easier to establish developmental experiments in yeast where the molecular biology was still relatively untouched, or at least, unparceled territory.

For former bacterial geneticists, the move into yeast was scientifically justified by the finding of different gene regulation in prokaryotic and eukaryotic cells. "[T]here was a realization that people have to study a eukaryotic microorganism," Fred Sherman recalled, "and the most logical choice was either *Neurospora* or yeast."[136] Based on earlier work done at Caltech and in the Lindegren laboratory in Carbondale, it had been shown that haploid *Neurospora* had approximately twice the nuclear DNA content of yeast.[137] Seattle researchers referred repeatedly to the quantity of DNA in yeast as an important criterion justifying research with their organism, claiming a small genome as an important practical advantage. Yeast was

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[134] The department is described in Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."; Robin Holliday, General Correspondence, 1941-1989, (October 13, 1965), Box 1, Folder 6, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.

[135] In the mid-1960s, "hypotheses capable of being generalized from genetic reasoning were permitted to originate only in Cambridge, Paris, or Pasadena." In von Borstel, "Taming the Oldest Domesticated Organism," 191.

[136] Sherman, "Oral History Interview."

[137] See Maurice Ogur et al., "The Nucleic Acids in a Polyploid Series of Saccharomyces," *Archives of Biochemistry and Biophysics* 40, no. 1 (1952): 175-184; NH Horowitz and H Macleod, "The DNA Content of Neurospora Nuclei," *Microbial Genet. Bull* 17, no. 6 (1960); R L Metzenberg, "Biochemical Aspects of Genetics," *Annual Review of Biochemistry* 34, no. 1 (1965): 527-564.

held to be an only slightly larger version of *E. coli*, so it offered a move into the eukaryotic cell without the complexity of a large genome.[138]After joining Roman's genetics department in 1967, for example, the microbiologist Walton Fangman reportedly switched from the study of prokaryotic chromosomes into yeast after being "seduced by the small size of the budding yeast genome."[139] Fangman and graduate student Thomas Petes later estimated the average DNA content of yeast eukaryotic chromosomes as "four times smaller than [*E.* coli] and only six times larger than phage T4..."[140] They also found that yeast contained a large number of chromosomes like the higher eukaryotes, but that each one of these was "usually small."[141] The finding helped to confirm yeast as simultaneously both complex and simple. Various structural semblances were identified as cytological evidence for yeast's eukaryotic status and began to contradict the claim that yeast "superficially" lacked homology with higher eukaryotes.[142] This evidence included descriptions of the yeast spindle which supported the belief "that yeast is a bona fida eukaryote whose study should yield cell biological insights of general significance."[143] Seattle's geneticists had already accepted yeast as a model eukaryote in order to justify the continuation of their

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[138] See Fred Winston, "Transcription," in *Landmark Papers in Yeast Biology*, ed. Patrick Linder, David Shore, and Michael N. Hall (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 67. Fungi were ordered above bacteria and before invertebrates. In M. Terzi, *Genetics and the Animal Cell* (Wiley, 1974), 181.

[139] "40 Years of the Yeast Genome: Walt Fangman - a Man Ahead of His Time," accessed August 24, 2015, www.gs.washington.edu/news/fangman. See also Fangman's interest in yeast cell cycle regulation in University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066).

[140] T. D. Petes and W. L. Fangman, "Sedimentation Properties of Yeast Chromosomal DNA," *Proc Natl Acad Sci U S A* 69, no. 5 (1972): 1188.

[141] T. D. Petes, B. Byers, and W. L. Fangman, "Size and Structure of Yeast Chromosomal DNA," *Proc Natl Acad Sci U S A* 70, no. 11 (1973): 3072.

[142] Breck Byers and Loretta Goetsch, "Duplication of Spindle Plaques and Integration of the Yeast Cell Cycle," *Cold Spring Harbor Symposia on Quantitative Biology* 38 (1974): 123.

[143] J.R. Pringle, "Cytoskeleton and Morphogenesis," in *Landmark Papers in Yeast Biology*, ed. P. Linder, D. Shore, and M.N. Hall (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 212; P.H. Matile, H. Moor, and C.F. Robinow, "Yeast Cytology," in *The Yeasts: Biology of Yeasts*, ed. A.H. Rose and J.S. Harrison (New York: Academic Press, 1969), 219-302.

program. Much of the evidence which later characterized yeast as a eukaryotic cell came to sustain and vindicate an existing practice.[144] Perhaps the most convincing argument to those outside of the field came from a set of studies by Seattle biologist Leland Hartwell on the yeast cell cycle. Hartwell analogized the life cycle of the cell to higher organism development through shared molecular homologies.

The Eukaryotic Cell Cycle

Hartwell felt that he had floundered during his postdoc in the early 1960s at the recently-established Salk Institute. There, he had attempted to pursue "fundamental" controls of cellular division and development using the techniques of animal virology. His mentors, Renato Dulbecco and Marguerite Vogt, had had successes with the study of tumor viruses, and Hartwell attempted similarly to infect animal cells in culture to observe heritable changes. As he later explained, he wanted to study the mechanisms controlling cell growth in order to understand the development of human cancer.[145]

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[144] In 1974, for example, University of Michigan botanist Julian Adams and University of California, Davis geneticist Paul Hansche ran up against some interpretive difficulties with the finding that yeast diploidy did not confer any direct selective advantage in a population of cells. Geneticists had believed that diploidy, with its higher content of DNA, was more complex molecularly. This agreed with the evolutionary observation that the life cycle of higher organisms was dominated by the diploid phase with haploids existing only as reproductive cells. New justifications were sought to support these conclusions even when they did not seem to hold up in yeast. The investigators hypothesized that "primeval diploids possessed special characteristics, long since lost, which enabled them to compete favorably with haploids." In J. Adams and P. E. Hansche, "Population Studies in Microorganisms. I. Evolution of Diploidy in Saccharomyces Cerevisiae," *Genetics* 76, no. 2 (1974): 337.

[145] L. H. Hartwell, "Nobel Lecture: Yeast and Cancer," in *Les Prix Nobel*, ed. Tore Frängsmyr (Stockholm University: Nobel Foundation, 2001), 246. This memory is partly teleological. Although his interest in cancer may have been as a "molecular disease", cancer causing mutations were realized out of work on the cell cycle. See also L Pray, "LH Hartwell's Yeast: A Model Organism for Studying Somatic Mutations and Cancer," *Nature Education* 1, no. 1 (2008): 183.

After three unsuccessful attempts to establish his own animal cell genetic system, Hartwell was losing faith in the approach.[146] Mammalian cells were not as tractable as bacteria for the genetic manipulations he had learned to perform at Caltech and MIT, and yet gene regulation in bacteria was already well-covered territory since Jacob and Monod had published their findings.[147] To establish himself as an independent investigator, Hartwell felt that he needed his own experimental system. A year and a half into his postdoctoral research at the Salk, he was contacted by virologist John Holland, chair of the department of molecular and cell biology at the newly-founded University of California, Irvine, and offered an assistant professorship.[148] In 1965, Hartwell headed north with grant funding to work in mammalian cells but no idea how this would be done.

In its inaugural year of instruction, the University of California, Irvine offered training in molecular and cell biology, organismal biology, population and environmental biology, and psychobiology because, the course catalogue explained, “the findings made at any one level of biology assist in understanding phenomena occurring at another level.” In 1965, microbes were a central focus only of experimental training in molecular and cell biology, and also for the study of population dynamics which might map onto the problem of the “human population

[146] L. H. Hartwell, interview by Rachel Easton Esposito, March 15, 2015, "Cell Cycle Control in Yeast," Fred Hutchinson Cancer Research Center, Seattle, Washington, Genetics Society of America and R. Easton Esposito, 18:23.

[147] At MIT, Hartwell studied with molecular biologist Boris Magasanik, graduating in 1964. Magasanik took up study of yeast molecular biology after Beth Jones brought yeast to his lab in the late 1960s. Jones had trained with Roman in Seattle and had completed the Ph.D. in 1964. See "Ascb Profile: Elizabeth Jones," *The ASCB Newsletter*, July 2004, 8-10.

[148] Holland’s training and recruitment to Irvine is described in Katherine R. Spindler and Bert L. Semler, "In Memoriam John J. Holland (1929-2013): A Pioneer in Molecular Virology," *Journal of Virology* 88, no. 11 (2014): 5903-5905.

explosion."[149] Microbes were not yet utilized in the study of organismal biology, which considered comparative morphology, physiology and development of the plants and animals.

While waiting for his mammalian cell culture equipment to ship to Irvine, Hartwell discussed his dilemma with another new hire at the University of California, Irvine, the biochemical geneticist Dan Wulff, who had trained at Caltech and done a postdoc with James Watson at Harvard.[150] Wulff recommended that Hartwell reconsider his choice of experimental material and look again to the microbes for a eukaryotic organism. A trip to the library convinced Hartwell to choose yeast. As a single-celled eukaryote, haploid yeast had the complexity of a eukaryotic cell but a small amount of genetic material, and it was amenable to simple genetic analysis which could show dominant and recessive mutations.[151] These traits allowed Hartwell to approach yeast with the same logic and techniques of bacterial genetics, but to characterize his work as something new. Besides, he later reflected, yeast "was really the only game in town."[152]

To get started in yeast genetics, Hartwell visited the laboratories of both Herschel Roman in Seattle and Robert Mortimer in Berkeley to "learn a little yeast methodology," get set up with

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[149] *University of California at Irvine Initial Bulletin / 1965-66 Catalogue*, vol. 1 (University of California at Irvine, 1965), 17-19. Although Paul and Anne Ehrlich's influential book, *The Population Bomb* would not be published for another three years, human overpopulation was already a major concern from the 1950s and 1960s. See Pierre Desrochers and Christine Hoffbauer, "The Post War Intellectual Roots of the Population Bomb. Fairfield Osborn's 'Our Plundered Planet' and William Vogt's 'Road to Survival' in Retrospect," *The Electronic Journal of Sustainable Development* 1, no. 3 (2009): 73.

[150] Daniel L. Wulff, Curriculum Vitae, (1963), JDW/2/2/2032/2173, James D. Watson Collection (1870-2012), Cold Spring Harbor Laboratory Archives, New York.

[151] L. H. Hartwell, "Macromolecule Synthesis in Temperature-Sensitive Mutants of Yeast," *J Bacteriol* 93, no. 5 (1967): 1662.

[152] In Brendan Maher, "Rising to the Occasion," *The Scientist*, June 2, 2003.

strains from their collections, and borrow some experimental equipment.[153] "I experienced this tremendous generosity," Hartwell recalled of the Seattle and Berkeley groups.[154] Hartwell telephoned them with questions and they opened up their laboratories. He returned to Irvine and set up his first experiments, venturing an update to Mortimer at Berkeley in June of 1966: "Dear Dr. Mortimer: The yeast are even mating in my lab now."[155] By the following year, Hartwell had isolated a number of temperature-sensitive mutants.

Hartwell's initial experiments borrowed a screening method developed in bacteriophage. When he exposed his haploid yeast to a certain "restrictive" or "nonpermissive" temperature, ten percent of cells showed conditional mutations – they stopped growing. The others continued to look and behave like the wild-type. As a consequence of years of industrial research on this yeast much was known of the organism's performance under various environmental conditions.[156] Among his mutants, Hartwell found that some yeast seemed to lack a number of normal processes such as protein synthesis at a particular elevated temperature.[157]

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[153] Hartwell names the sources of his material as Robert Mortimer and Rochelle Esposito, the latter who was then a graduate student in Herschel Roman's laboratory. See also his acknowledgements in Hartwell, "Macromolecule Synthesis in Temperature-Sensitive Mutants of Yeast," 1663, 1670. He recalled that Donald Hawthorne (also in Seattle) loaned him his first micromanipulator and taught him tetrad analysis to start the work. In Hartwell, "Leland H. Hartwell - Biographical."; L. H. Hartwell and C. S. McLaughlin, "Mutants of Yeast with Temperature-Sensitive Isoleucyl-tRNA Synthetases," *Proceedings of the National Academy of Sciences of the United States of America* 59, no. 2 (1968): 428.

[154] Hartwell, "Cell Cycle Control in Yeast," 22:52.

[155] L. H. Hartwell, Technical Documents, 1950-1999, (June 27, 1966), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425), Ernest Orlando Lawrence Berkeley National Laboratory Archives and Records, Berkeley, CA.

[156] In 1920, the French botanist Alexandre Guilliermond, for example, wrote that Carlsberg physiologist Emil Christian Hansen had shown that, "for each variety of yeast, there exist certain temperature limits outside of which sporulation becomes impossible. Between these limits, the time necessary for the formation of ascospores is constant for a variety for a given temperature." In Guilliermond, *The Yeasts*, 117.

[157] Hartwell teamed up with Irvine biochemist Calvin McLaughlin to figure out what these proteins did in cellular processes. See Hartwell and McLaughlin, "Mutants of Yeast with

In 1968, Roman recruited Hartwell to his genetics department at the University of Washington in Seattle to continue to explore this phenomenon. There, Hartwell and undergraduate student Brian Reid began to observe the temperature-sensitive mutants using photomicroscopy. They captured time-lapse images of the yeast budding and breaking off into daughter cells, and soon realized that bud size could be used as a temporal indicator. When ordered from small to large, the budding mutants offered a sequential picture of gene function at specific points in the yeast cell cycle.[158]

The English bacteriologist and visiting research professor to Seattle Don Williamson had previously assessed the age of a yeast cell by the size of its bud with a warning that defining cell cycle in this way "does not include any interval that may occur between the separation of parent and daughter" but only applied to the period from the appearance of a bud to its separation.[159] Williamson noted that this measure of the cell cycle excluded the "lag periods" which occurred under poor growth conditions. In other words, the period during which yeast cells were interesting and could be measured was during reproduction and not any period outside of that. This resonated with the earlier measure of yeast "mortality" as the point at which a cell could no longer divide and yeast "life span" as its number of cell divisions.[160] By defining the conditions in which yeast did not reproduce as "poor" by virtue of the lack of reproduction, Williamson

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Temperature-Sensitive Isoleucyl-tRNA Synthetases," 422-428; L. H. Hartwell and C. S. McLaughlin, "Temperature-Sensitive Mutants of Yeast Exhibiting a Rapid Inhibition of Protein Synthesis," *J Bacteriol* 96, no. 5 (1968): 1664-1671.

[158] Reid and Hartwell's "Eureka! evening" is described in Brian J. Reid et al., "Forty-Five Years of Cell-Cycle Genetics," *Molecular Biology of the Cell* 26, no. 24 (2015): 4308.

[159] Just prior to Hartwell's arrival in Seattle, Williamson had served as a research associate professor in the Seattle genetics department during a sabbatical from his post at the John Innes Institute in Hertfordshire.

[160] See Mortimer and Johnston, "Life Span of Individual Yeast Cells," 1751.

reinforced the idea that there was "little error" in the neglect of the nonreproductive period. The cell cycle was that sequence of events from bud development to separation only.[161]

Hartwell's laboratory adopted this definition of the cell cycle and the use of bud size as a marker within it. Different bud sizes, ordered sequentially, stood in for the temporal stages of development experienced by a single hypothetical cell. Using nutritional and other shocks to produce cycle synchronicity in the cells, the Hartwell laboratory began identifying mutants which arrested with particularly-sized buds.[162] These cells were stuck at particular points in the cell division cycle, Hartwell determined, because of their mutations which did not permit the orderly progression of events.[163] Hartwell was describing yeast variability - how yeast differed from itself at various points in time in terms of the proteins and genes involved. As a consequence he defined his mutants as molecular events.

These cell cycle experiments offered a new temporality to molecular genetics – that of developmental time. In the early 1970s, Hartwell worked with three graduate students, a postdoc, and a technician to develop a model of the eukaryote cell division cycle that included points of genetic execution and termination.[164] Normal cell growth was related to the prescribed order of

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[161] "The ages of these individuals within the cell cycle were estimated by measuring their sizes…. [B]ud length [a relative measure of bud size to parent cell] was converted to an estimate of age… based on measurements made on thirteen individuals…" In D. H. Williamson, "The Timing of Deoxyribonucleic Acid Synthesis in the Cell Cycle of Saccharomyces Cerevisiae," *J Cell Biol* 25, no. 3 (1965): 523, 526, 527.

[162] The production of synchronous cultures was used for cell cycle studies in many different fields in the late 1960s. See J. Murdoch Mitchison, "The Cell Cycle of Fission Yeast," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 318; Kim Nasmyth, "Cell Division," in *Landmark Papers in Yeast Biology*, ed. Patrick Linder, David Shore, and Michael N. Hall (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 110.

[163] L. H. Hartwell, J. Culotti, and B. Reid, "Genetic Control of the Cell-Division Cycle in Yeast. I. Detection of Mutants," *Proc Natl Acad Sci U S A* 66, no. 2 (1970): 352.

[164] See L. H. Hartwell, "Saccharomyces Cerevisiae Cell Cycle," *Bacteriol Rev* 38, no. 2 (1974): 164-198; L. H. Hartwell, "Getting Started in the Cell Cycle," in *The Early Days of Yeast*

function, and events such as bud emergence, DNA synthesis, nuclear division, and cell separation could be temporally ordered under gene control.[165] The work attracted new investigators to yeast molecular genetics in this period. David Botstein, for example, said that the cell cycle studies were "the single most important intellectual reason I decided to study yeast." He took up work with the eukaryotes at MIT in the belief that yeast molecular genetics "could lay bare the mechanisms underlying phenomena like eukaryotic DNA replication and mitosis."[166]

Yeast also allowed the continuation of existing experimental practices and their reinvigoration with new meaning. At the start of the 1970s there was no reason to believe that the biochemistry of cell cycle control would be so highly conserved among the eukaryotes. Yeast geneticist Kim Nasmyth later reflected, "Those who chose to study yeast did not do so in the conviction that the molecules controlling its chromosome segregation would prove identical to those in [humans], but did so rather in the belief that there was at least some chance of making progress with simpler systems with powerful genetics."[167] Yeast was easy to use and available for genetic study, and there had been a chance that as a microbial eukaryote it would offer useful molecular description no matter what the experimental outcome. Similarities to the higher

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Genetics, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 310; Donald H. Williamson, "Circles and Cycles: Early Days at Nutfield," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 329.

[165] In the 1980s, Hartwell elaborated on this picture of the yeast cell cycle with a theory that the cell moved through a series of dependent events like a clock, and if the DNA was damaged at any point in the cycle a built-in repair mechanism would be triggered at a "checkpoint" to stop and correct the cell's progression. When checkpoints failed, the result might be cancer. In Hartwell, "Nobel Lecture: Yeast and Cancer," 259.

[166] David Botstein, "A Phage Geneticist Turns to Yeast," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 365; David Botstein, interview by Mila Pollock, Jan Witkowski, and Kiryn Haslinger, May 29, 2003, "Oral History Interview," New York, Cold Spring Harbor Laboratory Archives.

[167] Kim Nasmyth, "A Prize for Proliferation," *Cell* 107, no. 6 (2001): 691. Nasmyth later completed a postdoc in Seattle in the laboratory of Benjamin Hall. His work is discussed in detail in the fifth chapter.

organisms could be justified on the basis of genetic dogma and differences on the basis of evolutionary theory.[168] Rather than to determine if a particular microbe functioned like a human cell, researchers could investigate what made a microbe and a human cell, as eukaryotes, distinct from prokaryotes.

In order to make a microbial claim to developmental biology, Hartwell and colleagues needed to mount this evolutionary defense for the relevance of the model. Hartwell claimed, that "it would *not be unreasonable* to expect that answers to these questions would have import beyond the boundaries of mycology."[169] This was because, "The events that comprise the cell division cycle have their origin in a distant evolutionary past common to all eukaryotic organisms."[170] The development observed in microbial models thus brought together molecular genetics and the homology of the microbiologists to produce a molecular biology of the cell.[171]

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[168] As an example, see Breck Byers on the hope that yeast would provide a broad outline of eukaryotic mechanisms. Byers joined the genetics faculty in Seattle in 1971. See University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066). He later claimed that, "Any similarities between processes occurring in yeasts and those in plants or animal cells may indicate useful experimental approaches for the latter organisms, which are less amenable to genetic analysis. In contrast, any differences should aid in defining those mechanisms that are fundamental to the eukaryotic mode of cellular function." Breck Byers, "Cytology of the Yeast Life Cycle," in *The Molecular Biology of the Yeast Saccharomyces, Life Cycle and Inheritance*, ed. J.N. Strathern, E.W. Jones, and J.R. Broach (Cold Spring Harbor, New York: Cold Spring Harbor Laboratory, 1981), 59.

[169] Hartwell, "Saccharomyces Cerevisiae Cell Cycle," 191. Italics added for emphasis.

[170] The Hartwell laboratory grounded this defense in an appeal to biological unity and the eukaryotic "basic plan." "[I]t is interesting to note that the only events of the *S. cerevisiae* cell cycle that are not common to most eukaryotes, bud emergence and nuclear migration, are on a separate pathway from the other events, as if they were appendages added to the basic plan." L. H. Hartwell et al., "Genetic Control of the Cell Division Cycle in Yeast," *Science* 183, no. 4120 (1974): 50.

[171] Michel Morange found that cell division models of the late 1970s sought to explain molecular mechanisms in higher organisms by changing the direction of explanation "from a molecular biology of the gene to a molecular biology of the cell." While Morange based this conclusion on the convergence of embryology and molecular genetics, yeast research provides an additional claim for microbiology in the origins of molecular cell biology. See Morange, "The

To support the popularity of his model, Hartwell freely shared his cell cycle mutants in the U.S. and abroad.[172] Robert Mortimer, who was by then the chair of medical physics for the University of California, Berkeley, visited Seattle in 1973 to add another fourteen cell cycle genes to the yeast genetic map.[173] Molecular descriptions of eukaryotic yeast models became potentially useful to studies of multicellular differentiation which addressed how the cells of higher organisms contained the same genetic information and yet took the form of different cell types. Hartwell and graduate student Lynna Hereford claimed "broad significance" for the genetic control of specific events in the yeast cell cycle in 1974, because, they wrote, "we view the initiation of DNA synthesis in *S. cerevisiae* as an act of differentiation." Just like the cell types of higher organisms which became skin cells or liver cells or eye cells, the yeast haploid was a model of differentiation because it had a "choice" of initiating DNA synthesis, fusing with another cell to create a zygote, or entering a stationary phase.[174] Hartwell described his cell cycle control research in part as trying to answer the question, "What events are involved in making the decision to change from one stage of the cell life cycle to another?"[175] Such "decisions" were

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Transformation of Molecular Biology on Contact with Higher Organisms, 1960-1980: From a Molecular Description to a Molecular Explanation," 370, 391.

[172] Herschel Roman, General Correspondence, 1941-1989, (January 18, 1983), Box 1, Folder 7, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.

[173] L. H. Hartwell et al., "Genetic Control of the Cell Division Cycle in Yeast: V. Genetic Analysis of cdc Mutants," *Genetics* 74, no. 2 (1973): 267-286. Mortimer's yeast genetic map is discussed in the previous chapter.

[174] L. M. Hereford and L. H. Hartwell, "Sequential Gene Function in the Initiation of Saccharomyces Cerevisiae DNA Synthesis," *J Mol Biol* 84, no. 3 (1974): 446.

[175] University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066).

mechanistic and generalizable. Additional investigators would further develop the potential of yeast models for use in the studies of cellular differentiation.[176]

In his 2001 Nobel lecture for this work, Hartwell claimed that "the yeast cell has revealed some of its secrets" and "has told us something that is relevant to mankind."[177] By then, the yeast cell cycle held not just for yeast but for all organisms undergoing eukaryotic cell division, and it promised to reveal what went awry in the runaway division of human cancer cells. Genetic engineering and sequencing efforts which had revealed the conservation of molecular sequences in yeast and higher organisms offered post hoc proof that the yeast cell cycle was generally representative of the eukaryotes.[178] The search for conserved sequences had predetermined that those sequences had relevance since the functional molecules found in humans were first given their identity in yeast.[179] Hartwell appeared to consider this when he stated, "It's beyond similarity. I mean, it's almost identity," he said of the shared eukaryotic controls.[180] It is not surprising then that the Human Genome Project revealed few additional cell cycle regulators, meaning that almost all of these had been identified in yeast during the 1970s and 1980s.[181]

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[176] University of Oregon yeast geneticist Ira Herskowitz and members of the Cold Spring Harbor Yeast Genetics Group will be discussed in the next chapter.

[177] Hartwell, "Nobel Lecture: Yeast and Cancer," 246.

[178] Yeast today shares roughly a third of its 6,000 genes with humans. See Kun Yang, "NYU Langone Medical Center Press Release," news release, (WordPress: NSF Science Across Virtual Institutes), March 27, 2014. This has had important consequences for yeast-based models of disease. See, for example, the claim that "*S. cerevisiae* is an informative predictor of human gene function; nearly 50% of human genes implicated in heritable diseases have yeast homologues." In Kumar and Snyder, "Emerging Technologies in Yeast Genomics," 302.

[179] Yeast geneticist Kim Nasmyth has written that it was not until yeast and mammalian cell cycle components were found to be molecularly conserved in the early 1990s that geneticists fully accepted the yeast cell cycle as generally representative of the eukaryotes. See Nasmyth, "Cell Division," 129. Since these studies first needed to determine which components would be relevant if conserved, I argue that such studies offered confirmation post hoc.

[180] Hartwell quoted in Maher, "Rising to the Occasion."

[181] See M. M. Barr, "Super Models," *Physiol Genomics* 13, no. 1 (2003): 18. The term eukaryotic "super model" has also been applied to *S. cerevisiae* by Rowland Davis who describes the

One of Hartwell's co-laureates, the British geneticist Paul Nurse, who shared the Nobel prize for his own cell cycle work in fission yeast during a slightly later period, told the *New York Time*s in 2003 that although yeast and humans "last were together 1,500 million years ago," yeast was a relevant model organism because, "The cell is the basic structural and functional unit of life. It is life itself. It is chemistry made into biology... organized in such a way that we get… purposeful behavior." Nurse referred to "the ability to reproduce yourself, the ability to organize yourself in space and time, the ability to maintain yourself. I am talking about "myself" as a cell."[182]

A Model Eukaryote

Microbiology had helped to transform the meaning of biological specificity in the transition from classical to biochemical genetics. Molecular biology, which rose on the successes of microbial genetics over the 1930s, 1940s, and 1950s, was again transformed at the start of the 1960s when it seemed that general genetic principles had specific operational contexts. The rules of genetic regulation appeared to differ among existing experimental systems and could be explained by an existing classification in cell biology of cell type differences between the prokaryotes and eukaryotes. Over the course of the decade, molecular biologists began to turn from characterizing the activity of the gene to the activity of the cell. Feeling that the former had largely been resolved, the latter enabled a redefinition of their project to continue generalizing

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yeast's contributions to the problems of genetic recombination, macromolecular synthesis, metabolic regulation, the cell cycle, general cell biology, mitochondrial genetics and organelle DNA. In Davis, "The Age of Model Organisms," 72.

[182] Claudia Dreifus, "New Rockefeller Chief Discovered Lessons of Life in a Cell of Yeast," *The New York Times*, May 13, 2003. Nurse had worked on the cell cycle of fission yeast *Schizosaccaromyces pombe*, whose genetics was developed independently from baker's yeast after Øjvind Winge first recommended the organism to Urs Leupold in the mid-1940s.

about biology within evolutionary limits. They began to remake the theory of natural selection as molecular.

Yeast molecular geneticists developed their experimental system from the early 1960s to provide an intellectual transition between the lower and higher organisms. As a simple eukaryote, yeast could be used experimentally like bacteria but compared to multicellular organisms like plants and animals, and especially humans. Support for this project came as their practices, concepts, and materials found applications in the molecular study of evolutionary and developmental biology.[183] The identification of shared molecular sequences built on a long tradition of analogizing yeast characters and borrowed from microbiology the concept of homology at the level of both organism and cell. Molecules themselves were anthropomorphized by this project, eventually preparing a role for yeast as a model organism in a new practice of molecular cell biology.[184] Carl Lindegren had argued as early as 1958 that yeast was representative of a human cancer cell because it contained a nucleus and that therefore "yeast cells are better scientific tools for study of heredity than bacteria." For Lindegren, the relevance of the yeast nucleus was to enable study of cytoplasmic heredity because, "The mechanisms of

[183] Charles Darwin had disentangled heredity, evolution, and development as separate problems in biology more than a century earlier and these investigations had since matured into the independent specialties of evolutionary biology, genetics, and developmental biology. See Comfort, *The Science of Human Perfection: How Genes Became the Heart of American Medicine*, 245. The molecular unification of these disciplines which began in the 1960s further developed into the "evo-devo synthesis" in the 1980s. See Alan C Love and Rudolf A Raff, "Knowing Your Ancestors: Themes in the History of Evo-Devo," *Evolution & development* 5, no. 4 (2003): 329.

[184] The origins of molecular cell biology have been explored in relation to the tradition of embryology. See Morange, "The Transformation of Molecular Biology on Contact with Higher Organisms, 1960-1980: From a Molecular Description to a Molecular Explanation," 369-393. There is likely much to be said for the influence of microbiology upon this discipline as a project of constrained generalization - what Hartwell and colleagues have termed "modular cell biology." See L. H. Hartwell et al., "From Molecular to Modular Cell Biology," *Nature* 402 (1999): C47-C52.

heredity are not necessarily confined to the nucleus, or genetic part of the cell."[185] This view ran contrary to the established dogma and at the time he was largely ignored. Yeast's nucleus did not become a relevant cellular homology until it represented the evolution of the eukaryotic organism.[186]

The effort to position yeast as an intermediary between the lower and higher organisms was not without its share of scientific dissenters. Hartwell recalled what he was up against in the early 1970s, noting that "yeast has, at various times, been accused of not being a proper eukaryote."[187] Outside of Seattle, early cytoplasmic and biochemical evidence for yeast's eukaryotic status was not universally convincing. When it was soon found to be politically expedient to characterize yeast in this way, however, the cultural motivations were enough to overcome any lingering scientific objections. Throughout the course of the 1960s, eukaryotic molecular biology enabled new disciplinary syntheses, continued exchanges, travel, construction, and development of research resources. This was the decade in which yeast molecular geneticists accessed NIH funding for human disease research and established a new research facility in Seattle, an informal stock center in Berkeley, regular international yeast meetings, and a common naming scheme for their practice. The next chapter examines the acceptance and widespread diffusion of yeast eukaryotic models over the course of the 1970s and 1980s when the benefits of these resources were recognized by New York's Cold Spring Harbor Laboratory.

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[185] "Calls Yeast Cells the Key to Study of Cancer Growth," *Chicago Daily Tribune*, March 1, 1958, 9.

[186] That yeast even had a nucleus has been in dispute as late as 1946. See the cytological evidence offered by a collaborator of the Lindegrens in Lillian Nagel, "A Cytological Study of Yeast (Saccharomyces Cerevisiae)," *Annals of the Missouri Botanical Garden* 33, no. 3 (1946): 249-289.

[187] Hartwell, "Nobel Lecture: Yeast and Cancer," 246.

Chapter 4

Molecularizing Humans in the Eukaryotic Turn

Many molecular biologists who had established themselves in prokaryotic systems moved away from bacteria and the phage during the 1960s. They, and their students, turned to mammalian cell lines, to older well-established multicellular eukaryotes like *Drosophila*, and to yeast where a burgeoning genetics community had begun to thrive. Some chose yeast for practical reasons: it was inexpensive, widely available, and easy to use and maintain. Others were drawn to uncharted molecular territory and enjoyed the welcoming department at the University of Washington in Seattle, where yeast molecular genetics had grown to have applications in studies of evolutionary and developmental biology. Still others were certain that yeast provided the logical next step in the study of the organization and functioning of heredity material, and they would spend years working to shore up this conclusion by establishing the microbe as a true eukaryote.

The politics of the eukaryotic turn in molecular biology at the end of the 1960s were similar to those characterizing many of the basic sciences at this time and involved several decades of ramped up federal research funding and questions about the return on this investment. The present chapter examines the impetus for this transition into the eukaryotes which would justify this move as an application of basic science and the prokaryotic dogma. Drawing from the examples of American space science and environmental health science, the chapter explores how yeast came to be applied not just as an experimental system with which to characterize the gene, nor simply as a eukaryotic cell with which to characterize the molecular biology of higher eukaryotes, but rather as a model organism representing the human body molecularly. Rather

than the study of molecules and molecular problems per se, eukaryotic genetics became the study of humans and human problems through molecularized organisms. On New York's Long Island, Cold Spring Harbor Laboratory recognized the benefits of applied molecular research in yeast models in the 1970s and 1980s as a means to access new funding streams, to attract new trainees, and to hold the interest of the genetics research community by shifting the center of yeast molecular research from Seattle. The latter half of the chapter describes Cold Spring Harbor's appropriation of the Seattle model along with the many politically beneficial manifestations of yeast eukaryotic models as applied tools for the study of human health and disease.

Politicizing the "Eukaryotic Turn"

The late 1960s brought a critique of the basic sciences: on the one hand, a desire for the application of research findings to work concretely in the world, and on the other, a cautionary tale especially from the physical sciences which had produced the applied means for atomic warfare.[1] The ongoing Cold War arms race including the space programs of the Americans and Soviets made visible the enormous power and consequences of applied science, as did the chemical technologies of war raining down upon Vietnam. Many university campuses were sites for intense political activity in the late 1960s and early 1970s, and scientists left this training

[1] Eric Vettel has examined the cultural (and countercultural) origins of Bay Area biotech in the postwar period, identifying the important shift from philanthropic to federal research funding, and the demand for return on basic research in the form of practical applications beginning in this period. In Eric James Vettel, *Biotech: The Countercultural Origins of an Industry* (Philadelphia: University of Pennsylvania Press, 2006), 129. Vettel also found that what was considered "basic" was often determined teleologically and that the research categories of "pure" and "applied" have been historically contingent.

wanting to effect social change in places where their predecessors had failed.[2] In this sense, the "eukaryotic turn" in molecular biology that occurred at the end of the 1960s offered a chance at engagement, an advance toward real interventions for humanity from the applied insights discovered in lower organisms. On the other side of the coin, the ethical critique that cautioned against physics as a model for the basic sciences also extended to genetic practice, and there was some hesitancy about what the next stage of molecular genetics would bring. The negative eugenic programs of the Second World War, including the racially-motivated mass murder carried out by the Nazis, were commonly understood as the misapplication of genetic science. Perhaps in the application of basic concepts to higher organisms, corrupt agendas in genetics might again mislead the science.

Although this discourse was the dominant ethical framing for applied eugenics, not everyone took for granted the "purity" of the basic sciences. The American microbiologist Catherine Roberts, who had joined Øjvind Winge at Carlsberg laboratory for fifteen years starting in 1946, had her own reasons for leaving yeast genetics and scientific practice more generally in the 1960s. Roberts, who had received her Ph.D. in botany from the University of California at Berkeley in 1943, performed early yeast genetic experiments, translated many of Winge's works into English, and published on yeast sugar utilization during her years in Copenhagen. In the early 1960s, Roberts returned to the United States where her beliefs about scientific practice underwent a strong reversal. She began to critique the biological sciences as dehumanizing particularly with respect to their physical, chemical, and mathematical

[2] One example of this practical turn is the emphasis by plant scientists upon the social impact of agricultural improvements. In Simmonds, *Community Matters: A History of Biological Nitrogen Fixation and Nodulation Research, 1965 to 1995*, 82.

reductionism of the phenomena of life.[3] In a series of essays during the period 1961 to 1966, Roberts declared that modern biology had "for the first time come face to face with moral values without recognizing its predicament." The modern biologist (a category which included the geneticist, the microbiologist, and the biochemist, who had come together under molecular biology) was now manipulating microorganisms, she explained, for the purpose of developing the genetic means to shape man's destiny. The consequences might be "a world so bleak and so devoid of human values that mankind, in its frustration, would take no further interest in scientific progress." The eugenic aim was, to her, inextricable from genetic practice. For the next several decades, Roberts extended the ethical critique of "applied" science to the biological sciences. She rejected the pursuit of scientific progress for what she saw as more critical humanistic needs of the era. She condemned the dispassionate and disinterested curiosity of scientists and warned the public against the "comfortable assurance that although we may possibly need to concern ourselves with the goals of applied science, the basic motivation of pure science need never be questioned." Instead, she made clear, "This assurance is fallacious: the motives and goals of scientific research do need to be questioned."[4] Amidst the cultural upheaval of the 1960s, scientific authority in molecular biology became another concentrated source of power to scrutinize and destabilize.[5]

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[3] See Catherine Roberts, "The Modern Biologist and Humanism," *Perspect Biol Med* 6, no. 2 (1963): 197; Catherine Roberts, "Some Reflections on Positive Eugenics," *Perspect Biol Med* 7, no. 3 (1964): 297-308; Catherine Roberts, "Biology and the New Age: An Evolutionary and Ethical Assessment," *Perspect Biol Med* 25, no. 2 (1982): 176-193. See also M.T. Phillips and J.A. Sechzer, *Animal Research and Ethical Conflict: An Analysis of the Scientific Literature: 1966–1986* (Springer New York, 2012), 119.

[4] Catherine Roberts, *The Scientific Conscience: Reflections on the Modern Biologist and Humanism* (Fontwell, Sussex: Centaur Press Limited, 1974), 4-7, 112.

[5] Scientific authority and the notion of linear progress were also being challenged in the sociology of science. The best known example in this period is Kuhn, *The Structure of Scientific Revolutions*.

A similar call for scrutiny was made regarding basic science funding. The U.S. government was infusing funds into science education, and the money for research "was almost too easy," according to yeast geneticist Fred Sherman. At the start of the 1960s, representatives of the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Atomic Energy Commission (AEC) were visiting universities "trying to encourage people to apply for their money," Sherman recalled.[6] The NIH had funded microbial mutation studies from the early 1950s to provide insights into the problem of drug resistance. From the end of that decade, the agency sponsored yeast genetics research with the distant promise of addressing molecular disease in humans.[7] The NSF Division of Biological and Medical Sciences had been founded in 1952 specifically to fund basic biological research. From the early 1960s, the NSF sponsored yeast genetics training and research, for example, in a fellowship to Robert Mortimer at the University of California in Berkeley and for Herschel Roman's genetics department at the University of Washington in Seattle.[8] The AEC had from its establishment in 1946 sought to study the biological effects of radiation. In the early 1950s, the agency was funding yeast research as a peaceful use of atomic energy in Carbondale and Berkeley, and at its own national

[6] Sherman, "Oral History Interview."
[7] Roman, W.U. Genetics Dept, (June 23, 1959), Box 6, Folder 1, Herschel Roman papers (#2955-001). See also Sapp, *Genesis: The Evolution of Biology*, 168.
[8] Robert Mortimer was an NSF fellow in early 1960s. See Technical Documents, 1950-1999, (February 17, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425). His stock center was funded by NSF from the early 1970s. See Mortimer, Technical Documents, 1950-1999, (undated), Box 1, Folder 19, Robert K. Mortimer Collection (ARO-5425); Mortimer, Technical Documents, 1950-1999, (1997), Box 5, Folder 19, Robert K. Mortimer Collection (ARO-5425). Herschel Roman reported his new department's funding sources in Roman, Annual Report No. 1, July 1, 1959 to June 30, 1960, (November 21, 1960), Folder 95-208, UW Genetics Department Records (#VF2395). See also T.A. Appel, *Shaping Biology: The National Science Foundation and American Biological Research, 1945-1975* (Baltimore: Johns Hopkins University Press, 2003), 1-3.

laboratory in Oak Ridge.[9] These sources of support continued into the 1960s. Almost all yeast genetics grants were funded at that time with the exception of "negative science" – those projects the agencies deemed outright harmful to science.[10]

From the mid-1960s, there began to be calls to evaluate the U.S. public investment in scientific research based on the rate of acquisition of new knowledge with applied benefits. While the NIH was expected to continue to garner public support for basic biological research related to human health, some believed that there ought to be greater justification for how basic research related to the agency's mission.[11] At SUNY Upstate Medical Center, for example, microbiologist Martynas Yčas thought it worthwhile to consider the practical benefits of molecular biology, much of which had been done "in the guise of" and "financed by the taxpayer as medical research."[12] Others had argued that knowing how a mechanism worked would allow for interventions into the process of molecular diseases. Given the rapid progress made in the prokaryotes on fundamental principles over the past several decades, one "rather easily predictable" application being discussed was the possibility of gene replacement therapy to correct defects in human proteins. Molecular biologists could soon expect to take the "right genes" and the "right proteins" from the test-tube to the human body.[13] The bridge would be through the eukaryotic cell.

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[9] See Lyons, "Release: Immediate."; Mortimer, "The Relative Radiation Resistance of Haploid, Diploid, Triploid and Tetraploid Yeast Cells."; United Nations and International Atomic Energy Agency, *Peaceful Uses of Atomic Energy: Proceedings* (United Nations, 1958).
[10] Sherman, "Oral History Interview."
[11] Growing public support for NIH is described in Alvin M. Weinberg, "Scientific Choice, Basic Science and Applied Missions," *Minerva* 3, no. 4 (1965): 515-523.
[12] Footnoted in Yčas, *The Biological Code*, 284.
[13] As reported by University of California in Riverside political scientist Michael Reagan in Michael D. Reagan, "Basic and Applied Research: A Meaningful Distinction?," *Science* 155, no. 3768 (1967): 1384.

The intellectual and practical turn to the molecular biology of higher organisms emerged together with these social and political discussions about the role of the basic sciences and public funding of scientific institutions more generally.[14] In a world that needed changing, molecular biology offered access to the basic units behind every living malaise. Although the science was quickly becoming routinized to fill in any remaining gaps in the deciphered code, it had also abstracted a vast amount of complexity into a relatively simple set of instructions.[15] Young scientists began transitioning out of *E. coli* and phage genetics into the eukaryotes in the hope that they were moving on to more complex problems. They recast their earlier work as "prokaryotic" and applied this outline of molecular principles - including what genes were and how they were perpetuated, reconfigured, and expressed - to studies of development and neurobiology in multicellular organisms.[16] They also sought opportunities to align basic biology with other types of applied problems - even, for example, those as complex as the political aspirations of American space science.

"Applicable to Man in Space"

The Soviets had triggered a new phase of the Cold War with the launch of the Sputnik satellite into orbit in 1957. The successful launch was said to have furnished the metaphorical "yeast" to raise American public support for a U.S. space program and had helped to establish

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[14] One early exception from the "science as culture" (philosophy) and "science as overhead" (technology) debate is found in Stephen Toulmin, "The Complexity of Scientific Choice II: Culture, Overheads or Tertiary Industry?," *Minerva* 4, no. 2 (1966): 155-169. Toulmin characterized science as a "tertiary industry" of post-manufacturing society, the outcome of which was not any specific output, but rather employment and prosperity for entire communities of scientists and nonscientists.

[15] Stent, "That Was the Molecular Biology That Was," 390-395.

[16] Gunther Stent, "Introduction: Waiting for the Paradox," in *Phage and the Origins of Molecular Biology*, ed. J. Cairns, J.D. Watson and G.S. Stent (New York: Cold Spring Harbor Laboratory of Quantitative Biology, 1966).

the National Aeronautics and Space Administration (NASA).[17] NASA began to study the survival of life forms in space as a demonstration of American technological prowess. In January 1958, the American popular press carried the news that yeast might travel on the first U.S. satellite to see if the organism could grow and ferment sugar in orbit. The experiment would transmit gas pressure and light projections by radio in order to examine the effects of radiation, zero gravity, and other space factors upon the simple organic matter of living cells. If the yeast developed normally, it "would prove that at least some life processes can go on as usual under space flight conditions."[18] Other reports on this mission held yeast to be a geopolitical "symbol in space" of American ingenuity and morals since the end result of the experiments would be "a palatable home-brewed beer." In contrast, the Soviet's choice to send a dog up with their second satellite was held to represent the inhumanity of the communist bosses.[19] "If a dead dog circling the earth may be accepted as symbolizing the Soviet way of life, a jug of home-brew in orbit might be a proper representation of our free-and-easy standards," it was reported.[20] The article failed to note that the U.S. had already sent species as diverse as monkeys, mice, moss, and fruit flies into space (but not into orbit), where many had died, or did so during the return flight.

In fact, yeast never made it into space on the early U.S. satellite launch. Delays on the ground meant that the "experiment ran out of time before the launch occurred," according to

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[17] James M. Grimwood, *Project Mercury: A Chronology*, trans. Manned Spacecraft Center Historical Branch (Washington, D.C.: National Aeronautic and Space Administration, 1963), xiv.

[18] John A. Barbour, "Celestial Homebrew: Biologist Says First Living Things Thrown into Space by U.S. Might Be Yeast in Malt," *Lewiston Evening Journal*, January 21, 1958, 6.

[19] The space dog Laika had likely undergone a "massive shock" at the sudden stop of acceleration into orbit, details were later spread, and the Soviets had followed her heart beat until she overheated. In "Can Man Survive without Weight?," *The San Bernardino County Sun*, June 8, 1958, 90.

[20] "Symbols in Space," *The Oregonian*, January 28, 1958, 12.

satellite designer Roger Easton, and no public report was ever made.[21] Instead, the Soviets were the first to report a successful experiment with yeast in space. On the 1961 Vostok-2 mission, the organism reportedly grew as usual over a 25-hour period, and "space flight factors" were shown to somewhat decrease the viability of haploid yeasts when compared to diploids.[22]

By the end of the decade, microbes including yeast had been studied by the Americans on the Nerv I, Discoverer XVIII, Gemini IX, X, and XII, Agena VIII, and Biosatellite II missions, and by the Soviets on Sputnik 4, 5 and 6, Vostok 1, 2, 3, 4, 5 and 6, Voskhod 1 and 2, and Kosmos 110. Early missions were concerned with the survivability of life forms in space and the effect of space travel at the level of the cell. The benefits of such studies extended beyond the competitive demonstrations of superior space flight technology to include direct technological impact on other industries. The U.S. pharmaceutical industry, for example, benefitted from the development of improved microbial environmental control methods in U.S. space science. Germ-free techniques, equipment, and other resources in the monitoring of environmental quality had originated in pharmaceutical manufacturing and were used to start the electronics laboratory of the space program. By the end of the 1960s, these roles had reversed. NASA became the premier

[21] Richard Easton and Roger Easton, *Broadcast 1025 (Special Edition)*, The Space Show, September 28, 2008, Dr. David M. Livingston and One Giant Leap Foundation, 1:29:06. NASA historians reported in 1970 that the yeast experiment was postponed and was never included on the satellite. See Constance McLaughlin Green and Milton Lomask, Vanguard - a History, (1970), NASA Historical Reference Collection, Office of Technology Utilization, National Aeronautics and Space Administration, Washington, DC, Section 13.

[22] N.V. Kovyazin, A.A. Lukin, and G.P. Parfenov, "The Effect of Space Flight Factors of the Satellite "Vostok-2" on Haploid and Diploid Yeasts," in *Problems of Space Biology* (1962), 149-153.

innovator in environmental control, and was estimated to have saved the drug industry millions of dollars over the course of the decade.[23]

Given the applied aims of space science, some academic scientists criticized the program as being only marginally scientific.[24] Berkeley biophysicist Robert Mortimer, for example, negatively reviewed one space study of microbial mutation submitted to *Science* in 1967, believing that it lacked adequate controls and the defined conditions expected of Mortimer's own studies of irradiated yeast. The study, "Survival of Unprotected Microorganisms in Space During Terrestrial Orbit," had been conducted under difficult conditions, Mortimer acknowledged, but this did not mean that the journal should accept "a lower standard of research," he argued persuasively to the editor.[25] The article was instead published in the sixth volume of a new journal, *Life Sciences and Space Research*.[26]

In the eukaryotic turn at the end of the decade, yeast became a substitute for human bodies in the space program. Yeast models became tools for the new field of bioastronautics – an ideal of applied research which combined space science, medicine and biology.[27] Following the second American moon-landing in April of 1972, for example, NASA scientists arranged for Apollo 16 astronauts to perform a microbial experiment on cellular-level changes in the space

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[23] John H. Brewer, G. Briggs Phillips, and L. C. Weaver, "Environmental Control in the Pharmaceutical and Biological Industries," *C R C Critical Reviews in Environmental Control* 1, no. 1-4 (1970): 467.
[24] "…a good portion of academic scientists… have also been castigating that program for some time..." In Reagan, "Basic and Applied Research: A Meaningful Distinction?," 1383.
[25] Mortimer, Technical Documents, 1950-1999, (October 23, 1967), Box 1, Folder 15: Correspondence 1967-1968, Robert K. Mortimer Collection (ARO-5425).
[26] John Hotchin, Peter Lorenz, and Curtis L Hemenway, "The Survival of Terrestrial Microorganisms in Space at Orbital Altitudes During Gemini Satellite Experiments," *Life Sciences and Space Research* 6 (1967): 108-114.
[27] A description of bioastronautics is provided by Romanian scientists in the translated work P. Octavian and D. Cristian, *Current Problems in Bioastronautics*, ed. Foreign Technology Division, vol. 15 (Ohio: Wright-Patterson Air Force Base, 1963), 19-21.

environment. 172,866 nautical miles away from Earth on the return flight from the moon, astronaut Thomas Mattingly floated nervously outside the hatch of his spacecraft and held a device containing 60 million microbes perpendicular to the rays of the sun. Then he waited, according to Apollo 16 commander John Young, for "one of the longest 10-minute periods in history" as microbes in the Microbial Ecology Evaluation Device (MEED) were exposed to radiant energy and direct solar ultraviolet (UV) light in a vacuum.[28] Earlier studies had indicated the possibility of genetic changes in microbes during long-duration space missions when later compared with ground controls, and the MEED experiment was designed specifically to test for evidence of these mutations with relevance to "the health of future astronauts." The microbes under investigation had been selected by government, private and university scientists for their ability to survive flight simulation and for being easy to house in spaceflight hardware. They had longevity and were nonpathogenic to avoid possible contamination of the crew members. In most cases, they represented "well-known model systems that… correlated with disease or other medically important conditions."[29] One organism under study was the yeast *Saccharomyces cerevisiae*, which had been chosen by a group at Eastern Michigan University for being a particularly sensitive indicator of antibiotic drug resistance and was expected to show possible

[28] During the experiment, crewmate Charles Duke laughed, "Ten minutes to look at the bugs. You got to be crazy!" Young told his colleagues that this was the "[f]irst time anybody ever laid it on the line for a microbe," and nervously joked that, "Listen, if anything happens during this period, the only thing we can say is that we died so that the germs may live, and that ain't no good at all…." In David Woods and Tim Brandt, "Day 10 Part 2: Eva and Housekeeping," in *The Apollo 16 Flight Journal*, ed. National Aeronautics and Space Administration (NASA History Office, 2009), 219:215:224 – 221:255:239; Training Office Crew Training and Simulation Division, "Apollo 16 Technical Crew Debriefing," ed. National Aeronautics and Space Administration (Houston, Texas: Manned Spacecraft Center, 1972), Section 14: 43.

[29] In G.R. Taylor et al., "Biomedical Experiments Part B Microbial Response to Space Environment," ed. National Aeuronautics and Space Administration Scientific and Technical Information Office, Apollo 16 Preliminary Science Report (Washington, D.C.: NASA Manned Spacecraft Center, 1972), Section 27: 12-13.

phenotypic alterations to growth rate, sporulation, pigmentation, texture, density, and size of the culture as a result of the exposure. Upon splashdown of Apollo 16, MEED was recovered and its microbes sent off to individual laboratories for analysis. The Michigan investigators found a small loss of viability for some yeast samples under certain spaceflight conditions and claimed broad relevance of these studies to "medically related fields applicable to man in space" since the "changes in the microorganisms under study relate to the comfort, safety, and health of the astronaut."[30] Yeast in space was seen to have direct relevance to human bodies though the molecular effects upon the cell. For more than fifteen years, post-flight studies on these yeasts continued, yielding differences in survival rates, phenotypic counts, nutritional requirements and growth rates compared to controls with relevance to the response of cells in harsh environmental conditions in space.[31]

In subsequent decades, yeast as a metaphor that had accompanied reports of the U.S. entry into the space race also ushered an exit from Cold War tensions as American and Soviet leaders signed the first nuclear disarmament treaty to eliminate intermediate-range missiles. In December 1987, U.S. President Ronald Reagan and Soviet General Secretary Mikhail Gorbachev met at the White House, where Gorbachev spoke about a "new thinking" in the Soviet Union. "I feel something very serious is happening, something very profound… an awareness among the people both in the United States and in the Soviet Union that we cannot leave our relations as they are… [There is] a ferment in the minds of people that always begins with the ferment of the

[30] Paul A. Volz et al., "The Microbial Ecology Evaluation Device Mycology Spaceflight Studies of Apollo 16," *Mycopathol Mycol Appl* 54, no. 2 (1974): 221. The study's first author, investigator Paul Volz, had trained with Everett Beneke, founder of the innovative medical mycology training program at Michigan State University in 1951. In A.V. Espinell-Ingroff, *Medical Mycology in the United States: A Historical Analysis (1894–1996)* (Springer Netherlands, 2013), 74.
[31] Paul A. Volz, "Mycology Studies in Space," *Mycopathologia* 109, no. 2 (1990): 89-98.

minds of intellectuals… They are the yeast of any society, as it were, the yeast that triggers new processes."[32] By 1990, this "yeast" had been firmly equated with Gorbachev's policy of *glasnost*, which called for greater transparency in government and freedoms in speech. That year, Reagan adopted Gorbachov's metaphor on a visit to Moscow: "we know we are seeing a new Soviet Union in the making… These are yeasty times; times of ferment… With your reforms, you have embarked on the right course, the democratic course," he told the Soviet leader.[33]

Following an official end to the Cold War, and into the twenty-first century, NASA continued to fund research on yeast in space. In 2009, the NASA Ames Research Center designed and launched into orbit the three million dollar nanosatellite PharmaSat alongside a military reconnaissance satellite. In 2006, the first nanosatellite had carried *E. coli*. Yeast was selected next for its ability to quantify the effect of weightlessness on drug resistance in the ten-pound satellite microlaboratory, with implications for humans on long-duration spaceflights to Mars, for example.[34] "Effective treatment of bacterial infections has required therapy customized for the space environment," Ames scientists explained. "The PharmaSat experiment was focused on directly documenting alterations in antimicrobial resistance in the space environment using a well defined microbial system - the yeast, S. cerevisiae." The experiment was conducted "in-situ," meaning that variable environmental conditions were included in the study design rather than trying to isolate yeast measurements from this context. The yeast showed slower growth in microgravity and was hypothesized to reveal differences in space versus terrestrial cellular

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[32] Gorbachev quoted in I. Korchilov, *Translating History: 30 Years on the Front Lines of Diplomacy with a Top Russian Interpreter* (Touchstone, 1999), 87. See also I. F. Stone, "Let Thinkers Be Leaven in Gorbachev 'Yeast' Bloc," *The New York Times*, December 17, 1987.
[33] Korchilov, *Translating History: 30 Years on the Front Lines of Diplomacy with a Top Russian Interpreter*, 340.
[34] Kenneth Chang, "Yeast Cells Are Set to Fly for Space Experiment," *The New York Times*, May 6, 2009. See also Rachel Prucey and Keith Koehler, "NASA Flight Facility Successfully Launches Nanosatellite," news release, (Moffett Field, CA: NASA), May 19, 2009, nasa.gov.

transport of nutrients and waste.[35] Recent commercial missions have continued to make the most of yeast space travel. In 2014, for example, the Ninkasi Brewing Company, an independent craft brewery based in Eugene, Oregon, sent brewer's yeast into space from Spaceport America. The yeast was recovered upon its return to Earth and was used to brew an Imperial Stout marketed under the name Ground Control.[36]After toppling walls and rising toward the stars, it would appear that yeast is also still active in American politics, at least through commercial lobbying. At the urging of local craft brewers in 2013, for example, the Oregon State Legislature adopted *Saccharomyces cerevisiae* as its official state microbe.[37]

The Detection of Environmental Hazards

Another complex problem to which yeast was applied with mixed success at the end of the 1960s and start of the 1970s was the detection of potential chemical hazards in the environment. This was a time of major environmental health advocacy in the U.S., including the inauguration of Earth Day, the creation of the National Institute of Environmental Health and the Environmental Protection Agency (EPA), and the passage of federal legislation to protect air, land, water, and endangered species. The international community also began to address environmental problems beginning with the United Nations Conference on the Human Environment in 1972. The branching of mutation research into environmental health science at

[35] Antonio J. Ricco et al., "Pharmasat: Drug Dose Response in Microgravity from a Free-Flying Integrated Biofluidic/Optical Culture-and-Analysis Satellite" (paper presented at the Proc. SPIE: Microfluidics, BioMEMS, and Medical Microsystems IX, San Francisco,CA, February 14, 2011), 1, 8.
[36] "Ninkasi Brewing Company Introduces Ground Control, Imperial Stout Fermented with Space-Traveled Yeast," news release, (Eugene, Oregon: Ninkasi Brewing Company), March 17, 2015, www.ninkasibrewing.com.
[37] 77th Oregon Legislative Assembly, *Designates Saccharomyces Cerevisiae as Official Microbe of State of Oregon*, 2013 Regular Session, HCR 12.

the end of the 1960s was shaped in part by a scientist social movement in environmentalism reflective of and responsive to these broader institutional changes and shifts in public opinion, and can be seen for example in the founding of the Environmental Mutagen Society at this time.[38] At the same time that U.S. federal funding was declining for basic research, the U.S. Congress and AEC were turning their support to environmentally-oriented research with direct social, health, and economic consequences. The molecular mechanisms of carcinogenesis had become a U.S. funding priority with the broadening of the scope of the National Cancer Institute (NCI) in 1971, and early on there appeared to be support for preventative research that would screen for carcinogens in the environment.[39] Yeast genetic models found applications as possible "indicator organisms" in environmental health science. Researchers trained at the University of Washington in Seattle hoped to analogize yeast mutagenesis to carcinogenesis at the level of the eukaryotic cell with relevance to human biology.

Genetic toxicology emerged at this time as an interdisciplinary field with a shared focus on particular chemical exposures. Whereas earlier genetic study of chemical mutagens had organized research communities around shared experimental organisms, genetic toxicologists applied basic biological research on mutagenesis to the study of environmental problems. Following on genetic study of atomic fallout and the UV rays of space, toxicologists considered using the methods of yeast biochemical genetics to study chemical exposures they deemed to be relevant as potential mutagens. Yeast geneticists like Carl Lindegren had from the 1940s tried to analogize human cancer to yeast genetic mutations through the homology of the cell. In the

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[38] Scientists' environmental movement is described in Scott Frickel, *Chemical Consequences: Environmental Mutagens, Scientist Activism, and the Rise of Genetic Toxicology* (New Brunswick, N.J.: Rutgers University Press, 2004), 15.
[39] Richard A. Rettig, *Cancer Crusade: The Story of the National Cancer Act of 1971* (Lincoln, NE: iUniverse, 2005), 305.

summer of 1968, Lindegren began to expand his chemical repertoire to study the effect of lysergic acid diethylamide (LSD) on yeast chromosomes. Then-professor emeritus at Southern Illinois University, he suggested that people who had taken the hallucinogenic drug refrain from having children for several years or "better yet, have themselves sterilized" because they had done probable damage to their genetic material.[40]

Some yeast geneticists in Herschel Roman's department at the University of Washington in Seattle had particular interest in yeast eukaryotic screening with expected relevance to human health and disease. The German yeast geneticist Friedrich Zimmermann, who had worked with Roman in Seattle early in the decade, published a study in 1966 relating known mutagens and carcinogens in humans to the triggering of yeast mitotic recombination.[41] At the start of the 1970s, Zimmermann had shown that 14 of these suspected chemicals also induced changes to yeast genetic material, suggesting that yeast might prove useful as a screening tool. Although cancer was a problem of multicellular organisms, Zimmermann argued that the yeast *Saccharomyces cerevisiae* was a known model of the somatic cell and therefore the mitotic recombination it exhibited was a possible mechanism behind the development of cancer.[42] He and colleagues at the University of Freiburg and the State Viticulture Institute Freiburg

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[40] Lindegren was quoted specifically in reference to *Drosophila* studies in Margaret Ann Niceley, "Killer Acid: Lindegren Says LSD Likely Harms User's Descendants," *Southern Illinoisan,* September 14, 1969. His work with LSD in yeast is described in "Hereditary Factors Considered: Siu's Lindegren to Test LSD Effects," *Daily Egyptian,* July 9, 1968, 5; "SIU Notables," 49.

[41] F. K. Zimmermann, R. Schwaier, and U. von Laer, "Mitotic Recombination Induced in Saccharomyces Cerevisiae with Nitrous Acid, Diethylsulfate and Carcinogenic, Alkylating Nitrosamides," *Molecular and General Genetics* 98, no. 3 (1966): 230-246. See also F. K. Zimmermann, "Chemically Induced Genetic Change in Yeast Cells," in *The Early Days of Yeast Genetics,* ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993).

[42] F. K. Zimmermann, "Genetic Aspects of Carcinogenesis," *Biochemical Pharmacology* 20, no. 5 (1971): 986, 991.

concluded that a lack of genetic activity in yeast did not rule out possible hazard, while the triggering of a yeast response served to document the possibility for other organisms.[43] They sought to develop particularly sensitive yeast tester strains.

Other investigators were skeptical about yeast's relevance for the potential risk to human cells, particularly when it came to extrapolating information about carcinogenesis in an organism which did not experience the disease. In 1973, Howard University microbiologist David Brusick and Food and Drug Administration (FDA) genetic toxicologist Vernon Mayer determined that although yeast was a practical and versatile genetic tool exhibiting many structures and functions of higher life forms, including a eukaryotic life cycle and similar organelles, it differed in the way that active compounds were metabolized. Using the same evolutionary logic that Leland Hartwell had used in his cell cycle studies – if the similarities between yeast and humans could not be proven, their status as eukaryotes could be used to identify shared differences with bacteria – Brusick and Mayer went on to propose that yeast genetic assays could be used as *complementary* tools for the safety evaluation of chemicals in relation to their risk in the human population. Alongside bacterial assays, yeast would have particular utility for comparing prokaryotic and eukaryotic cells types with implications for humans. "Obviously there exist qualitative and quantitative differences between the mutagenic sensitivity and specificity in pro- and eukaryotic cells, and until the mechanisms resulting in these differences are understood, it will be difficult to assess the relevance of a response obtained from a given indicator organism to the potential risk to human cells," they argued.[44]

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[43] D. Siebert, F. K. Zimmermann, and E. Lemperle, "Genetic Effects of Fungicides," *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* 10, no. 6 (1970): 541.
[44] D. J. Brusick and V. W. Mayer, "New Developments in Mutagenicity Screening Techniques with Yeast," *Environ Health Perspect* 6 (1973): 92-94.

Given that its representation of the human cell could not be established precisely, yeast was in this period connected in a web of experimentation with various other organisms and genetic models. In many cases, yeast offered an *in vivo* counterpart to animal carcinogen testing. In 1972, for example, University of Calgary cancer researcher Ronald Hancock established a possible correlation between mutagenesis in yeast cells and higher organism carcinogenesis in mice. Hancock, who had previously worked with mice models as an Associate Scientist at the Jackson Laboratory for Genetics and Cancer Research, had looked to yeast as "a more simple system." In theory, the rapid yeast reproductive cycle could speed up testing considerably. However, given that carcinogenesis was a concern of higher organisms, Hancock wondered, "By what mechanism does a cell [yeast], not capable of becoming cancerous, perceive the difference between chemicals capable of causing the neoplastic phenotype and chemicals not having this capacity?"[45] Such questions provided a basis in 1974 for the establishment of a Subcommittee on Environmental Mutagenesis by the U.S. Department of Health, Education and Welfare in order to aid regulatory agencies with evaluating the results of mutagenicity tests.[46]

More than a decade after Rachel Carson popularized the concept of environmental mutagens in *Silent Spring*, there was still a challenge of which biological systems might be most representative of human health and biology in decisions about chemical regulation.[47] The NCI

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[45] R.L. Hancock, "Carcinogen-Induced tRNA Methylase Activity in Yeast Cells," *Biochimica et Biophysica Acta (BBA)-Nucleic Acids and Protein Synthesis* 281, no. 3 (1972): 472, 474. See also the testing of yeast and rats in R.L. Hancock and P.I. Forrester, "Increase of Soluble RNA Methylase Activities by Chemical Carcinogens," *Cancer Research* 33, no. 7 (1973): 1747-1753.
[46] *Biological Concepts and Techniques in Toxicology: An Integrated Approach*, ed. J.E. Riviere (New York: CRC Press, 2006), 257.
[47] *Silent Spring* was first published as a serial in the American magazine, *The New Yorker*, which had been established with the support of Fleischmann family yeast heir Raoul Fleischmann. For the complete text see Rachel Carson, *Silent Spring* (New York: Fawcett Crest, 1962). Carson focused extensively in her book on the harmful environmental and health effects of the pesticide DDT. The year after its publication, researchers of the Fish-Pesticide Research Laboratory at

bioassay program developed mouse and rat models into a long-term rodent bioassay at this time as an initial screen for carcinogens to be followed up with additional testing for specific activity and possible relevance to humans.[48] In the absence of alternate forms of evidence, the intended use of this bioassay changed from general screening to specific testing for related human biological response. While rodent models have in recent decades come to be seen as gold standards for carcinogenicity research, their relevance to human disease risk has been subjected to continuous scrutiny.[49] The search for a relevant surrogate for humans has become paradoxical since if carcinogenic activity is species-specific, carcinogens may act equally specifically in humans.

The yeast-human homology of the eukaryotic cell had the political potential for research funding in Seattle, but was not readily accepted outside of that community in the early 1970s. In the United Kingdom, for example, yeast-based genetic testing was found to be inadequate in the assessment of certain hazards. In 1974, radiobiologist John Thacker studied medical applications of ultrasonic radiation at the Queen Mary University of London and determined that deleterious effects were very unlikely. While it would be naïve to attempt to compare the yeast tests to therapeutic irradiations of the human body, Thacker wrote, "[a]t another level… the relevant "target" (the genetic material) has essentially similar properties in all cells." Yeast shared the

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Denver Federal Center found that Fleischmann's yeast converted DDT to DDD, a form slightly less toxic to animals, although just as persistent in the environment. See J. Kallman Burton and Austin K. Andrews, "Reductive Dechlorination of Ddt to Ddd by Yeast," *Science* 141, no. 3585 (1963): 1050-1051.

[48] W.M. Haschek, C.G. Rousseaux, and M.A. Wallig, *Fundamentals of Toxicologic Pathology* (Elsevier Science, 2009), 32.

[49] See, for example, P Grasso and RF Crampton, "The Value of the Mouse in Carcinogenicity Testing," *Food and Cosmetics Toxicology* 10 (1972): 418-426; Palma Ann Marone, William C. Hall, and A. Wallace Hayes, "Reassessing the Two-Year Rodent Carcinogenicity Bioassay: A Review of the Applicability to Human Risk and Current Perspectives," *Regulatory Toxicology and Pharmacology* 68, no. 1 (2014): 108-118.

structure and complexity of mammalian cells and existed in the haploid state much like the human reproductive gametes. “Further than this, [however] comparisons cannot be made,” he stated. Thacker concluded that a parallel study of genetically well-defined multicellular organisms was needed to conclusively establish the lack of genetic hazard.[50]

The same was true for other potential mutagens. In 1973, Jim Parry, a genetic toxicologist at the University College of Swansea, found that commercial herbicides induced gene conversion in yeast. While the relevance of yeast environmental screening to human health was “debatable” according to Parry, he believed that yeast could be used to test the virulence of fungal pathogens and fungicide resistance for agriculturally-important microbes with “considerable economic importance.”[51] Yeast had previously been deployed in biological treatment of industrial wastes and the recovery of biomasses with potential economic value, in the processing of potato, cheese whey, and corn wastes, and was being tested for use with fuel oil paraffin and domestic wastewater.[52] Unlike yeast genetic screening, this extensive agricultural and environmental commercial history did not require the additional step of homologizing the eukaryotic cell.

As the 1970s progressed, yeast was used as an *in vitro* mutation assay in combination with mammalian metabolic tests. Animals exposed to potential mutagens were injected with yeast as a screening tool in a “host-mediated assay.” The metabolism of the animal hosts might then detoxify the compound, or else, once the yeast was removed from animal fluids and

[50] John Thacker, "An Assessment of Ultrasonic Radiation Hazard Using Yeast Genetic Systems," *British Journal of Radiology* 47 (1974): 136-137.
[51] J. M. Parry, "The Induction of Gene Conversion in Yeast by Herbicide Preparations," *Mutat Res* 21, no. 2 (1973): 84, 90.
[52] See a review of this literature in N. C. Thanh and R. E. Simard, "Biological Treatment of Wastewater by Yeasts," *Journal - Water Pollution Control Federation* 45, no. 4 (1973): 674.

compared to controls, mutations might be detected and attributed to the exposure of interest.[53] This combined yeast-mammalian testing was performed to study the mutagenic effects of vinyl chloride in 1976, for example.[54] The decade witnessed a marked increase in published uses of the terms *in vitro* and *in vivo* as homologies of the eukaryotic cell and the organism helped to legitimatize the use of microbial screening assays.[55]

The absence of definitive information about mutagens became an opportunity for claiming possible yeast-human homology. Yeast geneticist John Pringle, for example, who had completed his postdoctoral research on the yeast cell cycle with Leland Hartwell in Seattle described how carelessness with potential mutagens could result in counterproductive and disagreeable friction between colleagues. In a 1975 chapter for *Methods of Cell Biology*, Pringle recounted the rumored conflict in one yeast laboratory where potential mutagens had been misused. He urged caution when dealing with potent chemicals in yeast research precisely because of the unknown relationship between yeast mutagenesis and the effect on humans.[56]

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[53] *Principles for Evaluating Chemicals in the Environment: A Report of the Committee for the Working Conference on Principles of Protocols for Evaluating Chemicals in the Environment, Environmental Studies Board, National Academy of Sciences-National Academy of Engineering, and Committee on Toxicology, National Research Council*, (Washington, DC: National Academy of Sciences, 1975). See also MS Legator and HV Malling, "The Host-Mediated Assay, a Practical Procedure for Evaluating Potential Mutagenic Agents in Mammals," in *Chemical Mutagens* (Springer, 1971), 569-589.

[54] N. Loprieno et al., "Evaluation of the Genetic Effects Induced by Vinyl Chloride Monomer (Vcm) under Mammalian Metabolic Activation: Studies in Vitro and in Vivo," *Mutation Research/Genetic Toxicology* 40, no. 2 (1976): 85-95.

[55] According to a search of Google Books Ngram Viewer, which had indexed 5 million books as of 2008, frequency of the terms “in vivo” and “in vitro” in the English corpus rose sharply over the 1970s and peaked in the early to mid-1980s. While use of these terms had been on the rise since at least the mid-1930s, they very nearly doubled in the course of a single decade. The phrase “in vitro screening” more than tripled in use. This search result held controlling for the phrase “in vitro fertilization” during the period. In "Ngram Viewer," accessed June 7, 2016, http://books.google.com/ngrams.

[56] Pringle, "Induction, Selection, and Experimental Uses of Temperature-Sensitive and Other Conditional Mutants of Yeast," 239.

The commitment to a human application for yeast studies was the most compelling rationale for grant funders of the research, who required increasingly detailed justifications over the course of the 1970s. At the University of California in Berkeley, the yeast geneticist Robert Mortimer received grant-writing guidance in 1977 to more explicitly extrapolate the relevance of his yeast studies to humans. He was developing a proposal to the Environmental Design Research Association (EDRA) to identify environmental contributions to coronary heart disease using a yeast environmental mutagen screening system. If energy-related pollutants could be identified, Mortimer supposed, "[h]eart disease could be looked upon as an environmental disease in much the same way as cancer is now being regarded." He was advised to make a stronger case for the human relevance of yeast genetic recombination to bolster his proposal.[57]

By the start of the 1980s, technological developments enabling the design of new material and a growing network of experienced yeast geneticists helped to enable a shift from uncertainty to prominence for yeast's utility as an indicator organism for chemical screening related to human health and disease. Recombinant DNA developments enabled the acceptability and use of yeast models on the premise that species barriers could be rewritten for greater accuracy. Recombinant yeast assays were used to detect mutagenic agents with likely carcinogenicity in food, drugs, and the environment, and to formulate safer handling and manufacturing procedures for the chemicals. Yeast became a pollutant reporter organism for environmental biomonitoring.[58] In more recent years, such applications have been adapted for

[57] Mortimer, Technical Documents, 1950-1999, (January 27, 1977), Box 1, Folder 21: 189, Robert K. Mortimer Collection (ARO-5425).
[58] See B. J. Dean et al., "Genetic Toxicology Testing of 41 Industrial Chemicals," *Mutat Res* 153, no. 1-2 (1985): 75; Alan Wiseman, *Enzyme Induction, Mutagen Activation and Carcinogen Testing in Yeast* (New York: Ellis Horwood; Halsted Press, 1987); "Book Review: Yeast as a Tool for Carcinogen Screening," *Yeast* 3, no. 4 (1987): 271; R. L. DeRoos et al., "Observations

drug development, with high-throughput yeast screening now oriented to identifying potential drug efficacy and toxicity in humans.

The growing yeast research community played a significant role in this effective promotion of yeast as a molecular model. By 1984, Zimmerman and colleagues in the EPA's Gene-Tox Program working group on *Saccharomyces cerevisiae* reviewed 173 articles published before January 1980 and found that 492 chemicals had been tested for yeast mutagenicity, with 249 of these showing mutagenic effects. They characterized this record as a surprisingly "sparse use of yeast in environmental mutagen screening" given yeast's utility, and believed it was due to inexperience with the large variety of yeast strains available for study. The group identified three yeast strains to serve as "good complementary assays" to the Ames test, which was a bacterial screen developed in the early 1970s by Bruce Ames and colleagues in the biochemistry department at the University of California in Berkeley with the support of AEC. They also recommended the hiring of experienced yeast geneticists to help with the abundance of strain options.[59]

Their recommendations followed the same route of development as the successful "Ames test" which used *Salmonella typhimurium* as an initial prokaryotic screen of new chemicals and drugs for submission of data to regulatory agencies. From the late 1960s, Ames and colleagues had equated the activity of carcinogens with mutagens by drawing upon the somatic mutation theory of cancer. Since, Ames claimed, "all DNA is basically the same," and microbial testing could be performed much more rapidly and inexpensively than rodent assays, the Ames test

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on Work Force and Training Needs for Assessing Environmental Health Risks," *Public Health Rep* 103, no. 4 (1988): 349.

[59] F. K. Zimmermann et al., "Testing of Chemicals for Genetic Activity with Saccharomyces Cerevisiae: A Report of the U.S. Environmental Protection Agency Gene-Tox Program," *Mutation Research/Reviews in Genetic Toxicology* 133, no. 3 (1984): 236, 239-240.

gained ground as the premier microbial assay.[60] While Zimmermann had developed a yeast screening alternative which utilized a diploid yeast strain to study mitotic crossing over, mitotic gene conversion, and reverse mutation in the mid-1970s, this alternative did not catch on.[61] The EPA has recommended and used the yeast-based screen since 1996, but it remains lesser known compared to the Ames test.[62] This difference can be attributed to the Ames test priority as well as scientists' political engagement in and outside the U.S. during the 1970s. At the Darmstadt University of Technology in Germany, Zimmermann studied the effects of UV and other chemical exposures to identify the eukaryotic mechanisms of mutagenesis, while at Berkeley Ames took on bacterial testing of high-profile commercial chemicals. Ames contributed to the withdrawal of certain hazardous formulations from the market and won the political support of environmentalists for a time. His political fortunes underwent a strong reversal at the end of the decade, however, as Ames began to examine the genetic damage caused by naturally-occurring compounds and to downplay the role of industrial contaminants in cancer causation.[63] Regardless, his test gained prominence.

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[60] Bruce N. Ames et al., "Carcinogens Are Mutagens: A Simple Test System Combining Liver Homogenates for Activation and Bacteria for Detection," *Proceedings of the National Academy of Sciences of the United States of America* 70, no. 8 (1973): 2284; Bruce N. Ames, Joyce McCann, and Edith Yamasaki, "Methods for Detecting Carcinogens and Mutagens with the Salmonella/Mammalian-Microsome Mutagenicity Test," *Mutation Research/Environmental Mutagenesis and Related Subjects* 31, no. 6 (1975): 347-363.

[61] F. K. Zimmermann, R. Kern, and H. Rasenberger, "A Yeast Strain for Simultaneous Detection of Induced Mitotic Crossing over, Mitotic Gene Conversion and Reverse Mutation," *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* 28, no. 3 (1975): 381-388.

[62] "Health Effects Test Guidelines Oppts 870.5575 Mitotic Gene Conversion in Saccharomyces Cerevisiae," ed. Pesticides and Toxic Substances Office of Prevention, United States Environmental Protection Agency (Washington DC: U.S. Government Printing Office, 1996).

[63] Angela N. H. Creager, "The Political Life of Mutagens: A History of the Ames Test," in *Powerless Science?: Science and Politics in a Toxic World*, ed. S. Boudia and N. Jas (Berghahn Books, 2014), 53.

By the mid-1980s, scientists' environmental advocacy had fallen away as politically unfavorable in the U.S. The Reagan administration sought to minimize the restrictions of environmental regulation upon American businesses, and environmentalism came to be expressed through more radical and localized grassroots efforts.[64] Shared molecular effects upon the eukaryotic cell made yeast models directly relevant to human bodies at that time as biomedical research. The molecular mechanisms identified in the yeast cell were by then not descriptions of mutagenesis in eukaryotes but rather explanations for human carcinogenesis. Cold Spring Harbor Laboratory was integral to this transition in the successful politicization of Seattle's research agenda with yeast molecular models.

Cold Spring Harbor Laboratory as International Hub

Model organism research had produced shared experimental materials and techniques in an attempt to standardized observations in genetic practice. A supranational network had grown up around yeast molecular genetics, and by the early 1970s, worldwide academic and commercial laboratories reached from the Netherlands, France and Italy to the U.S. and Japan. American universities with prominent yeast genetics laboratories included Yale, Stanford, the University of Washington in Seattle, the University of Rochester, the University of Illinois in Urbana, and the University of California campuses in Berkeley, San Francisco, Davis and Irvine. Whole distribution networks formed to supply these groups with the materials they needed for reproducible laboratory work.

The 1973 oil embargo produced a negative shock to the U.S. economy which rippled into the basic sciences. Toward the end of a second decade of struggle in Vietnam War, the energy

[64] Philip Shabecoff, "Reagan and Environment: To Many, a Stalemate," *The New York Times*, January 2, 1989.

crisis again showed the nation as vulnerable to challenges from abroad, and American yeast workers were no exception. At the Massachusetts Institute of Technology (MIT), yeast geneticist David Botstein recalled how his laboratory was affected during this time by the "agar crisis" in genetics, during which there was a shortage of the solid substrate for the growth of microorganisms.[65] Reportedly this was due to the problem of oil pollution killing off the algae sources of agar.[66] The international dimensions of yeast scientific practice were laid bare as agar suppliers came up short around the globe. The price of the remaining substrate doubled as laboratory shortages forced a search for substitutes.[67]

New York's Cold Spring Harbor Laboratory was instrumental in producing new practices and practitioners for yeast research as a global hub for the field over the 1970s and 1980s. Leveraging the hard-won material standards established by early yeast geneticists such as Øjvind Winge at Carlsberg Laboratory in Copenhagen, Carl Lindegren at Southern Illinois University in Carbondale, Robert Mortimer at the University of California in Berkeley, Herschel Roman at the University of Washington in Seattle, and the growing training communities which diffused from these centers, the Laboratory on Long Island's north shore became a site of development and exchange for the proliferation of yeast molecular models as applicable systems to the study of higher organism biology. Seattle's researchers resisted relinquishing their leadership role to yeast

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[65] In Botstein, "A Phage Geneticist Turns to Yeast," 369.

[66] See J. D. Walker, H. F. Austin, and R. R. Colwell, "Utilization of Mixed Hydrocarbon Substrate by Petroleum-Degrading Microorganisms," *The Journal of General and Applied Microbiology* 21, no. 1 (1975): 37; C.S. Lobban and P.J. Harrison, *Seaweed Ecology and Physiology* (Cambridge University Press, 1994), 293.

[67] See Robert C. Thatcher and Terry L. Weaver, "Simplified Method for the Preparation of Silica Gel Media," *Applied Microbiology* 28, no. 5 (1974): 887-888; N. Watson and D. Apirion, "Substitute for Agar in Solid Media for Common Usages in Microbiology," *Applied and Environmental Microbiology* 31, no. 4 (1976): 509-513. The need for agar substitutes is described in E.H. Asheshov and R. Skalova, *International Committee on Systematic Bacteriology. Subcommittee on the Phage-Typing of Staphylococci. Minutes of the Meeting.*, vol. 25 (Int J Syst Bacteriol, 1974), 233-234.

geneticists at Cold Spring Harbor, and certainly Herschel Roman's genetics department at the University of Washington continued to attract international recognition from funders and collaborators. The Seattle department had grown to a moderate size since its establishment in 1959, and in the early 1970s it had a total of twenty-one faculty, thirty-three graduate student trainees, and fourteen postdocs and visiting investigators.[68] The existing affiliations and broader networks of Cold Spring Harbor Laboratory, however, enabled the appropriation and more rapid politicization of the Seattle model for wider recognition and diffusion of yeast as a model eukaryote – in particular, for biomedical research.

Since the early 1930s, the Cold Spring Harbor Laboratory had hosted regular international symposia on the developing science of molecular biology. The campus was home to staff scientists and visiting researchers, and the Laboratory had welcomed new students to the profession since 1945 with the offering of a summer course on phage genetics established by Max Delbrück, Salvador Luria, and other early members of the Cold Spring Harbor "phage group." The decades leading up to the 1970s had been oriented separately toward the development of bacterial genetics, determination of the physical nature of the gene, the structure of DNA, and the deciphering of the genetic code. Yeast genetics had maintained a small presence on the campus during these years. Prior to Hershel Roman's talk on gene conversion at the 1956 symposium, yeast had uncertain utility for investigating the structure and function of hereditary material and was seen as at best redundant of the microbial research already underway at the Laboratory in bacteria and the phage. A decade later, it looked like yeast research might be

[68] Since half of the faculty held joint appointments in medicine, microbiology, biochemistry, botany, zoology, and forestry, and did not engage in teaching, Herschel Roman considered the department to be moderately sized by national standards. See University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066).

of greater interest to the Laboratory. Cold Spring Harbor's former director, Milislav Demerec planned to convene the yeast community to discuss genetic nomenclature rules at the thirty-first symposium on the Genetic Code in June of 1966, but this session was not to be.[69] Demerec died that April, and for many his passing marked "the end of an era" which had witnessed the first early successful chapter of molecular biology.[70]

The history of these events was being written as scientific memoir at the end of the 1960s. Incoming Laboratory director James Watson had just published a first-person account of his role in the resolution of the structure of DNA and had won a Nobel Prize for this work.[71] Watson was taking over at Cold Spring Harbor Laboratory of Quantitative Biology after the five-year tenure of British physician John Cairns.[72] He wanted to see the Laboratory continue as a place where cutting-edge science was made and not merely disseminated. In 1968, Watson was reportedly "very concerned whether our current series of summer courses is still worthwhile, or whether we should move in a more avant-garde direction." In the past, he claimed from personal experience in the phage course, the Laboratory's summer courses had taught distinguished investigators "what was important to do" so that they could go "back home" to do it.[73] Watson

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[69] Herschel Roman, for example, was in 1966 a "friend" of Cold Spring Harbor according to the Laboratory's ranked fundraising contribution levels, but he did not attend the annual symposium that year. In *Annual Report*, (New York: Cold Spring Harbor Laboratory of Quantitative Biology, 1966), 27; "List of Those Attending the Symposium," in *The Genetic Code*, ed. Leonora Frisch (Cold Spring Harbor, New York: Cold Spring Harbor Symposia on Quantitative Biology, 1966), xv.

[70] *Annual Report*, 4. The 31st Symposium on the Genetic Code commemorated Demerec's contributions to the science in June 1966. See H. Bentley Glass, "Milislav Demerec, 1895-1966," in *The Genetic Code*, ed. Leonora Frisch (Cold Spring Harbor, New York: Cold Spring Harbor Symposia on Quantitative Biology, 1966), xxi-xxii.

[71] See Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*.

[72] The Laboratory was so-named from 1962-1969, after which point the name was simplified in 1970 to Cold Spring Harbor Laboratory.

[73] *Annual Report*, (New York: Cold Spring Harbor Laboratory of Quantitative Biology, 1968), 4-5.

wanted to elevate the summer course programming as a means of advancing the Laboratory as a center for basic science research. Specifically, he had in mind additional training in molecular biology, since the discipline was still being "created much more effectively than it [wa]s being assimilated."[74] If the right summer course could be developed, it might serve as a rallying point for new molecular concepts and methods with Cold Spring Harbor at its center.

Watson recognized the political advantages to eukaryotic analyses in yeast for a growing range of stakeholders. At the start of the 1970s, he believed that students needed a proof-of-concept demonstration that would translate their training through more complex organisms to more complex problems. Funding agencies from NASA to the EPA had supported applications of basic yeast genetic research, and Watson had a particular interest in rebuilding Cold Spring Harbor Laboratory with cancer funding from the NCI.[75] The National Cancer Act signed by President Richard Nixon in 1971 increased U.S. appropriations to the NCI with the promise that a collective "war on cancer" could bridge the gap between research and patient care. The policy was intended as a response to concerns about the need for a return on the federal biomedical research dollar expessed since at least the mid-1960s.[76]

In 1970, Watson discontinued the twenty-five year-old phage course and reoriented the Laboratory's research to the study of cancer.[77] He had begun to search for a new course subject

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[74] *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1970), 4.
[75] Watson also critiqued aspects of the NCI program focused on treatment, particularly those overpromising a quick cancer cure, possibly as "a rear-guard action to protect long-term basic research." In V.K. McElheny, *Watson and DNA: Making a Scientific Revolution* (Perseus Publishing, 2003), 220.
[76] As a result of this focus, NCI appropriations increased from $233 million in 1971 to $815 million by 1977. See Rettig, *Cancer Crusade: The Story of the National Cancer Act of 1971*, 282-299.
[77] M Susman, "The Cold Spring Harbor Phage Course (1945-1970): A 50th Anniversary Remembrance," *Genetics* 139, no. 3 (1995): 1101-1106; Sherwood, "The Yeast Genetics Course at Cold Spring Harbor Laboratory: Thirty Years and Counting," 1399-1402.

and instructor even before assuming the director position, and had asked the Laboratory's assistant director Ray Gesteland to approach University of Rochester scientist Fred Sherman at a 1967 meeting in Europe to invite him to campus for a trial seminar.[78] Sherman was a yeast geneticist who had trained with many of the early leaders in the field: Mortimer at the University of California in Berkeley, Roman at the University of Washington in Seattle, and Ephrussi at the French National Center for Scientific Research (CNRS) genetics laboratory in Gif-sur-Yvette. In the late 1960s, he was gaining recognition for his work on the yeast *CYC1* gene.

When Sherman arrived at Cold Spring Harbor Laboratory to give his seminar in 1968, Watson reportedly interrupted the talk multiple times probing for yeast trivia that would useful to a second edition of his book, *The Molecular Biology of the Gene*.[79] When it was published in 1970, a new section heading of the widely-read text declared that, "THERE ARE NOW MANY REASONS TO INTENSIFY WORK ON ORGANISMS LIKE YEAST."[80] While Watson's comments in this text were termed "prophetic" by some in the field who observed the later migration of molecular geneticists from bacteria into yeast, they can also be read as calculated advocacy on behalf of Cold Spring Harbor Laboratory.[81] Bacteria and the phage were well travelled-intellectual ground, and although they too boasted a proud scientific heritage and strong shared material culture, this territory was crowded and funding support was dwindling. Newly-

[78] According to yeast geneticist Gerald Fink, Sherman inspired Watson to inaugurate the yeast course at Cold Spring Harbor. In Fink, *Tribute to Fred Sherman*, 2014, (B&B), 14:30.
[79] Sherman, "Oral History Interview."
[80] James D. Watson, *Molecular Biology of the Gene, 2nd Ed.* (New York: W. A. Benjamin, 1970), 519.
[81] See, for example, Sherwood, "The Yeast Genetics Course at Cold Spring Harbor Laboratory: Thirty Years and Counting," 1399. This prophetic portrayal of Watson is similar to other representations of the previous director of Cold Harbor Laboratory, Milislav Demerec. Demerec's promotion of bacteria and the phage as research materials is claimed to have moved the institution intentionally from classical to molecular genetics. In Anderson, "Electron Microscopy of the Phages," xiv.

minted and veteran geneticists alike cared less for filling in the specific details of a species then they did for finding novel molecular puzzles with secure funding sources and perhaps even applied benefits. Watson saw yeast as avant-garde in the early 1970s because it provided access to novel molecular relationships, including those between funding agencies, biochemists, biophysicists, geneticists and microbiologists, as evidenced by the department in Seattle. In 1970, a projected budgetary increase to Cold Spring Harbor's annual NIH training grant for the summer courses made it possible to add the new course in yeast genetics.[82]

The course "Molecular Biology and Genetics of Yeast" was introduced in the summer of 1970, and ran for the three weeks from the middle of June through the Independence Day holiday out of what was then a very old and moldy Davenport building. For seventeen summers thereafter, it was led by Sherman and his co-instructor Gerald Fink of Cornell University, who were often supported by a third rotating instructor.[83] Fink had been one of the few yeast geneticists to attend the 1966 meeting. A Yale graduate, he was at that time working as a postdoctoral researcher for Bruce Ames at NIH's Laboratory of Molecular Biology.[84] He had since gone on to an independent career as an Assistant Professor at Cornell University, where Watson approached him about the summer yeast course.[85] Fink has described his work with

[82] *Annual Report*, (New York: Cold Spring Harbor Laboratory of Quantitative Biology, 1969), 7.
[83] "With only a one-year hiatus they continued to teach this course each summer through 1986." In Elizabeth L. Watson, *Houses for Science: A Pictorial History of Cold Spring Harbor Laboratory* (Cold Spring Harbor Laboratory Press, 1991), 208; Emily Boynton, "Fred Sherman, Major Contributor to Modern Genetics, Dies," *URMC Newsroom*, September 18, 2013; Liebman and Haber, "Fred Sherman (1932–2013)," 1059.
[84] "2010 Genetics Prize: Gerald Fink," accessed January 27, 2016, http://gruber.yale.edu/genetics/gerald-fink.
[85] Fink, "Getting Along with a Little Help from My Friends," 23889.

microorganisms at the end of the 1960s as experimental systems having human relevance. They were "not as complicated as humans."[86]

Sherman and Fink designed the yeast course as a nonstop three-week immersion in yeast molecular biology. While the course was intensive, the experience evokes fond memories from trainees in particular because of the instructors' playful sense of humor. To take a break from the "killer" 12+ hour days filled with laboratory work and seminars, the instructors would play ping pong and go out dancing with the students.[87] According to Fink, the atmosphere at Cold Spring Harbor Laboratory fostered collegial interaction between scientists, who attended each other's courses, dined together, and lived in close proximity to one another as part of a closed community completely oriented towards science.[88]

The subject of the course attracted many "immigrant" prokaryotic geneticists changing fields out of *E. coli* and the phage, and these were the instructors' first choice of students in an attempt to expand the field.[89] Initial enrollment in the yeast course was capped at ten students,

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[86] Gerald Fink, interview by Mila Pollock, September 8, 2003, "Oral History Interview," New York, Cold Spring Harbor Laboratory Archives.

[87] A course schedule is available in Ira Herskowitz, Undated), Series 4: Professional Activities, Carton 89 Seminar and Research Notebooks, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25), University of California, San Francisco Archives & Special Collections, San Francisco, CA. The course continued at this intense pace in later years as well. See one description in Evelyn Witkin, Letter to Joshua Lederberg, (July 22, 1982), Box 38, Folder 73, BBAGBG, Profiles in Science: The Joshua Lederberg Papers, National Library of Medicine, Bethesda, MD.

[88] Fink, "Oral History Interview."

[89] See Botstein, "A Phage Geneticist Turns to Yeast," 361. While Botstein was referring specifically to the influx of investigators from foreign organisms, his use of the term "immigrant" also calls to mind the shifting national membership in eukaryotic genetics. While earlier in the century European giants such as Cambridge University and the Pasteur Institute had led in genetic research alongside American strongholds such as Caltech, by 1970, American institutions dominated the field. This was especially the case in yeast genetics. In Denmark, Carlsberg yeast geneticist Øjvind Winge had died in 1964. In France, Boris Ephrussi had quit his investigations in yeast at the start of the 1960s, and his former student and successor Piotr Slonimski had not yet been made director of the CNRS genetics laboratory in Gif-sur-Yvette. There was yeast genetics being done in Belgium and England, and a longer line of work out of

reportedly because of the limited housing availability at Cold Spring Harbor in 1970, and in the Laboratory's annual report Watson described his fundraising efforts for future construction and renovation of Cold Spring Harbor's buildings.[90] The inaugural class included researchers from the NCI, Berkeley, Brandeis, Cornell, Vanderbilt, Albert Einstein College of Medicine, and the German Research Institute. FDA genetic toxicologist Vernon Mayer, who would later go on to propose a yeast genetic assay for chemical safety evaluations, was also part of this initial cohort.[91] Sherman characterized these students as people who could not learn yeast where they were but who brought with them high recommendations. They were accomplished scientists who "just want to know the latest facts and latest technologies."[92] For a time the course provided access to techniques that were being offered only in Seattle.

Fink credited Sherman with drawing many new scientists to view yeast as the premier eukaryotic model system. "[Sherman] deserves the title, the founder of yeast molecular biology."[93] Sherman felt that he and Fink "did a very good job convincing people… [of] the virtues of yeast and why to start working with yeast," but Sherman credited Watson for yeast's successful "start." Even though Watson sometimes had unrealistic expectations for the course (he once tried to stop the instructors from teaching tetrad analysis because it seemed "old-

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Italy under Giovanni Magni, former president of the Italian Genetics Association and director of a genetics institute at the University of Pavia, and later in Parma and Milan University. But these programs did not see the same number of student and postdoc trainees and visitors on sabbatical as did the University of Washington in Seattle. In 1970, Seattle was the global center of training in yeast genetics at the very moment the new yeast course was getting started at Cold Spring Harbor Laboratory. On the admissions preferences for the course, see Sherman, "Oral History Interview."

[90] *Annual Report*, 7.

[91] "Meetings & Courses Program: Cold Spring Harbor Yeast Course," accessed June 23, 2015, https://meetings.cshl.edu/alumni.

[92] Fink, "Oral History Interview."

[93] Fink, *Tribute to Fred Sherman*, 2014, (B&B), 14:30.

fashioned"), still, Sherman has said, "the yeast community owes him."[94] By the end of the first summer, Watson reported to Cold Spring Harbor supporters that students of the yeast course had become "highly enthusiastic about leading a role for yeast in the molecular biology research."[95]

While the founders' views are relevant, the diffusion of yeast molecular biology to new practitioners was already well-underway in places like Berkeley and Seattle. The Cold Spring Harbor yeast course, like its phage course, helped to perpetuate this informal network and the adoption of standardized methods and materials. Sherman and Fink, like Delbrück, established their leadership in the field by sharing or selling their innovations, shortcuts and equipment designs. Sherman, for example, used the yeast course laboratory manual to advertise an inexpensive mechanical micromanipulator he had designed, mountable on the scope of a microscope, and available for $125 for use in tetrad dissections, as opposed to the older, separate and expensive machine designed by Mortimer at Berkeley.[96] Sherman's machine had been developed out of necessity in a humid summer classroom where the air conditioners caused too much vibration for the micromanipulations.[97]

While this cooperative culture had already been formed out of the compromises of a previous generation of yeast researchers, resulting in the open distribution of yeast strains and techniques, Cold Spring Harbor offered a ready institutionalization of these norms. The Laboratory's press, for example, generated a laboratory manual for yeast genetics and for the

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[94] In Sherman, "Oral History Interview."
[95] *Annual Report*, 7.
[96] Sherman also described his machine in a journal article: "The low price makes this model ideal for class instruction when large numbers are required." In Fred Sherman, "Micromanipulator for Yeast Genetic Studies," *Appl Microbiol* 26, no. 5 (1973): 829.
[97] Fred Sherman, Gerald Fink, and Christopher Lawrence, Laboratory Manual for a Course: Methods in Yeast Genetics, (1972), Cold Spring Harbor Laboratory Meetings and Courses Department Collection, 1890-2010, Cold Spring Harbor Laboratory Archives, New York, 59. Several companies built the apparatus, which was meant as an attachment for existing equipment of the established genetics laboratory. In Sherman, "Oral History Interview."

first time yeast geneticists' "secret tricks" became publically accessible.[98] Students of the course were told from the start that the techniques and strains they developed would be made freely available to anyone who asked. Fink attributed this tradition to earlier Cold Spring Harbor geneticists, like Max Delbrück, who worked in phage and bacteria, but the yeast geneticists and ecologists had freely exchanged strains. Mortimer, for example, distributed strains of *Saccharomyces cerevisiae* informally out of Berkeley since the 1960s, and received formal funding for his stock center beginning in 1970.[99]

In the early years of the course, students were able to carve out individual claims on the young field because there were so few practitioners. "[E]veryone in the course had to say what the problem was that they would then work on," Fink explained. "[I]t gave everyone who took the course a sense of what direction they were in the field already going on and what areas were unknown so they might work in those areas."[100] To well-placed converts from prokaryotic bacterial biology in the late 1960s and early 1970s, then, the yeast field was open and welcoming. People working in tissue culture of mammalian cells appreciated learning the techniques and tried to mimic them to "follow yeast."[101]

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[98] The manual of techniques replaced individual collections of 3x5 index cards. In Fink, "Oral History Interview."

[99] See a description of the center in "Listing of Genetic Stock Centers and Newsletters," *The Journal of Heredity* 66 (1975): 105.

[100] The decision to share materials was, according to Fink, "enormously important for the development of any young field because it means that a young scientist who is starting out isn't dependent upon anyone for getting the reagents that they need to get going." In Fink, "Oral History Interview."

[101] Students in the 1974 tumor virus workshop held concurrently with the yeast course, for example, saw that a study of cell cycle control would have "far-reaching implications for the understanding of cellular differentiation and proliferation of mammalian cells." In *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1974), 50. Several yeast geneticists went into mammalian cells with ideas from yeast. In Sherman, "Oral History Interview."

The instructors taught yeast mitotic recombination, x-ray fine structure mapping, isolation of chromosomal and cytoplasmic mutants, and biochemical analyses. The primary experimental organism was the baker's yeast *Saccharomyces cerevisiae*, although, students learned, genetics studies had been performed with other species, especially *Schizosaccharomyces pombe*. The latter was a fission yeast which had been developed as a model eukaryote system by the Swiss geneticist Urs Leupold at the urging of Carlsberg yeast geneticist Øjvind Winge.[102] S288C was the course's standard wild type strain.[103] The first-year laboratory manual claimed that baker's yeast was "an ideal eukaryotic microorganism… [with] greater genetic complexity than bacteria [and many shared]… technical advantages."[104]

Sherman and Fink taught and recruited their peers into working with this yeast, and in turn many of these scientists returned to guest lecture about new techniques and experiments in subsequent years of the course. They also sent detailed protocols prior to publication to keep course laboratory manuals up-to-date.[105] In the first summer, Carl Lindegren made a guest appearance to instruct on tetrad analysis. Robert Mortimer arrived to give a seminar on gene mapping, and in later years addressed gene conversion.[106] R.C. "Jack" von Borstel spoke to the class about mutator genes.[107] Fink looked forward to the summer as an exciting and stimulating

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[102] Beginning in 1952, Leupold had studied *S. pombe* genetics at the Universities of Zürich and Bern. By the 1970s, several *S. pombe* workers in the United Kingdom, Europe and Japan were using Leupold's strains to isolate mutants and map fission yeast genes. See Mitsuhiro Yanagida, "The Model Unicellular Eukaryote, Schizosaccharomyces Pombe," *Genome Biology* 3, no. 3 (2002): 3-4.
[103] Botstein, "A Phage Geneticist Turns to Yeast," 361-364.
[104] From the 1970 Laboratory Manual for "Methods in Yeast Genetics", in Herskowitz, (Undated), Series 4: Professional Activities, Carton 89 Seminar and Research Notebooks, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[105] Gerald Fink, "The Double Entendre," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 436, 444.
[106] *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1973), 36.
[107] *Annual Report*, 23.

time with bright, hardworking, and sometimes quite senior and distinguished students who taught him equally.[108]

There was one visitor to the course who vocalized his disapproval that Cold Spring Harbor Laboratory should introduce new investigators to yeast. In 1973, Herschel Roman was invited by Fink and Sherman to give a guest seminar on yeast recombination, and he "was quite outspoken" that the center of yeast should be Seattle and that the course was "a mistake." Sherman recalled that Seattle's Donald Hawthorne felt similarly that there were "already too many people in yeast and it was getting too crowded."[109] Leland Hartwell was likely persuaded by these opinions in Seattle. Although he lectured on the yeast cell division cycle in the course's inaugural year, Hartwell later regretted not teaching more in the Cold Spring Harbor yeast genetics course.[110] "Even more would have happened in the lab faster if we had been better connected with a whole variety of other developments that were occurring," he determined.[111]

The group in Seattle saw the Cold Spring Harbor course as encroaching upon their leadership position in yeast genetics.[112] Years later, Seattle yeast geneticist Benjamin Hall remarked that the course leveraged the groundwork that had already been laid by Herschel Roman:

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[108] Fink described having to teach recombination to American bacterial geneticist Frank Stahl, whom he considered to be the world's authority on the topic. In Fink, "Oral History Interview." Stahl was a student of the yeast course in 1981. See "Meetings & Courses Program: Cold Spring Harbor Yeast Course," accessed June 23, 2015, https://meetings.cshl.edu/alumni.

[109] Sherman, "Oral History Interview." See also Roman's participation in the course in *Annual Report*, 36.

[110] For a glimpse of Hartwell's teaching at that time, see notes on a 1971 university lecture in Herskowitz, (Undated), Series 4: Professional Activities, Carton 89 Seminar and Research Notebooks, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

[111] Hartwell, "Cell Cycle Control in Yeast," 48:46.

[112] The department was still well-recognized internationally, and was attracting, for example, postdocs from Carlsberg Laboratory. In University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066).

> It certainly didn't spring out of Jim Watson's head… It didn't happen in any one place … least of all Cold Spring Harbor… it's much to Herschel Roman's credit that, as he built up this department …… he recruited a variety of types of people hoping that something like this would happen. I think he gets some of the credit for… being a successful administrator.[113]

At the end of the 1960s, Roman was completing a term as president of the Genetics Society of America and serving as a founding editor for the *Annual Review of Genetics.* His department in Seattle was doing well. Student demand for genetics training was rising and more than 1700 students had enrolled in the department's courses. The department had research and fellowship grants totaling $480,272 in 1972 from NIH, NSF, AEC, and the American Cancer Society.[114] Despite its continued leadership role in yeast genetics, however, the Seattle department was ranked eighth behind genetics training programs at Chicago, Harvard, Johns Hopkins, Caltech, Rockefeller, Stanford, Berkeley, Wisconsin, MIT, and Yale in a 1970 report from the American Council on Education. Roman feared his department's current training might be too skewed toward regulatory and developmental genetics and, given the expansion of health research facilities across the country at that time, he worried about the recruitment of top researchers to Seattle. He might have targeted more molecular biologists. The medical school at the University of Washington had a separate division of medical genetics for the study of human diseases and genetic counselling but given the NIH's recent emphasis on "a growing need for geneticists as health specialists," faculty recruits to the basic genetics department in animal virology, immunogenetics, or behavioral genetics could have been especially helpful to access national cancer research funding.[115] There was a sense that Seattle was losing ground to the Laboratory in New York. Members of the genetics department may have been particularly

[113] Hall, "Oral History with Ben Hall, Part 2."
[114] University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066).
[115] Hall, "Oral History with Ben Hall, Part 2."; University of Washington Department Plan, (1974-1981), Box 3, Folder 1969-1974, UW Genetics Department Records (#89-066).

sensitive to this given the general feeling of decline then characterizing Seattle. After two decades of post-war growth and prosperity, the major commercial airplane, aerospace and defense contractor Boeing Co. had begun mass layoffs in its hometown of Seattle beginning a spiraling downturn in the local economy. The University of Washington was also lamenting the end of its "golden era," which had expanded enrollment and modernized facilities on a growing operating budget and easy federal grant dollars.[116] The competition for funding would only grow tougher as trainees of the yeast course began to pursue NCI funding for yeast work at their respective institutions.

By 1975, Cold Spring Harbor Laboratory was positioning itself as an international clearinghouse for the latest information on yeast molecular biology and had begun to host a biennial yeast meeting with celebratory banquet, live music and dancing.[117] While three years earlier, Roman and Hartwell had organized a meeting which brought 60 people - or about half the entire yeast community at the time - to Seattle to exchange their ideas on the "Genetic and Biochemical Control of Development in Yeast," by 1975, 167 participants were in attendance at the first yeast meeting on Long Island.[118] The field was growing as a direct consequence of the

[116] The Boeing workforce plummeted from 100,000 in 1968 to 32,500 in 1971. Each layoff was estimated to cost a second job in the local economy, prompting the posting of a satirical billboard by the airport: "Will the last person leaving SEATTLE - Turn out the lights." In Sharon Boswell and Lorraine McConaghy, "Lights out, Seattle," *The Seattle Times*, November 3, 1996.

[117] Berkeley yeast geneticist Jasper Rine held that, "Cold Spring Harbor Laboratory deserves special credit [for…] their support of the early yeast meetings." Jasper Rine, "Introduction," in *Landmark Papers in Yeast Biology*, ed. Patrick Linder, David Shore, and Michael N. Hall (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2006), 7. The 1975 meeting was arranged by David Botstein of MIT and Gerald Fink of Cornell with partial funding from the NCI.

[118] See the Seattle meeting details in Anne Cori and Carl F. Cori in Seattle Riding Bus, (1972), VC143126, Medical Journeys, Bernard Becker Medical Library Archives, St. Louis, Missouri. By 1986, the Cold Spring Harbor meeting had grown too large and was moved to alternating years at Genetics Society of America Meeting. At that point, a smaller meeting on Yeast Cell Biology was held at Cold Spring Harbor in alternating years. See Karen Goodman, *An Abridged*

yeast course which ran with the same instructors through 1986, and continues to the present day.[119]

Origins of the Cold Spring Harbor Yeast Group

Two trainees in the second annual 1971 yeast course were Ira Herskowitz and David Botstein. Herskowitz was a prokaryotic geneticist who had trained at Caltech and MIT, and had just been offered at job at the University of Oregon in Eugene. Rather than begin immediately, he chose to postpone the offer for a postdoctoral year with Botstein at MIT, where the latter was on the faculty. Both were inspired by Leland Hartwell's recent series of publications on the yeast cell cycle, which had begun to show the potential of yeast as a model of higher organism development using the systematic arrangement of different mutants to represent the stages of a single cell.[120] Herskowitz and Botstein signed up for the yeast course together with the recognition that "the end of the road was near" in terms of funding and practitioners for phage molecular genetics. Botstein recalled being impressed in the course by yeast's "eukaryotic

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History of the Genetics Society of America: Compiled from the Records of the Genetics Society of America and the Genetics Journal, 1931-2008 (Genetics Society of America, 2008); Watson, *Houses for Science: A Pictorial History of Cold Spring Harbor Laboratory*, 208.

[119] Sherman and Fink had a seventeen-year run. They skipped one summer to offer the course in Sao Paulo, Brazil. Watson had been thinking about cancelling the course, but after that summer he was convinced that the course should continue. See "Yeast Genetics: July 24-August 13," in *Annual Report* (New York: Cold Spring Harbor Laboratory, 1984), 294; *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1986), 309; Sherman, "Oral History Interview." See also the 1995 "Harbor Transcript" in Michael Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25), University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[120] Hartwell's publications then included Hartwell and McLaughlin, "Mutants of Yeast with Temperature-Sensitive Isoleucyl-tRNA Synthetases," 422-428; Hartwell and McLaughlin, "Temperature-Sensitive Mutants of Yeast Exhibiting a Rapid Inhibition of Protein Synthesis," 1664-1671; L. H. Hartwell and C. S. McLaughlin, "A Mutant of Yeast Apparently Defective in the Initiation of Protein Synthesis," *Proc Natl Acad Sci U S A* 62, no. 2 (1969): 468-474; Hartwell, Culotti, and Reid, "Genetic Control of the Cell-Division Cycle in Yeast. I. Detection of Mutants," 352-359.

novelties," including stable diploidy, chromosomes, centromeres, mitosis, mating, and meiosis. Yeast was inexpensive compared to the cost of animal tissue, and the field was still relatively new, open and interactive. As a simple eukaryote, yeast provided comparable access to the biochemistry of genetics, but, he recalled, students had "a deeply ambivalent feeling" when similarities were confirmed between yeast and bacteria. "After all, if something turned out to work in yeast just as it did in bacteria, it would not be the kind of novel "eukaryotic" principle that conventional wisdom dictated we pursue," he explained.[121]

Herskowitz had spent a summer on the Cold Spring Harbor campus during his first year of graduate school and was happy to return to learn more about the genetics of a single-celled eukaryote.[122] Initially, he, Botstein, and the course instructor Fink hoped that they might identify a "yeast phage" tool capable of modifying yeast genetic material as was done in bacteria. They called brewers and vintners asking about any problems with yeast in production, hoping they might find a virus which would help them to isolate yeast genes for study. The Spanish geneticist Jaime Conde, who had done postdoctoral work in Carbondale with Carl Lindegren, answered their call from his post at the University of Seville. Conde had collected several yeast cultures that were able to kill other strains.[123] While none of these yielded a yeast virus, Herskowitz

[121] Botstein, "A Phage Geneticist Turns to Yeast," 361-364.
[122] Herskowitz, (Undated), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[123] Herskowitz, (Undated), Series 4: Professional Activities, Carton 89 Seminar and Research Notebooks, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25). They found that this was due to a yeast "killer factor", whose action was first observed by Pasteur and later examined in EA Bevan and M Makower, "The Physiological Basis of the Killer Character in Yeast" (paper presented at the Proc. Int. Congr. Genet, 1963), 202-203; D. R. Woods and E. A. Bevan, "Studies on the Nature of the Killer Factor Produced by Saccharomyces Cerevisiae," *Journal of General Microbiology* 51, no. 1 (1968): 115-126. Fink later invited Conde to Cornell as a visiting assistant professor during the period 1974-1976. Their collaboration resulted in the publication of J Conde and G R Fink, "A Mutant of Saccharomyces Cerevisiae Defective for Nuclear

continued to pursue the possibility until the end of the decade at which point the development of yeast transformation made the search unnecessary.[124]

Following the summer training, Herskowitz returned to Botstein's laboratory at MIT where he began to develop a research agenda on yeast mating type differentiation that would form his life's work. He later credited the yeast course instructors for having provided the important introduction to yeast.[125] Herskowitz had studied transcriptional activators which controlled "alternative fates" of lambda phage as a student at MIT.[126] The phenomenon of mating type switching appeared to be a similar problem in eukaryotic yeast. Herskowitz determined that yeast's two mating types existed in diploid yeast as three cell types, a/a, a/α, and α/α. He wanted to understand what regulated a given yeast to become one of these cell types, since generations of yeast cells could differ. As yeast divided, it switched between two mating types, converting one mating type into the other even though these traits were co-dominant. Robert Mortimer and Donald Hawthorne had mapped yeast mating types to a single genetic locus in 1966.[127] Herskowitz now wanted to understand the regulatory circuits controlling their alternative fates. His question supposed that yeast, a single-celled organism, could be useful for the study of cellular differentiation and complex development.[128]

Fusion," *Proceedings of the National Academy of Sciences* 73, no. 10 (1976): 3651-3655. See also Botstein, "A Phage Geneticist Turns to Yeast," 366.

[124] In 1974, Herskowitz wrote to a colleague: "Unfortunately, we (and everyone else!) have yet to find any infectious virus for yeast." In Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

[125] In addition to Fink and Sherman, Herskowitz also credited Chris Lawrence who was the rotating third instructor of the course in 1971.

[126] Ira Herskowitz and E. R. Signer, "A Site Essential for Expression of All Late Genes in Bacteriophage Lambda," *J Mol Biol* 47, no. 3 (1970): 545-556; Ira Herskowitz, "Control of Gene Expression in Bacteriophage Lambda," *Annu Rev Genet* 7 (1973): 289-324.

[127] Robert K. Mortimer and D. C. Hawthorne, "Yeast Genetics," *Annu Rev Microbiol* 20 (1966): 151-168.

[128] D. Botstein, "Ira Herskowitz: 1946-2003," *Genetics* 166, no. 2 (2004): 657.

Following his postdoctoral studies with Botstein, Herskowitz joined the University of Oregon in 1972 as an assistant professor in the Institute of Molecular Biology. Although he had trained in bacteriophage and was "imprinted by the gospel of microbial genetics," in November 1972 Herskowitz claimed to be interested only in doing "my brand of science, molecular genetic studies of gene control… more recently with yeast." He had no interest in building a "research empire."[129] The first graduate student to join Herskowitz's laboratory in 1972 was Jim Hicks, a third-year student who had heard that a "real hotshot" was coming from MIT to work on a new subject. Hicks thought that the interesting aspects of *E. coli* had already been investigated and that the field was too crowded, and he was intrigued by Herskowitz's suggestions of the yeast mating type problem.[130] The Cold Spring Harbor yeast course had introduced Herskowitz and Botstein to a paper in a 1970 issue of *Genetics* by Yasuji Oshima and Isamu Takano from the Central Research Institute of Suntory Ltd. in Osaka, Japan, in which the researchers had identified "transposable elements" controlling the change in yeast mating type.[131] Herskowitz showed the paper to Hicks.

Japanese yeast genetics had been driven by the fermentation industry, and "applied microbiology" had had a presence in the universities since the University of Tokyo established

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[129] Herskowitz understood his own approach to molecular biology to be of the "nucleic acid/genetic school" rather than "structuralist/chemical." In Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25); Jasper Rine, "The 2002 Thomas Hunt Morgan Medal Ira Herskowitz," *Genetics* 164, no. 2 (2003): 419; Herskowitz, (Undated), Carton 11 Correspondence Fo-La, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

[130] J. B. Hicks, interview by Ludmila Pollock and Jan Witkowski, August 8, 2001, "Oral History Interview #2037," New York, Cold Spring Harbor Laboratory Archives.

[131] Isamu Takano and Yasuji Oshima, "Mutational Nature of an Allele-Specific Conversion of the Mating Type by the Homothallic Gene HO Alpha in Saccharomyces," *Genetics* 65, no. 3 (1970): 421-427; Isamu Takano and Yasuji Oshima, "An Allele Specific and a Complementary Determinant Controlling Homothallism in Saccharomyces Oviformis," *Genetics* 57, no. 4 (1967): 875; Isamu Takano and Yasuji Oshima, "Allelism Tests among Various Homothallism-Controlling Genes and Gene Systems in Saccharomyces," *Genetics* 64, no. 2 (1970): 229.

an institute for its study in 1953.[132] Japanese scientists recruited visiting researchers from abroad, and traveled to learn the latest genetic methods.[133] Oshima, for example, studied with Carl Lindegren at Southern Illinois University in Carbondale and returned to Japan in the mid-1960s to join Suntory, a new brewery just entering the Japanese market in competition with leading brands Asahi, Kirin and Sapporo. He later left Suntory for Osaka University in 1970.[134] Eukaryotic genetics at the start of the 1970s was a continuation of this tradition of applied microbiology for yeast scientists. At the nearby Kobe University School of Medicine, other biochemists were working to establish the similarities between eukaryotic yeast and higher organisms by comparing the biological function of enzymes in microbes and mammals.[135]

While at Suntory, Oshima and his student Takano submitted their paper on genetic control of yeast mating type switching to the American journal, *Genetics*. Fink reviewed the paper and, perplexed by the finding that two chromosomes could behave differently, asked the authors to tone down their initial discussion. Transposable genes were a very different mechanism of gene control than the known prokaryotic lac operon. As a result, the researchers adopted the vague terminology of an analogous mechanism in maize which had been coined by geneticist Barbara McClintock some fourteen years earlier: "controlling elements."[136] While Hicks later learned that Oshima and Takano may have better understood the mutational

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[132] Gene Gregory, "Biotechnology - Japan's Growth Industry," *New Scientist*, July 29, 1982, 309.
[133] See Kin-Ichiro Sakaguchi, Letter to Joshua Lederberg, (December 28, 1953), Box 13, Folder 144, Profiles in Science: The Joshua Lederberg Papers, National Library of Medicine, Bethesda, MD.
[134] See Ira Herskowitz and Erin O'Shea, "The 2001 Thomas Hunt Morgan Medal: Yasuji Oshima," *Genetics* 160, no. 2 (2002): 367; Oshima, "Homothallism, Mating-Type Switching, and the Controlling Element Model in *Saccharomyces Cerevisiae*," 291-292.
[135] Y. Takai et al., "Functional Similarity of Yeast and Mammalian Adenosine 3',5'-Monophosphate-Dependent Protein Kinases," *Biochem Biophys Res Commun* 59, no. 2 (1974): 646-652.
[136] Barbara McClintock, "Controlling Elements and the Gene" (paper presented at the Cold Spring Harbor Symposia on Quantitative Biology, 1956), 197-216.

conversion of mating types than their published paper let on, he was intrigued by their findings and set about constructing and testing models that could explain the mating type switching phenomenon.[137]

Next to join the Herskowitz laboratory in Oregon was student Jeff Strathern, who came to work on lambda bacteriophage and got fairly far along in his dissertation project when his research was scooped. After scrambling to find a new topic that would allow him to finish graduate school in a timely fashion, Strathern spent two weeks during winter break working with yeast and, in that short of a period, found some significant results.[138] "[Yeast] was too easy. It was a picnic," he recalled.[139] He began to collaborate with Hicks on the yeast mating type question. The students worked well together with Strathern posing interesting scientific questions and Hicks setting about to test and answer them experimentally. Hicks fondly recalled listening to the Watergate hearings together across a shared lab bench.[140] Hicks' laboratory notebooks from his Oregon years are an assortment of scrawls on scrap paper, and include crossed out notes-to-self: "JH – HAVE YOUR GUITAR IN IH'S [Herskowitz's] OFFICE. JH," and self-reprimands for occasional forgetfulness: "YOU DUMB SHIT! USE LOW POS. ON LAMP," "You dummy again! They need trp!"[141] Strathern described Hicks as a "spectacular and

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[137] Hicks, "Oral History Interview #2037." See also the related work of the Soviet scientists GI Naumov and II Tolstorukov, "Comparative Genetics of Yeast. X. Reidentification of Mutators of Mating Types in Saccharomyces," *Soviet Genetics* (1973). See also Oshima, "Homothallism, Mating-Type Switching, and the Controlling Element Model in *Saccharomyces Cerevisiae*."
[138] Jeffrey N. Strathern, "Regulation of Cell Type in Saccharomyces Cerevisiae" (PhD diss., University of Oregon, 1977).
[139] Jeffrey N. Strathern and Amar Klar, interview by Mila Pollock, 2000, "Oral History Interview #2016," New York, Cold Spring Harbor Laboratory Archives.
[140] Jeffrey N. Strathern, Jim Hicks, and Amar Klar, August 10, 2001, "Guest Speakers, Molecular Biology of Yeast Course: Oral History Interview #2039," New York, Cold Spring Harbor Laboratory Archives.
[141] James Hicks Papers, 1971-1984, (Undated), Series 1: Lab Notebooks Box 1, Yeast I, Yeast Collection, Cold Spring Harbor Laboratory Archives, New York; James Hicks Papers, 1971-

interesting person" with "the lowest activation barrier for starting an experiment."[142] They were using strain S288C from the yeast course as their wild type.[143]

Hicks discovered that Oregon's prokaryotic geneticists in the Institute of Molecular Biology were not interested in the laboratory's work on yeast mating type switching. "[T]he first time I tried to get it in an institute weekly seminar," he recalled, "I was shouted down by the bacterial geneticists that no one really believed that stuff." The variable reception of this early work frequently related to the percentage of "yeast freaks" in the crowd.[144] Although the mating type genetic paradox was incontrovertible to scientists familiar with yeast, Hicks claimed, at that time the "existing paradigm was really the only way to think."[145] As late as October 1974, Herskowitz continued "to straddle the fence scientifically." He wrote James Watson at Cold Spring Harbor that his laboratory was working on both phage and yeast genetics. Elsewhere, Herskowitz had expressed his strong interest in yeast as "a lower higher organism."[146]

1984, (Undated), Series 1: Lab Notebooks Box 1, Yeast IV, Yeast Collection, Cold Spring Harbor Laboratory Archives, New York. This habit later stuck at Cold Spring Harbor Laboratory, and Fink recalled that Hicks "used to keep his records, if you could call them that… in layers on his desk in sort of disarray." See Fink, "Oral History Interview."

[142] Strathern and Klar, "Oral History Interview #2016."

[143] Herskowitz's stock list of strains gives the origins of S288C as from "Fink via Botstein." Stock list available in James Hicks Papers, 1971-1984, (Undated), Series 1: Lab Notebooks Box 1, Yeast I, Yeast Collection.

[144] Phrase taken from a 1975 letter to Ira Herskowitz from Jeremy Thorner at the University of California at Berkeley, offering an assessment of Jim Hick's presentation performance. "Jim was just great… If he gives the talk someplace else (e.g. Lake Arrowhead) where the percentage of yeast freaks is considerably lower, you might suggest to him that he try not to cover so much..." In Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

[145] Jeffrey N. Strathern, Amar Klar, and Jim Hicks, interview by Mila Pollock and Peter Sherwood, August 8, 2001, "Oral History Interview #2038," New York, Cold Spring Harbor Laboratory Archives.

[146] As described in a letter to Volker M. Vogt at the Swiss Institute for General Microbiology in December of 1973. In Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

After graduation, Strathern and Hicks wanted to continue collaborating and were looking for an opportunity to work together again. Hicks, the more senior of the two, graduated in 1975 and began a postdoc with Gerry Fink at Cornell. Strathern, still back in Oregon, had some significant results on the yeast mating type question, which he took to the yeast meeting that year. Cold Spring Harbor's Ray Gesteland met both of them there. In 1975, Cold Spring Harbor adopted an egalitarian meeting style with a 15-minute talk format. "It was very like the phage meetings organized by Luria and Delbrück about 30 years before, and we were proud of that comparison," David Botstein recalled. "Everybody seemed to feel this sense of community, that our science was moving ahead [and] was somehow going to make it into the vanguard of molecular biology."[147] On the meeting program that year were Strathern, Hicks and Herskowitz on yeast mating type, and Hartwell on the cell cycle, among many others. Herskowitz wrote Watson shortly after the meeting with a description of what he saw as the significance of the alternative fates of yeast mating type: "I think of it as distilled development."[148] He was updating Cold Spring Harbor on the results of his training there.

During the 1974-1975 academic year, Botstein, Fink, and John Roth from the University of California at Berkeley had planned a shared sabbatical to study the phenomenon of yeast gene suppression using Leland Hartwell's cell cycle mutants in the S288C "background."[149] They had sponsorship from NSF but needed to find a space for a mutual yeast research program. After being turned away by the Salk Institute on the unfounded basis that yeast would "contaminate"

[147] Botstein, "A Phage Geneticist Turns to Yeast," 371.
[148] Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[149] Before the sequence of action of various yeast cell-cycle genes could be determined, cell-cycle mutants had to be "genetically removed" from their heavily mutagenized backgrounds to produce "cleaned" cell-cycle mutants using S288C. In *Annual Report,* (New York: Cold Spring Harbor Laboratory, 1975), 37. See also Botstein, "A Phage Geneticist Turns to Yeast," 367.

other microbial cultures, they received an invitation from James Watson to come to Cold Spring Harbor.[150] There they could use the recently-winterized Davenport Laboratory, where equipment had been left behind after the summer yeast course, and collaborate with Ray Gesteland, then permanently on staff.[151] According to Elizabeth Watson, who published an architectural history of the campus where she and her family lived for four decades, the arrival of the yeast researchers "greatly raised the level of intelligent discourse along Bungtown Road" that year.[152] They conducted some of the first recombinant DNA studies on yeast and worked on cloning yeast genes using restriction enzymes. The annual report proclaimed their stay a resounding success.[153] Their presence in Davenport also laid the foundation for the formation of a full-time staff yeast research group later in the decade when Herskowitz's students would work together again.[154]

In 1976, Hicks and Herskowitz published a paper in *Genetics* that hypothesized structural change at the mating type locus allowing for genetic "interconversion." Their findings showed that yeast mutants consistently switched mating type in pairs, leading them to determine that "all cells contain information to be both **a** and α [mating types], but only one of these states is expressed… [T]he stable switch in mating types involve[s] DNA modification… or DNA

[150] "We wrote learned things [to the Salk] about how yeast wouldn't grow in their medium. That the yeast that they're thinking of is a different yeast — *Candida albicans* has nothing to do with *Saccharomyces cerevisiae* all to no avail. We got really annoyed at them," Botstein recalled. In Botstein, "Oral History Interview."
[151] *Annual Report*, 36. Davenport did not have an ultra-centrifuge, Botstein explained, so the team bought one and got it running after an initial mishap dropping it off a backhoe. In Botstein, "Oral History Interview."
[152] Watson, *Houses for Science: A Pictorial History of Cold Spring Harbor Laboratory*, 208.
[153] *Annual Report*, 12.
[154] Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

rearrangement at the mating-type locus."[155] They soon had a name and a structural model for the phenomenon, "the cassette model for mating type interconversion."[156] It proposed that the genetic locus for mating-type was filled by one of two gene sequences, called "transposable cassettes," which could replace one another through programmed DNA rearrangement.[157] An early draft of their 1977 paper shows the care with which Herskowitz and Hicks tried to distinguish between mating type behavior as phenotypically "allelic" versus defining the alternative forms molecularly as "alleles" which would not allow for them to be coded by closely linked genes.[158] At stake was the construction of a eukaryotic model proposing transposable coding blocks, transposable regulatory sites, or some combination of the two.[159] They determined that informational cassettes (the coding blocks) inserted adjacent to the regulatory site, and that the mating type locus could be silenced under gene control.

Jasper Rine, a geneticist at the University of California, Berkeley, later called this body of work "the last great problem in biology that was fundamentally resolved purely by classical genetic analysis."[160] The genetic basis for mating type switching was a surprise, but it was thought to be a fundamental observation for developmental biology. The researchers were

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[155] In J. B. Hicks and I. Herskowitz, "Interconversion of Yeast Mating Types I. Direct Observations of the Action of the Homothallism (HO) Gene," *Genetics* 83, no. 2 (1976): 256. Text bolded in original.
[156] J. B. Hicks and I. Herskowitz, "Interconversion of Yeast Mating Types II. Restoration of Mating Ability to Sterile Mutants in Homothallic and Heterothallic Strains," *Genetics* 85, no. 3 (1977): 388-389.
[157] The "cassette model" was proposed at the same time the compact cassette was taking over for the 8-track on the portable music scene.
[158] Herskowitz, (Undated), Carton 69 Subseries B Manuscript materials, "MSS I", Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[159] Herskowitz later wrote to historian of science Nathaniel Comfort: "What we showed is that the transposable DNA elements involved in mating type interconversion contained coding information." In Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[160] Rine, "The 2002 Thomas Hunt Morgan Medal Ira Herskowitz," 420.

prepared, based on this activation of genes in yeast, to "speculate [about the] determination of cell type in higher eukaryotic cells."[161] Cell type differentiation was under the control of an element that went on to make continuous decisions, rather than, as in the prokaryotes, to merely maintain those decisions. A controlled asymmetrical choice of cell type explained how cells appeared when and where they were needed in multicellular organisms. Single-celled yeast could be leveraged as a major tool in the study of higher organism development. Physicist Robert Haynes remembered that this shift took him by surprise in the mid-1970s. "What I had thought to be a wallflower organism in the eyes of mainstream molecular biologists suddenly became fashionable among the *avant garde*."[162]

Hicks acted as a rotating instructor for the yeast course in the summer of 1976. Back at Cornell, Gesteland talked to Hicks about the possibility of a reunion with Strathern at Cold Spring Harbor following the latter's graduation from the University of Oregon in 1977. With Watson's approval, Gesteland might appoint Hicks to the faculty and bring on Strathern as a postdoctoral fellow to continue their collaboration on yeast mating type research. Hicks was thrilled and Herskowitz, too, supported the idea, writing to Watson in January of 1977 that, "Jim and Jeff have not been dependent on me for our intellectual progress on yeast."[163] Watson later credited Herskowitz for proposing the idea of a yeast research group in a letter which made the suggestion that his students work year-round at Cold Spring Harbor to identify the yeast mating

[161] Herskowitz, (Undated), Carton 69 Subseries B Manuscript materials, "MSS I", Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[162] Haynes, "My Road to Repair in Yeast: The Importance of Being Ignorant," 168. Italics in original.
[163] Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

type locus. “Why not here at Cold Spring Harbor, provided we continue our habit of giving labs to younger scientists and encouraging them to work at maximal speed,” Watson agreed.[164]

Strathern moved with his wife to Cold Spring Harbor in November 1977. He recalled being charmed by the Laboratory’s very present sense of the early history of molecular biology, with many of the campus’s buildings named for famous researchers in whose footsteps he was determined to follow.[165] Hicks moved to campus shortly thereafter with a high-scoring federal grant in support of the mating type research. The original yeast group was completed with the addition of geneticist Amar Klar and his “strains and plates” from Berkeley in April of 1978.[166] Klar was an Indian scientist who had his PhD in bacteriology from the University of Wisconsin in 1975. He had done his postdoctoral research in genetics with Sy Fogel at University of California at Berkeley, where he had become interested in mating type differences between haploid and diploid yeast.[167] He took up the mating type question with encouragement from Oshima and Takano after the two came for a visit to Fogel’s laboratory. Herskowitz had

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[164] *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1979), 7.

[165] Strathern and Klar, "Oral History Interview #2016." Herskowitz wrote Watson again that December: “I am glad to hear from Jeff Strathern that he is enjoying Cold Spring Harbor.” In Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

[166] Jeffrey Strathern Papers, 1977-1982, (Undated), Series 1: Lab Notebooks 4,5,6 Box 2, Folder 4 (1/2), Yeast Collection, Cold Spring Harbor Laboratory Archives, New York.

[167] Klar and Fogel reported a summary of their work on yeast mating type genetics in the June 1976 Yeast News Letter, which had indicated co-dominant loci involved in the mating type switch. See Amar J. S. Klar and S. Fogel, "The Action of Homothallism Genes in Saccharomyces Cerevisiae Diploids," in *Yeast: A News Letter for Persons Interested in Yeast*, ed. Herman J. Phaff (International Commission on Yeast and Yeast-like Microorganisms of the International Association of Microbiological Societies (IAMS), 1976), 27. Fogel had trained in Seattle, worked independently at Brooklyn College, and was now running the yeast stock center with Mortimer at Berkeley. His biographical sketch is available in Mortimer, Technical Documents, 1950-1999, (undated), Box 2, Folder 1, Robert K. Mortimer Collection (ARO-5425). Fogel and Mortimer had published an influential theory of yeast gene conversion as a process of “informational transfer.” See S. Fogel and R. K. Mortimer, "Informational Transfer in Meiotic Gene Conversion," *Proc Natl Acad Sci U S A* 62, no. 1 (1969): 96-97.

reviewed some of Klar's postdoctoral work and realized they were working in a common area.[168] When Klar presented his research at the August 1977 yeast meeting, Strathern and Hicks saw that his work offered proof of their cassette model. Strathern recalled the group's excitement. "This was at a time when it was difficult simply to discuss the concept of the cassette model. Amar was this wonderful exception… we could finish each other's sentences."[169]

Gesteland made the suggestion to recruit Klar to the Cold Spring Harbor yeast group.[170] Hicks described how this was a surprise because "in a lot of places if you had one yeast person you couldn't have another one," particularly working jointly on the same experiments. "[W]e wouldn't have been able to do it in any place else literally in the world." Strathern agreed.[171] Because Klar had already held a postdoctoral position, he was brought on without an interview as a member of the faculty, and in a somewhat bewildering turn of events found himself more senior to Strathern who was newly a fellow.[172] The group moved into the laboratory in Davenport for several weeks leading up to the summer of 1978. Then, they had to make way for the yeast course, and moved across campus to the Demerec laboratory until September.[173] Grants from NSF and NIH let them develop this mutual research program.[174] They soon incorporated

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[168] Strathern, Hicks, and Klar, "Guest Speakers, Molecular Biology of Yeast Course: Oral History Interview #2039."; Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[169] Strathern and Klar, "Oral History Interview #2016."
[170] Hicks, "Oral History Interview #2037."
[171] Strathern, Klar, and Hicks, "Oral History Interview #2038."; Strathern and Klar, "Oral History Interview #2016."
[172] The unusual circumstances of Klar's hire are described in Strathern and Klar, "Oral History Interview #2016."
[173] An addition was later built onto Davenport (then renamed for Max Delbrück) so they would not have to keep moving. See J. B. Hicks et al., *Yeast Genetics*, Annual Report (New York: Cold Spring Harbor Laboratory, 1979), 58; *Annual Report*, 7; J. B. Hicks et al., *Yeast and Plant Genetics*, Annual Report (New York: Cold Spring Harbor Laboratory, 1981), 68.
[174] Klar's proposal to NIH in October of 1977 suggested that they would understand how cellular fates were programmed so that cancer cells made cancer cells and plasma cells produced

Kim Nasmyth, who had been working in the same area in Benjamin Hall's lab in Seattle, Jim Broach, a postdoc in Gesteland's lab who had trained with Mortimer at Berkeley, and several others.[175] Hicks credited Watson with bringing together talented scientists without regard for academic hierarchy. The group shared intellectual credit for their discoveries to the point where outsiders warned them that, "no one can tell who's who in this because all your names are on all the papers." Hicks was told that they would ruin their careers.[176]

The yeast group members agreed to the common purpose of answering three main research questions about yeast mating type: what the genes did, how mating type was silenced, and how it switched. That was a time of major technological change in yeast genetics, and molecular biology more broadly, and the group thought they could harness emerging tools of genetic engineering to get answers to these questions.

Cold Spring Harbor and Yeast Genetic Engineering

"Yeast transformation" was a technique developed in Fink's lab at Cornell University during 1976 and 1977 by Fink, Hicks and another postdoctoral fellow, the Swiss scientist Albert Hinnen. Other groups within the U.S. were subjected to an NIH freeze on recombinant DNA technology in the mid-1970s, but because Fink also had basic yeast genetics support from the

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particular antibodies. In Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 1, Yeast Collection.

[175] The annual report saw space to grow the group to "six or maybe seven members." In *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1978), 13.

[176] In Hicks, "Oral History Interview #2037." Strathern also considered their shared impact: "My colleagues and I have published fifty papers on this topic in the last couple of decades. That's the ones that I'm on with these gentlemen. And there are hundreds of other papers that derive from aspects of this story; extensions of how this gene regulation occurs; extensions of how this silencing process occurs and extensions of the actual mechanics of the mating type switching… I tried to count labs, and… lost track when I got to thirty-five." In Strathern, Hicks, and Klar, "Guest Speakers, Molecular Biology of Yeast Course: Oral History Interview #2039."

NSF, he was able to move ahead on a bureaucratic loophole. The ban was concerned with specifically human consequences of genetics applied in biomedical research. Using cloning tools developed in *E. coli* which Fink had learned during his Cold Spring Harbor sabbatical from prokaryotic geneticists, they showed that prokaryotic DNA extracted from bacteria could be expressed in yeast and transmitted as a heritable component of the eukaryotic genome.[177] Their recombinant strains were derived from strain S288C. There had been earlier attempts at yeast transformation. Herschel Roman had tried it during a visit to Carlsberg in 1960, and the Dutch scientist W.F. Oppenoorth reported a successful attempt in 1962, but his results could not be repeated.[178] With the finding of yeast transformation by bacterial plasmid DNA, Hinnen, Hicks and Fink demonstrated the practical utility of genetic techniques and raised the possibility that the addition of new genes, including homologous yeast genes, could "diversify the species."[179] While they wrote up these results for publication, Fink brought the technique to the yeast course, and Hicks introduced the yeast group to this approach.[180] They published their study in April 1978, giving them a five-month margin of priority in the literature over Jean Beggs at the University of Edinburgh who developed the technique independently.[181]

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[177] The next chapter describes the development of recombinant DNA technology, the cloning ban and Fink's NSF loophole in greater detail and discusses how baker's yeast was preferred over *E. coli* for the expression of pharmacologically important genes because the familiar eukaryote was viewed as nonpathogenic, more human-like, and already industrially useful.

[178] W. F. Oppenoorth, "Transformation in Yeast: Evidence or a Real Genetic Change by the Action of DNA," *Nature* 193 (1962). See also Friis, "The Carlsberg Laboratory: Historical Retrospect and Personal Reminiscence," 449.

[179] A. Hinnen, J. B. Hicks, and G. R. Fink, "Transformation of Yeast," *Proc Natl Acad Sci U S A* 75, no. 4 (1978): 1933. See also John Tooze, *50 Years Ago: Bacterial Transformation* (Elsevier/North-Holland Biomedical Press, 1978), 261-262; Kim Nasmyth, "Eukaryotic Gene Cloning and Expression in Yeast," *Nature* 274, no. 5673 (1978): 741-743.

[180] *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1977), 66; *Annual Report*, 76.

[181] Beggs' article was published on September 14. J. D. Beggs, "Transformation of Yeast by a Replicating Hybrid Plasmid," *Nature* 275, no. 5676 (1978): 104-109.

In June of 1978, Hicks, Hinnen, and Fink attended the Third International Symposium on Genetics of Industrial Microorganisms at University of Wisconsin-Madison, where the British microbiologist David Hopwood declared in his opening address that the prokaryotic-eukaryotic boundary was collapsing.[182] University of Manchester microbiologist John D. Bu'lock agreed noting that, "We are not necessarily 'condemned' to the yeasts" since fermentation products might now be found among the prokaryotes, but applications of the "new genetics" might still be found "in the organism where it is still most at home."[183] Hinnen's talk at the symposium echoed this point that, yeast was "probably the best understood lower eucaryote [*sic*]… [and was therefore] ideal as a host for the genes of higher eucaryotes."[184]

Transformation allowed for *in vivo* experimentation to determine the role of particular proteins and decades of collecting yeast mutants meant that there was a ready pool of catalogued genes to test.[185] This "reductionist approach to studies of gene action" became standard for the field, according to Seattle yeast geneticist Benjamin Hall.[186] Others have claimed that transformation "provide entrée into the molecular basis of processes common to all eukaryotic

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[182] David Hopwood, "Opening Address: The Many Faces of Recombination" (paper presented at the Genetics of Industrial Microorganisms, The University of Wisconsin, Madison, June 4-9, 1978), 1.
[183] J.D. Bu'lock, "Process Needs and the Scope for Genetic Methods" (paper presented at the Genetics of Industrial Microorganisms, The University of Wisconsin, Madison, June 4-9, 1978), 111.
[184] "Eucaryote" was a common alternative spelling. See A. Hinnen et al., "Yeast Transformation: A New Approach for the Cloning of Eucaryotic Genes" (paper presented at the Genetics of Industrial Microorganisms, The University of Wisconsin, Madison, June 4-9, 1978), 42-43.
[185] The new transformation systems were used to create single gene knock-outs of yeast as a way of deriving gene function by mutation. This is described as the "reverse" of classical genetics in that intentional manipulation of the genome was followed "upward" to observe phenotype. See D. Botstein and G. R. Fink, "Yeast: An Experimental Organism for Modern Biology," *Science* 240, no. 4858 (1988): 1441.
[186] Benjamin D. Hall, "Starting to Probe for Yeast Genes," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 400.

cells."[187] Indeed, transformation greatly furthered yeast's potential to describe other organisms, no longer by generalizable analogy, but now in the borrowed terms of their own molecules. Yet this work was also already being done by the homology of the eukaryotic cell. According to Fink, recombinant DNA technology set the stage for the Yeast Genome Project at the start of the 1990s, and "it became possible to basically engineer yeast to produce virtually anything" – including, as its ideal, the molecular human.[188]

The Cold Spring Harbor yeast group used yeast transformation to develop a yeast DNA cloning vector which could isolate DNA from mating-type locus. This application of the new technology to clone the mating type gene confirmed their cassette model "almost as an anticlimax," according to yeast researcher Vivian MacKay.[189] Given the excitement over the new technology, however, it served as conclusive proof to the wider field of geneticists. Strathern claimed that the cassette model had been proven as a mechanism.[190] To some extent, the development of yeast transformation marked a turning point for the visibility of molecular

[187] Linder, Shore, and Hall, *Landmark Papers in Yeast Biology*, 2. See also Walton Fangman and Virginia Zakian, "Genome Structure and Replication," in *The Molecular Biology of the Yeast Saccharomyces: Life Cycle and Inheritance*, ed. Jeffrey N. Strathern, Elizabeth W. Jones, and James R. Broach (Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press, 1981), 27.

[188] Fink, "Oral History Interview." Others have held that yeast transformation enabled yeast to begin replacing *E. coli* "as the model organism of choice." See Kenneth S Zaret, "At the Revolution with Fred Sherman," *Molecular and cellular biology* 34, no. 6 (2014): 922. The "first eukaryotic organism to have its genome sequenced" served as a pilot study for the sequencing of the human genome. See Goffeau et al., "Life with 6000 Genes," 546-567.

[189] Vivian L. MacKay, "**A**'s, A's, and Schmoos: Mating Pheromones and Genetics," in *The Early Days of Yeast Genetics*, ed. Michael N. Hall, and Patrick Linder (Plainview, NY: Cold Spring Harbor Laboratory Press, 1993), 282.

[190] According to Strathern, "The cassette model was genetically proven…. [but] people couldn't handle those genetic arguments. They needed the physical proof." The clone was proof of the cassette model. In Strathern and Klar, "Oral History Interview #2016." See also Strathern, Klar, and Hicks, "Oral History Interview #2038."; Strathern, Hicks, and Klar, "Guest Speakers, Molecular Biology of Yeast Course: Oral History Interview #2039."

modeling. No longer was yeast *like* the human organism and vice versa. Their molecules, already analogous, had become physically interchangeable as well.

Yeast Models of Development, Human Health and Disease

Yeast transformation, gene cloning, and the mating type cassette model generated a lot of excitement at the 1979 yeast molecular biology meeting. Four hundred scientists headed to Cold Spring Harbor that summer, and this yeast community only continued to grow.[191] One 1983 review estimated that the population of yeast workers had doubled every two years between 1975 and the year the article was published.[192] The scientific journal *Yeast* was established in 1985 to accommodate the vast literature accruing on the organism.[193] By the early 1990s, attendance at international yeast meetings regularly exceeded 1,000.[194]

The yeast group tried to set some standards of collaboration for the field with their distribution of the mating type clone. “Absolutely, you can have the gene,” Strathern recalled saying to other investigators, “but I’ve also sent it to this person and this person and this person, and you have to communicate with them about what you’re doing.”[195] The group also followed Herskowitz’s lead in trying to extrapolate from their work to the development in higher eukaryotic organisms. Herskowitz had determined early on that yeast mating behavior had implications for many different branches of molecular and cell biology and tried to captivate

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[191] Jeffrey N. Strathern, E.W. Jones, and J.R. Broach, *The Molecular Biology of the Yeast Saccharomyces, Life Cycle and Inheritance* (New York: Cold Spring Harbor Laboratory, 1981), ix.
[192] Kevin Struhl, "The New Yeast Genetics," *Nature* 305, no. 5933 (1983): 391-397.
[193] Gianni Litti (ed.), *Yeast (1985-2016)*, http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1097-0061.
[194] In David D Perkins, "Neurospora: The Organism Behind the Molecular Revolution," *Genetics* 130, no. 4 (1992): 691.
[195] Strathern, Hicks, and Klar, "Guest Speakers, Molecular Biology of Yeast Course: Oral History Interview #2039."

audiences by relating his work to "a bigger picture" of gene control and genetic rearrangement.[196] Yeast to Herskowitz represented the "universal cell."[197] Cold Spring Harbor regularly echoed this message in the Laboratory's annual reports, and the members of the yeast group made clear their expectations to funders and other scientists that the work should have implications for higher organisms' growth and development.[198] According to Hicks, "what we really considered ourselves doing was development biology using genetics in a very elegant system where you could get yes or no answers very quickly… we looked at [yeast] literally as stem cells."[199] Strathern later recalled, "We always had the feeling that we didn't have to leave yeast or mating type switching because all of those things would remain some part in the yeast system and… in the mating type story."[200] This indeed proved to be true. Botstein later characterized yeast gene-controlled cellular differentiation as one of "the best-understood regulatory system in eukaryotic biology… taught in every textbook of genetics and cell biology."[201]

Following a 1978 sabbatical at the University of California, San Francisco (UCSF), Herskowitz determined that he "wanted to be stretched in new directions, notably in the area of cell and molecular biology of eukaryotes."[202] He left Oregon in 1981 to join the UCSF faculty as vice-chair and professor of biochemistry and biophysics, and head of the genetics division, and

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[196] Herskowitz, (Undated), Carton 11 Correspondence Fo-La, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[197] He credited Herschel Roman for helping to develop this concept. In Herskowitz, (Undated), Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[198] Hicks et al., *Yeast Genetics*, 1979, 58.
[199] Strathern, Hicks, and Klar, "Guest Speakers, Molecular Biology of Yeast Course: Oral History Interview #2039."
[200] Strathern and Klar, "Oral History Interview #2016."
[201] Botstein, "Ira Herskowitz: 1946-2003," 659.
[202] Herskowitz, (Undated), Carton 11 Correspondence Fo-La, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25); Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

he continued to study asymmetric yeast cell growth and division as a eukaryotic model.[203] The Oregon press lamented the loss of one of the University of Oregon's "truly outstanding" molecular biologists because of limited resources in Eugene. Herskowitz reportedly left because "his specific area of scientific interest was poorly represented."[204] At UCSF, he became even more of a vocal advocate for the use of yeast as a model organism to study fundamental biological problems. It was there too that a fellow member of the faculty in biochemistry and biophysics, the yeast geneticist Christine Guthrie, coined the field's successful slogan: "the awesome power of yeast genetics."[205]

Herskowitz's papers from this time reveal a thoughtful and creative person concerned with public service to the "yeast + general community."[206] He had a reputation for playing folksy guitar and composing scientific tunes like "the Double Talking Helix Blues," which he would perform at the yeast meetings.[207] His unique diagramming style using arrows to stand in for molecular mechanisms became a standard for the rest of the field (called "Ira-grams," according to David Botstein) as a means of simplifying complex processes.[208] He trained more than 70

[203] Herskowitz, (Undated), Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25). See also Alexander Johnson and Mark Ptashne, "Obituary: Ira Herskowitz (1946-2003)," *Nature* 424, no. 6947 (2003): 1.
[204] Julie Tripp, "Better Salaries, Opportunities Lure Teachers, Administrators," *The Sunday Oregonian*, August 29, 1982, C3. He joined the department of William Rutter, whose specific interest in developing eukaryotic molecular biology is discussed in the next chapter.
[205] Christine Guthrie, Conversation with the Author, September 15, 2015.
[206] Herskowitz, (Undated), Carton 69 Subseries B Manuscript materials, "MSS I", Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[207] Herskowitz, (Undated), Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25); Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[208] Botstein, "Ira Herskowitz: 1946-2003," 657.

graduate students and postdoctoral fellows during his career, many of whom went on independent to successful careers in science.[209]

When Herskowitz suggested to Strathern and Hicks that they write a review in *Science* so that "people who aren't already tuned into the subject… will have the opportunity to 'get religion,'" he was also aiding in these efforts himself.[210] He considered extending the mating type work to studies of sex determination in goats, for example, and promoted the work to explain development in higher eukaryotic organisms "such as ourselves."[211] He was contacted, in turn, by investigators who considered yeast a "role model" for work on developmental problems in other systems. For her work on liver cell differentiation in the mouse, for example, Yeshiva University geneticist Salome Waelsch was "much impressed by the conceptual and interpretive broadness" in Herskowitz's analysis.[212] Perhaps Herskowitz's most measured assessment of yeast's contributions to developmental biology over a fifteen-year period was written in response to a letter from Amarillo, Texas, high school student Kathy Plat in March of 1987. He wrote, "it may be that what we've found out for yeast is true for humans... Our explanation for yeast is

[209] Rine, "The 2002 Thomas Hunt Morgan Medal Ira Herskowitz," 420; Johnson and Ptashne, "Obituary: Ira Herskowitz (1946-2003)," 384.
[210] Herskowitz, (Undated), Carton 69 Subseries B Manuscript materials, "MSS I", Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25). See also Ira Herskowitz and Yasuji Oshima, "Control of Cell Type in *Saccharomyces Cerevisiae*: Mating Type and Mating-Type Interconversion," in *The Molecular Biology of the Yeast Saccharomyces, Life Cycle and Inheritance*, ed. J.N. Strathern, E.W. Jones, and J.R. Broach (Cold Spring Harbor, New York: Cold Spring Harbor Laboratory, 1981).
[211] Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25); Herskowitz, (Undated), Carton 11 Correspondence Fo-La, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[212] Herskowitz, (Undated), Correspondence Carton 14: Si-Zi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

either correct, or it is incorrect. *In either case*, the yeast work will help to pose the proper questions for human cells."[213]

The yeast mating type model was taken up as a subject with cultural relevance as well. For example, Klar's work as part of the yeast group was fictionalized by Jeffrey Eugenides in the novel *The Marriage Plot* (2011), a coming-of-age story which has one of the protagonists working in a genetics laboratory to investigate why the progeny of a given cell division can acquire different developmental fates.[214]

Yeast mating analogies had a much longer history, and research on yeast sexuality appropriated ideas from human culture in addition to naturalizing them as eukaryotic biology. Since the late 1960s, for example, an ongoing source of humor among yeast biologists has been the use of the term "shmoo" to describe the elongated shape formed by the yeast cell just prior to sexual reproduction. Two cells of "budding" or "shmooing" yeast projected toward one another to join and separate in the generation of a new cell. In its preparation for this mating act, yeast has resembled the bowling pin-shaped "shmoos" created by cartoonist Al Capp. Shmoos featured on Capp's "Lil' Abner" comic strip from August to December of 1948, and set off a

[213] Italics added and emphasis changed from original. Herskowitz, (Undated), Carton 11 Correspondence Fo-La, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[214] J. Eugenides, *The Marriage Plot: A Novel* (New York: Farrar, Straus and Giroux, 2011). In the novel's acknowledgements section, Eugenides specifically cites his source for yeast genetics information as the publication Amar J. S. Klar, "The Mother-Daughter Mating Type Switching Asymmetry of Budding Yeast Is Not Conferred by the Segregation of Parental HO Gene DNA Strands," *Genes Dev* 1, no. 10 (1987): 1059-1064. See also a review of the novel in Gina Kolata, "The Scientist Was a Figment, but His Work Was Real," *The New York Times*, February 14, 2012, D2. The study of yeast mating type as a model of human development was perhaps a fitting sequel for the author whose best-known work is the Pulitzer Prize-winning story of a hermaphroditic Greek immigrant living in America. See J. Eugenides, *Middlesex: A Novel* (New York: Farrar, Straus and Giroux, 2002).

merchandizing craze across the U.S. after that short time.[215] In the genetics department of the University of Washington in Seattle, Roman is believed to have first recognized the likeness and appropriated the shmoo into the scientific lexicon.[216]

Capp's comic had featured an asexual organism which lived on air and was eager to serve and be eaten by humans. Shmoos reproduced rapidly, "like the fruit fly," and readily supplied humans with every conceivable need, including eggs, milk, butter, and amiable companionship, or by sacrificing themselves altruistically to deliver the meat of several different animals, toothpick whiskers, button eyes, cloth and leather hides, or lumber for houses.[217] Because of this versatility, humans in the comic strip no longer had to work, and shmoos became - in the words of one of Capp's characters - "th' greatest menace to hoomanity th' world has evah known."[218] The storyline followed systematic slaughtering of the shmoos by the capitalists in order to save the economy, but concluded with two of the creatures escaping to survive another day.[219] At the start of the Cold War, the popular narrative ping-ponged between accusations of socialist propaganda and an exploitative "Capp-italism" as the profits racked up for the cartoonist.

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[215] The shmoo grossed $25 million dollars in the first year. See M. Schumacher and D. Kitchen, *Al Capp: A Life to the Contrary* (Bloomsbury USA, 2013), ix; W.H. Young and N.K. Young, *World War II and the Postwar Years in America: A Historical and Cultural Encyclopedia* (ABC-CLIO, 2010), 307. Apart from toys and household products, shmoos also feature in two graphic novels by Capp, *The Life and Times of the Shmoo* and *The Return of the Shmoo*, reprinted together in A. Capp, *The Short Life & Happy Times of the Shmoo* (Overlook Press, 2002).
[216] MacKay, "**A**'s, A's, and Schmoos: Mating Pheromones and Genetics," 274.
[217] "Capp-Italist Revolution: Al Capp's Shmoo Offers a Parable of Plenty," *LIFE Magazine*, December 20, 1948, 22.
[218] Schumacher and Kitchen, *Al Capp: A Life to the Contrary*, 136.
[219] More than half a century later, the fictional execution had its repetition in *The Journal of Cell Biology*, with a review of work done at Yale to terminate a shmoo by control of its proteins. See Alan W. Dove, "How to Terminate a Shmoo," *The Journal of Cell Biology* 164, no. 2 (2004): 162-163. The research article was S. Bidlingmaier and M. Snyder, "Regulation of Polarized Growth Initiation and Termination Cycles by the Polarisome and Cdc42 Regulators," *J Cell Biol* 164, no. 2 (2004): 207-218.

In the early years of its use, the shmoo was limited to a model of budding yeast in the sense that it looked and behaved comparably. As early as 1935, Øjvind Winge reported that haploid yeast cells were attracted to one another "probably [as] a question of chemical stimulation, as suggested by the direction of the growth of the conjugating offshoots in several yeasts."[220] Research in the late 1960s identified hormones which attracted different yeast mating types to grow toward one another.[221] Identified publically as α-factor or **a**-factor, these hormones were privately referred to using additional references from Capp's comic, "Schmoo-ogenic Hormones" and "Kickapoo Joy Juice."[222]

In 1967, Robert Mortimer had written "schmoos" into his recommendation letter on behalf of undergraduate applicant Donald Hawthorne for a U.S. Public Health Service fellowship.[223] Hawthorne's proposed research would utilize yeast mutants to investigate the sexually-suggestive phenotypes of "frigidity" (a response to molar diethylene glycol) and "frustration" (described as the ballooned spherical cells with multiple incipient copulation tubes). According to Mortimer, Hawthorne would develop a meaningful working model of yeast mating and seek a genetic basis for this "rather arbitrary" description of events.[224] At the University of Washington in Seattle, Leland Hartwell may have been the first to use the term "shmoo" in print

[220] Winge, *On Haplophase and Diplophase in Some Saccharomycetes*, 107.
[221] See Hick's detailed description of shmoos in yeast mating-type research. In James Hicks Papers, 1971-1984, (Undated), Series 1: Lab Notebooks Box 1, Yeast II, Yeast Collection.
[222] MacKay, "**A**'s, A's, and Schmoos: Mating Pheromones and Genetics," 275.
[223] Mortimer's misspelling of the word "shmoo" was possibly due to his lack of familiarity with the postwar reference. A Canadian native, Mortimer began his PhD in the United States at the University of California in Berkeley a year after Capp's comic ran. The different Berkeley-UW spellings offer a brief glimpse of the growing yeast genetics community during this period which was growing more culturally and generationally diverse by the late 1960s.
[224] Mortimer, Technical Documents, 1950-1999, (March 1, 1967), Box 1, Folder 16: Lindegren [Correspondence], Robert K. Mortimer Collection (ARO-5425).

in a 1973 publication on yeast DNA synthesis to describe elongated yeast cells.[225] The term caught on more broadly after Berkeley postdoctoral researcher Vivian MacKay and co-author Thomas Manney explained the reference to Capp's comic, attributed the analogy to Roman, and took up its use "for brevity" in a February 1974 publication.[226]

In the early 1980s, yeast mating type research was extended to examine the similarities between yeast and human reproductive hormones. Yeast mating pheromone was one of the phylogenetically oldest reproductive hormones and was shown to have comparable biological activity and sequence homology to a mammalian hormone. The finding seemed to indicate evolutionary conservation of reproductive function from yeasts to humans.[227] The development of recombinant engineering techniques in the late 1970s was central in enabling geneticists to further anthropomorphize the organism along these lines. Following development of the technique for yeast transformation, the shmoo allegory was reinvigorated for early yeast genetic engineers of the late 1970s and 1980s when the limitless utility of the shmoo became an ideal to be pursued. Indeed, the spinoff televised animated series *The New Shmoo* and *Fred and Barney Meet the Shmoo*, which were broadcast Saturday mornings in the U.S. on NBC during 1979-1980, featured the same accommodating creature who helped to solve crime mysteries by

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[225] L. H. Hartwell, "Three Additional Genes Required for Deoxyribonucleic Acid Synthesis in Saccharomyces Cerevisiae," *J Bacteriol* 115, no. 3 (1973): 969.

[226] Occasionally, the term appeared with their alternate spelling "schmoo." Vivian L. MacKay and T. R. Manney, "Mutations Affecting Sexual Conjugation and Related Processes in Saccharomyces Cerevisiae. I. Isolation and Phenotypic Characterization of Nonmating Mutants," *Genetics* 76, no. 2 (1974): 256. In 1982, MacKay would join the yeast biotech company ZymoGenetics in Seattle, described in the next chapter. See Hubert A. Lechevalier, "The Waksman Institute of Microbiology 1954 to 1984," *The Journal of the Rutgers University Libraries* 50, no. 1 (1988): 38.

[227] Ernest Loumaye, Jeremy Thorner, and Kevin J. Catt, "Yeast Mating Pheromone Activates Mammalian Gonadotrophs: Evolutionary Conservation of a Reproductive Hormone?," *Science* 218, no. 4579 (1982): 1324-1325. See also "Ancient Hormone in Yeast," *The New York Times*, January 4, 1983, C3.

transforming into any conceivable shape or object, as needed, to assist its human teammates.[228] In a later period, scientists demonstrated that an essential component of the yeast mating process, "spermidine," was needed to induce shmoo formation and this cell fusion mechanism showed evolutionary conservation with human fertilization.[229]

In addition to the mating-type research, Cold Spring Harbor continued to extend yeast as a simple and powerful molecular model in other areas as well. In 1983, cell-cycle studies on "yeast oncogenes" provided the basis for a new Oncogene Section at the Laboratory led by geneticist Michael Wigler. Wigler's group had seen potential to develop yeast as a model for cancer biology after finding a group of genes called *ras* in both human and yeast cells. The *ras* genes were implicated in human cancer and appeared to play a role in normal cell metabolism and control of the cell cycle.[230] They found *ras* genes to be so well conserved across species that human genes could be inserted into yeast and the cells would still function normally.[231] The Laboratory's 1984 annual report declared this recombinant procedure a highlight of the year, one which allowed "a genetic analysis far more subtle than would ever be possible with mammalian cells."[232] Together with Jeff Strathern and other Cold Spring Harbor colleagues, Wigler developed a model of human oncogenesis which was seen to have moved yeast from the identification of fundamental mechanisms toward "direct applications to human health and

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[228] Oscar Dufau et al., *The New Shmoo*, National Broadcasting Company (NBC), September 22, 1979, Hanna-Barbera Productions, 30 minutes; Ray Patterson and George Gordon, *Fred and Barney Meet the Shmoo*, National Broadcasting Company (NBC), December 8, 1980, Hanna-Barbera Productions, 90 minutes.
[229] Maria Anna Bauer et al., "Spermidine Promotes Mating and Fertilization Efficiency in Model Organisms," *Cell Cycle* 12, no. 2 (2013): 346.
[230] "Yeasts," in *Annual Report* (New York: Cold Spring Harbor Laboratory, 1983), 81. Several other groups were also studying the link between human *ras* genes and cancer at this time.
[231] Harold M. Schmeck, "Cancer Genes Described as Having Jekyll and Hyde Role," *The New York Times*, November 6, 1984, C3.
[232] *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1984), 4.

disease."[233] The report declared that, "yeast oncogenes in M. Wigler's laboratory, will keep Cold Spring Harbor Laboratory at the forefront of efforts to use these simple microorganisms to uncover the reasons behind the unchecked growth of human cancer cells."[234] Yeast geneticist Kim Nasmyth, who had done a postdoc with the yeast group in the early 1980s, later declared the *ras* experiments the fulfillment of "much of the expectation that yeast studies could provide a shortcut in understanding the biology of a human protein."[235] In the late 1980s, the expectation for yeast-cancer analogies was that the information might be put "to real use" for human health.[236] The clinical development of targeted *ras* cancer treatments has continued in recent years.[237]

In the mid-to-late 1980s, the Cold Spring Harbor yeast group began to disband. Strathern was the first to leave in 1984. He was offered a position at the Frederick Cancer Research Facility, where he continued to study yeast gene regulation and genetic recombination. He sought to replicate the laboratory environment at Cold Spring Harbor for the NCI in order to produce direct daily interaction between scientists.[238] Hicks left two years later to direct the PPG

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[233] Claim found in Rine, "Introduction," 4. For examples of this group of studies, see T Kataoka et al., "Genetic Analysis of Yeast Ras1 and Ras2 Genes," *Cell* 37, no. 2 (1984): 437-445; Takashi Toda et al., "In Yeast, Ras Proteins Are Controlling Elements of Adenylate Cyclase," *Cell* 40, no. 1 (1985): 27-36. See also the account of this work by American science writer Natalie Angier, who described how "Through more than a billion years of evolution, the DNA sequence of the [onco]gene had been conserved… Wigler could raise that insight up the phylogenetic stepladder to humans." In Natalie Angier, *Natural Obsessions: The Search for the Oncogene* (Boston: Houghton Mifflin, 1988), 270.
[234] *Annual Report*, 101-102.
[235] Nasmyth, "Cell Division," 131. See also Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 1, Yeast Collection.
[236] Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).
[237] See, for example, Jonathan M. Ostrem et al., "K-Ras(G12c) Inhibitors Allosterically Control Gtp Affinity and Effector Interactions," *Nature* 503, no. 7477 (2013): 548-551.
[238] *Annual Report*, 5; Strathern and Klar, "Oral History Interview #2016."

Industries' joint research group at Scripps Clinic in La Jolla, CA.[239] He became an entrepreneur and investor in the internet and health sciences before returning to Cold Spring Harbor in 2004 and becoming active in breast cancer research.[240] Klar stayed at Cold Spring Harbor until 1988, when he decided to make new colleagues and "try new things in a slightly different atmosphere."[241] He had taken up the study of developmental asymmetry in the fission yeast *Schizosaccharomyces pombe* to see how it compared to their baker's yeast model.[242] Then, he too, left to lead developmental genetics at the NCI.

The yeast mating type model has been related to cancer in higher eukaryotes, and in various "side projects" Klar continued to extend the logic of mating type differentiation into human development and behavior.[243] Some of these efforts have been contested.[244] In several studies, Klar proposed a genetic mechanism to account for functional asymmetry between the brain hemispheres. In 2003 and 2004, Klar linked this genetic mechanism to human right- and left-handedness, the direction of "scalp hair-whorl," and perhaps most problematically, to sexual

[239] PPG Industries is a Fortune 500 company originally founded as the Pittsburgh Plate Glass Company in 1883. The company changed its name to PPG Industries, Inc. in 1968. "Company History: Celebrating 130 Years of Innovation and Color Leadership," accessed March 6, 2016, corporate.ppg.com.
[240] *Annual Report*, 11; "Single Cell Analysis Summit (2012): James Hick's Biography," accessed June 6, 2016, selectbiosciences.com.
[241] Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 1, Yeast Collection; Strathern and Klar, "Oral History Interview #2016."
[242] Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 2, Yeast Collection.
[243] See T. Li et al., "Fertility and Polarized Cell Growth Depends on Eif5a for Translation of Polyproline-Rich Formins in Saccharomyces Cerevisiae," *Genetics* 197, no. 4 (2014): 1191; Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 1, Yeast Collection.
[244] See the argument that complex behavioral traits cannot be linked to single gene control in David E. Rosenbaum, "On Left-Handedness, Its Causes and Costs," *The New York Times*, May 16, 2000.

preference in males.[245] "It's the same question," he has claimed, "to see what can be used from the yeast to a more complicated system."[246]

Klar has also argued that the yeast group's original mating type research provided an origin to the term "epigenetics," a word which he says goes beyond how it is commonly understood to provide a gene-environment "feedback loop." In a proposal on "the molecular mechanisms of difference" dating to the early 1990s, Klar mentioned epigenetic chromosomal modification wherein "some chromosomes are potentiated to switch whereas others are not."[247] Strathern, too, has more recently characterized the group's finding of yeast DNA rearrangement as "epigenetic," or "on top of" traditional gene control, given the finding of yeast cis- and trans-acting regulatory elements.[248] In the eukaryotic paradigm, higher organism development is an epigenetic process involving gene switching and propagation of transcriptional states.[249] Yeast models helped to transform the prokaryotic molecular biology of the gene with this more dynamic molecular biology of the eukaryotic cell.[250]

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[245] The latter was posed as a binary of homo-/heterosexuality in a poorly-controlled study which had not asked subjects about their sexual orientation. See Amar J. S. Klar, "Excess of Counterclockwise Scalp Hair-Whorl Rotation in Homosexual Men," *Journal of Genetics* 83, no. 3 (2004): 251. See also Amar J. S. Klar, "Human Handedness and Scalp Hair-Whorl Direction Develop from a Common Genetic Mechanism," *Genetics* 165, no. 1 (2003): 269-276.

[246] Strathern and Klar, "Oral History Interview #2016."

[247] Amar Klar Papers, 1976-2001, (Undated), Series 1: Lab Notebooks, Box 1, Yeast Collection.

[248] Klar challenged Mark Ptashne's claim to priority in epigenetics. In Strathern, Klar, and Hicks, "Oral History Interview #2038." See the discussion of cis- and trans- acting elements for gene control in "Yeasts," 82; *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1985), 192; C. T. Chien et al., "Targeting of Sir1 Protein Establishes Transcriptional Silencing at Hm Loci and Telomeres in Yeast," *Cell* 75, no. 3 (1993): 531.

[249] O. M. Aparicio and D. E. Gottschling, "Overcoming Telomeric Silencing: A Trans-Activator Competes to Establish Gene Expression in a Cell Cycle-Dependent Way," *Genes Dev* 8, no. 10 (1994): 1134.

[250] Morange observed a similar transition in the late 1970s during the intersection of molecular genetics with embryology. See Morange, "The Transformation of Molecular Biology on Contact with Higher Organisms, 1960-1980: From a Molecular Description to a Molecular Explanation," 370, 391.

A Model for Molecularizing the Human

In the late 1970s and early 1980s, it was plain that yeast was no longer just a model *of* higher organism biology, it had become a model *for* studying that biology as molecular. The exemplar cell had become a model organism – applied specifically to the human. Rising NIH support for molecular cell biology in subsequent years speaks to the growing expectations for human health and disease applications from molecular investigations of the cell.[251] Federal funding for multiple model organism genome sequencing projects and shared sequence databases at the end of the 1980s and into the 1990s also suggests the intentions of connecting organism-specific data across species. Yeast genetic research had previously required the buildup of other types of infrastructure, such as culture collections and stock centers, for example, but these did not have the same integrative and comparative intent of extending biological research to the

[251] An early introduction to the field is provided by Bruce Alberts et al., *Molecular Biology of the Cell* (New York: Garland Publishing, Inc., 1983). According to the NIH Research Portfolio Online Reporting Tools (RePORT), six NIH institutes supported fifty-seven training grant projects in molecular cell biology with total funding of just under eleven million dollars during the years 1991-2016 (representing the total period for which RePORT data is available). This support peaked in the mid-1990s. See U.S. Department of Health & Human Services, "Research Portfolio Online Reporting Tools (Report)," accessed June 7, 2016, projectreporter.nih.gov.

molecularized human.[252] Today, *Saccharomyces cerevisiae* is one of thirteen species listed as common model organisms on the NIH website.[253]

The path which had taken yeast researchers from molecularizing the organism to molecularizing human biology in the form of a model had run through Cold Spring Harbor Laboratory. While University of Washington researchers such as Leland Hartwell developed the biomedical implications of their work from the mid-1970s, the politicization of Seattle's single-celled eukaryote was achieved earlier in the decade in an effort to access new environmental and human health funding streams for the continued buildup of molecular-based practice. This was achieved with broad and lasting effect by the Cold Spring Harbor Laboratory yeast course and yeast group in the pursuit of basic research support from the NIH, and in particular, basic cancer funding from the NCI. Just as Cold War politics had shaped the mutation research of prior decades in space and the radiation laboratory for a molecular biology of the gene, so too did a desire for concrete social, economic, and health benefits shape public support for an applied molecular biology of the eukaryotic cell.

The next chapter will examine how yeast became a molecular tool for recombinant DNA research by the start of the 1980s with commercial applications for human biology. It will argue that yeast translated molecular knowledge of the basic sciences for biotechnological and

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[252] Sabina Leonelli and Rachel Ankeny have recognized these features as characteristic of model organism research. They write, "Model organisms… are always taken to represent a larger group of organisms beyond themselves… [They] are often claimed to be representative of processes that it is hoped will be shared by higher level organisms, especially human beings… Second, they bring together large-scale comparative work across multiple disciplines under an interdisciplinary and resource-intensive infrastructure to compare across species." In Leonelli and Ankeny, "Re-Thinking Organisms: The Impact of Databases on Model Organism Biology," 30; Ankeny and Leonelli, "What's So Special About Model Organisms?," 319; Leonelli and Ankeny, "What Makes a Model Organism?," 210.

[253] National Institutes of Health, "Model Organisms for Biomedical Research," accessed April 14, 2016, http://www.nih.gov/science/models.

industrial production while pulling from well-established cultural ideas about the organism's safety and industrial utility. That yeast molecular models pre-date the development of yeast transformation suggests that yeast genetic engineers relied upon the comparability of molecules which many previous generations of researchers had helped to establish. As genetic engineering forced confrontations within universities between basic and applied research agendas and called into question the public sponsorship and private ownership of academic research, the practice leveraged eukaryotic molecules which had already been applied to the project of molecularizing the human. As Botstein has claimed, "Few, if any, of the scientists who discovered how to isolate genes, manipulate them in model organisms, and sequence DNA had any specific disease in mind, even though they knew that eventually knowledge and understanding would make applications to human health possible."[254] Genetically-engineered cells, including yeast, *E. coli*, and Chinese hamster ovary cells, were transformed into hybrid eukaryotes at the end of the 1970s not for specific diseases, but rather to specify the human.

In more recent years, scientists using recombinant methods to diagnose human gene function in the yeast context have begun to describe their work as "humanizing" yeast.[255] They

[254] David Botstein, "Why We Need More Basic Biology Research, Not Less," *Molecular Biology of the Cell* 23, no. 21 (2012): 4160.

[255] The "humanization" of yeast is today a common genetic practice. See, for example, Amadou Bah et al., "Humanized Telomeres and an Attempt to Express a Functional Human Telomerase in Yeast," *Nucleic acids research* 32, no. 6 (2004): 1917-1927; Stephen R Hamilton and Tillman U Gerngross, "Glycosylation Engineering in Yeast: The Advent of Fully Humanized Yeast," *Current opinion in biotechnology* 18, no. 5 (2007): 387-392; Aashiq H Kachroo et al., "Systematic Humanization of Yeast Genes Reveals Conserved Functions and Genetic Modularity," *Science* 348, no. 6237 (2015): 921-925. "[Y]east offers an attractive system to investigate even disease-related proteins that have no apparent homology to yeast genes. Several interesting cases are reported in the literature where this humanized yeast approach has been fruitful and provided valuable mechanistic information." In J.M. Hancock, *Phenomics* (Taylor & Francis, 2014), 197. Humanization or anthropomorphization is not limited to bioengineering technologies. Historian of Science Sophia Roosth has examined another recent practice of sonocytology in yeast, which uses a scanning probe microscope to record and amplify the

have forgotten where these molecules came from. Yeast's analogy to humans is always one that humans have had a hand in creating, as, for example, in Botstein's description of yeast in 1991 as "the Model T to the human's Cadillac."[256] At its core has always been how humans wish to be represented. Yeast had long been anthropomorphized in biological investigations, but the widespread adoption and circulation of yeast models worked in the reverse to "zymomorphize" human biology from the 1970s, and indeed to molecularize it.[257]

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vibrational movements of cell walls. Roosth described the tendency of scientists to describe the organism as "speaking" or "screaming" during this process. She has written, "Interpreting cellular noise as screams forces attention on the shared cellularity of humans and yeast, as well as the fact that yeast are model organism that stand in for humans in biomedical experiments." In Sophia Roosth, "Screaming Yeast: Sonocytology, Cytoplasmic Milieus, and Cellular Subjectivities," *Critical Inquiry* 35, no. 2 (2009): 339.

[256] D. Botstein, "Why Yeast?," *Hosp Pract (Off Ed)* 26, no. 10 (1991): 158.

[257] Zymomorphization from the Greek zymos (yeast). Lorraine Daston and Gregg Mitman have explored the idea of "animalizing humans" in Daston and Mitman, *Thinking with Animals: New Perspectives on Anthropomorphism*, 8.

Chapter 5

Model Molecules for Genetic Engineering: The Therapeutic Cell Factory

By the late 1970s, the industrial yeast *Saccharomyces cerevisiae* had emerged as a molecularly-standardized experimental system, a referent eukaryote cell, and a model organism with which to molecularize human biology in particular. Biologists saw in eukaryotic molecular modeling the potential for interventions in human health and disease.[1] While in many respects, the 1980s offered a continuation of this trajectory for yeast, the decade also witnessed a transformation of yeast's molecular processes into its molecular possibilities.[2] In this period, yeast and other laboratory organisms could be used to demonstrate and enhance the precision of

[1] Karen-Sue Taussig and colleagues have described how "potentiality" and "humanness" interact in contemporary biomedicine. They argue that, "the boundaries of humanness are understood and created through social action." In terms of model organisms, "natural potential" has manifested as a pre-social phenomenon ripe for discovery on the part of researchers, many of whom do not recognize the role of culture (human action or choice) in producing nature. In Karen-Sue Taussig, Klaus Hoeyer, and Stefan Helmreich, "The Anthropology of Potentiality in Biomedicine," *Current Anthropology* 54, no. S7 (2013): S5, S7.

[2] I refer to the canon of scholarship on "biocapital" with particular foundations in Karl Marx, *Capital, a Critical Analysis of Capitalist Production*, vol. 1 (1867); Max Weber, *The Protestant Ethic and the Spirit of Capitalism*, trans. Anthony Giddens Talcott Parsons (Boston: Unwin Hyman, 1905); Michel Foucault, *The History of Sexuality*, 1st American ed. (New York: Pantheon Books, 1978). "Biopower", "biosociality", "biovalue", "speculative" genomics, "bioeconomics", and "surplus health" are just some of the variations on "biocapital" scholarship, which considers various forms of capital appropriation of living nature. For an early example, see Yoxen, "Life as a Productive Force: Capitalising the Science and Technology of Molecular Biology." See also Rabinow, "Artificiality and Enlightenment: From Sociobiology to Biosociality."; Catherine Waldby, *The Visible Human Project: Informatic Bodies and Posthuman Medicine* (Routledge, 2000); Michael Fortun, "Mediated Speculations in the Genomics Futures Markets," *New Genetics and Society* 20, no. 2 (2001); Rose, *The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century*; S.H. Franklin and M.M. Lock, *Remaking Life and Death: Toward an Anthropology of the Biosciences* (School of American Research Press, 2003); Joseph Dumit and Kaushik Sunder Rajan, "Biocapital, Surplus Health, and Clinical Trials: Toward a Health Theory of Value" (paper presented at the Conference on Experimental Systems, States, and Speculations: Anthropology at the Intersection of Life, Science and Capital, University of California, Irvine, 2007).

scientists' molecular tools to such an extent that, by the end of the decade, genetic technologies ran up against the limits of a piecemeal approach to molecularization and gave way to large-scale genome sequencing projects.

This chapter examines how and why yeast was able to become a molecular technology for the new science of genetic engineering in the 1980s contemporaneously with its continued rise as a "nearly ideal model system" for molecular biology.[3] It will argue that genetic engineers relied upon the biomedical significance of yeast-human molecular homology established in an earlier period in order to make their technologies function as post hoc proof of that homology. The organization of this chapter differs from earlier chapters of this work in that offers a case study of hepatitis B vaccine development and commercialization by collaborators at the University of Washington in Seattle, University of California, San Francisco, Chiron Corporation, and Merck, Sharp and Dohme Research Laboratories. In doing so, it aims to situate a genetically-engineered yeast "promotor" against competing molecular technologies at this time in order to examine how yeast molecular technology became the "right tool" for the vaccine job in the early 1980s.[4]

The yeast cell, once bound by its mannan wall as an industrial and scientific resource, was reframed during this period as a key molecular means of production.[5] As this case will show, genetic engineers applied the eukaryotic molecular biology of the cell in order to scale their technology into a vast manufacturing network of cell factories. The technologies of genetic

[3] This phrase is taken from Botstein and Fink, "Yeast: An Experimental Organism for Modern Biology," 1442.
[4] The emergence of "the right tools for the job" at just the right moment has been justified as the co-construction of interests and materials in Clarke and Fujimura, *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences*.
[5] J. Kocourek and C. E. Ballou, "Method for Fingerprinting Yeast Cell Wall Mannans," *J Bacteriol* 100, no. 3 (1969): 1175-1181.

engineering did not open all life forms universally to the possibility of commercial exploitation, and yeast was among the very few which offered the advantage to build an industry quickly. Bioentrepreneurs rearranged fungal molecules in the hopes of synthesizing human enzymes with expected biomedical value. Their use of the safe and familiar industrial organism *Saccharomyces cerevisiae* made recombinant DNA (rDNA) technology palatable for public consumption on a mass market. The success of recombinant hepatitis B vaccine was thus less the result of the technological "revolution" in genetic engineering than it was a further application of yeast models as nature-culture hybrids capable of producing human molecules.[6]

Building upon the significant molecular transformations which preceded the engineering of a yeast-based hepatitis B vaccine during the period 1981-1986, this chapter explains how a network of yeast molecular biologists who had come to appreciate yeast's value as a model eukaryote could conceive of their expressive organism as a potential protein-manufacturing technology for vaccine development. Previous histories of genetic engineering and the biotech industry have focused on particular individuals, institutions, diseases, or technologies to tell the story of diagnostic and therapeutic breakthroughs, the transformation of scientific disciplines, cultures and practices, the remaking of academic-industry relations, the emergence of specific companies, and conflicting public perceptions of the new science.[7] A model organism lens

[6] Earlier chapters have explored the hybridity of the genetic wild-type strain S288C as both a participant in a Latourian network of 'nature-culture' and as the cohabiting and interdependent model organism with which to molecularize humans in the sense of Haraway's collapsed duality and contracted term 'naturecultures'. For an introduction to these concepts see Latour, *We Have Never Been Modern*; Haraway, *Simians, Cyborgs, and Women: The Reinvention of Nature*.

[7] Select examples which cover this spectrum include S.S. Hall, *Invisible Frontiers: The Race to Synthesize the Human Gene* (Atlantic Monthly Press, 1987); Alberto Cambrosio, Peter Keating, and Michael Mackenzie, "Scientific Practice in the Courtroom: The Construction of Sociotechnical Identities in a Biotechnology Patent Dispute," *Social Problems* (1990); R. Bud, *The Uses of Life: A History of Biotechnology* (Cambridge University Press, 1994); Sally Smith Hughes, "Making Dollars out of DNA: The First Major Patent in Biotechnology and the

contributes to this historiography to reveal the political work done by eukaryotic molecules both in receptive hosts like Chinese hamster ovary (CHO) cell line and as transplanted genes into prokaryotes like *E. coli*. The harnessing of eukaryotic molecules as evolutionarily complex and "human-like" shows the new biotechnologies as continuous with other applied aims of molecular biology after 1970. Genetic engineering was a further manifestation of the molecularized human which represented the potential of evolution through biomedicine, in terms economic, natural, cultural, and political.

New Methods, Same Eukaryotic Molecules

In the late 1960s, molecular biologists working in the prokaryotes believed that most of the interesting problems in their field had been solved, and that further investigations would simply be derivative. In 1968, Gunther Stent, a leader in the field at the University of California at Berkeley pronounced an end to the romantic and dogmatic phases of "the Molecular Biology that Was." In their wake, he saw emerging a new humdrum academic phase, in which the remaining problems of molecular biology were merely technical and would be worked out over time.[8] Stent's hasty prediction that molecular biology had been routinized faded into distant memory in the mid-1970s with the emergence of the eukaryotic molecular biology of the cell. New genetic tools developed at that time were designed to get at the problems of eukaryotic

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Commercialization of Molecular Biology, 1974-1980," *Isis* (2001); Vettel, *Biotech: The Countercultural Origins of an Industry*; D. Yi, "Cancer, Viruses, and Mass Migration: Paul Berg's Venture into Eukaryotic Biology and the Advent of Recombinant DNA Research and Technology, 1967-1980," *J Hist Biol* 41, no. 4 (2008); Doogab Yi, "Who Owns What? Private Ownership and the Public Interest in Recombinant DNA Technology in the 1970s," *Isis* 102, no. 3 (2011); Sally Smith Hughes, *Genentech: The Beginnings of Biotech* (University of Chicago Press, 2011); N. Rasmussen, *Gene Jockeys: Life Science and the Rise of Biotech Enterprise* (Johns Hopkins University Press, 2014).

[8] Stent, "That Was the Molecular Biology That Was." See also Stent's introduction to Anderson, "Electron Microscopy of the Phages."

transcription and translation. The cutting, cloning, amplification, and sequencing of genes between species was - like eukaryotic modeling - motivated by the political project of molecularizing humans. The technology relied upon physical substitution of molecules already expected to show homology. This was the context shaping both the fears and the aspirations of scientists in the first rDNA experiments. Paul Berg's group at Stanford, for example, had been interested in comparing the regulation of gene expression in prokaryotic and eukaryotic cells. In the early 1970s, the Berg laboratory sought to reproduce the DNA of SV40 monkey tumor virus within an *E. coli* host cell by cutting and connecting pieces of DNA originating from different organisms.[9] The proposal offered the first rDNA gene-splicing experiment between in a prokaryote, but immediately raised a molecular threat to humans. Other scientists cautioned the wisdom of introducing a cancer virus to a pathogenic bacterium normally found in the human intestine, particularly given the molecular analogies between mutagenesis and carcinogenesis.

Stanley Cohen's laboratory at Stanford was another early prokaryotic contributor to the new technologies. Cohen was developing a method of removing and reasserting plasmid DNA into bacteria to study how genes were expressed. He believed that foreign DNA might be taken up from bacteriophage and reproduced in bacterial clones.[10] He was interested in the recent characterization of the *E. coli* endonuclease enzyme EcoRI by Herbert Boyer in the University of California, San Francisco microbiology department. In November of 1972, the two agreed to collaborate, and their laboratories published a series of cloning experiments.[11] Boyer's interests

[9] D. A. Jackson, R. H. Symons, and P. Berg, "Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular Sv40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia Coli," *Proc Natl Acad Sci U S A* 69, no. 10 (1972): 2904-2909.
[10] Hall, *Invisible Frontiers: The Race to Synthesize the Human Gene*, 62.
[11] S. N. Cohen et al., "Construction of Biologically Functional Bacterial Plasmids in Vitro," *Proc Natl Acad Sci U S A* 70, no. 11 (1973): 3240-3244; A. C. Chang and S. N. Cohen, "Genome

had been in the restriction and modification of DNA and his laboratory found that EcoRI cleaved DNA specifically, essentially clipping DNA into fragments at target sites comprised of several nucleotides.[12] The work enabled new types of biological experiments through this chemical reorganization of DNA fragments.

Early on in his investigations, Boyer was invited to present the cloning experiments at a meeting of the University of California, San Francisco biochemistry department. There departmental chair William Rutter was supervising more than a dozen students in a laboratory focused on enzymology. Rutter had been offered the chair at the University of California, San Francisco in the late 1960s while on the University of Washington faculty in Seattle with a joint appointment in biochemistry and genetics. He had hesitated to leave Herschel Roman's "avant-garde" department for what he saw at the time as San Francisco's mediocre research program, but ultimately he was persuaded by the significant hiring capacity he would have to fill nearly twenty open positions on the faculty.[13] He wanted to build a department with a specific focus on eukaryotic biology, and he recruited researchers with a range of scientific backgrounds, from

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Construction between Bacterial Species in Vitro: Replication and Expression of Staphylococcus Plasmid Genes in Escherichia Coli," *Proc Natl Acad Sci U S A* 71, no. 4 (1974): 1030-1034; J. F. Morrow et al., "Replication and Transcription of Eukaryotic DNA in Escherichia Coli," *Proc Natl Acad Sci U S A* 71, no. 5 (1974): 1743-1747.

[12] Herbert W. Boyer, interview by Sally Smith Hughes, 1994, "Recombinant DNA Research at UCSF and Commercial Application at Genentech," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

[13] "Bill went to UCSF with a scheme to deliberately recruit a whole bunch of people who were interested in the same things he was interested in." In Edward E. Penhoet, interview by Sally Smith Hughes, 1998, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders," Berekely, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley. He was offered the chair in 1967 and initially expressed interest. He turned the role down several times before ultimately accepting in 1968. The transition took some time, and he only formally resigned from the University of Washington in June of 1969. See William J. Rutter, Correspondence WJR on Chairmanship 1964-1969, (July, 1967), Box 1 of 13, Subgroup 11, Series 11, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

biophysics and genetics to biochemistry and molecular biology.[14] He hoped their interdisciplinary efforts would yield insights into eukaryotic development, gene function, and gene expression with a focus on the cell, and he brought with him from Seattle the idea that these molecular insights would eventually translate into clinical benefit in humans.[15]

After Boyer's talk, Rutter recalled, the group's "orientation to higher organisms and humans began to be more serious and practical." During the period 1969 to 1974, the Rutter laboratory and other groups worked to refine the rDNA technologies.[16] They were attempting to rework the dogma which had largely been established and limited to bacteria, and yeast was one place where this could happen.[17] The potential biomedical implications of the new technologies sparked their interest and they continued to work across disciplinary lines driven equally by competition and collaboration.[18]

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[14] In an unusual move for the period, the department would also house several biomathematicians.

[15] Eric Vettel explains that Rutter's clinical vision for the department was a matter of some debate. During the hiring process, the search committee had to relax their preference for a basic science focus after a number of other candidates turned down the position. In Vettel, *Biotech: The Countercultural Origins of an Industry*, 164.

[16] Rutter's laboratory was interested in the question of cellular differentiation of the pancreas, and began to develop systems for the study of insulin production. In 1973, Rutter submitted a proposal to the NIH for the isolation of the insulin gene and study of its regulation. This was rejected perhaps, Rutter later speculated, because the expertise for these new tools lay outside his department. Boyer, for example, who had not been included in the application, was in microbiology and only joined biochemistry in 1975. In Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

[17] Pierre Chambon explained this transition into the eukaryotes as the reworking of Jacques Monod's aphorism: what was true of *E. coli* was still roughly true for an elephant, but what was true for the elephant was not necessarily true for *E. coli.* In Chambon, "Albert Lasker Basic Medical Research Award," minutes 11:00, 11:20.

[18] In Penhoet, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders." See also H.R. Bourne, *Paths to Innovation: Discovering Recombinant DNA, Oncogenes, and Prions, in One Medical School, over One Decade* (University of California Medical Humanities Consortium, 2011).

The power and novelty of the rDNA technologies warranted caution, warned some concerned scientists, and some believed the risks were so great that the experiments should be stopped.[19] Safety concerns that had been raised in 1971 by Berg's SV40 experiment were at first left to be handled by scientists' individual discretion, but by June 1973, the U.S. National Academy of Sciences and Institute of Medicine were asked to weigh in.[20] In July 1974, *Science* published a piece by Berg and other prominent molecular biologists which asked for a voluntary, worldwide moratorium on certain types of experiments. They recommended an international conference and the formation of a National Institutes of Health (NIH) advisory committee to study rDNA knowledge and technology, including survival of recombinant organisms in nature, the transferability of their genetic material, and the possible hazards to public health and the environment.

In the 1970s, new environmental funding authorities were dedicated to research in the environmental health sciences. During the years 1971 to 1975, NIH grant funding for genetics research grew faster than the overall budget (85% increase vs 64% increase), while NIH funding for environmental health sciences slowed and the number of grants awarded fell as this support moved away from biomedicine.[21] The possibility of an existential molecular threat was shaped by the day's environmentalism but also the arrival of applied eukaryotic molecular biology since the molecular tampering with "nature" was understood to extend to humans through homologies

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[19] *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*, ed. United States Congress and Office of Technology Assessment (DIANE Publishing, 1981).

[20] In response to a talk by Boyer, chairs of the Gordon Research Conference on Nucleic Acids asked these groups for guidance. In Donald S. Fredrickson, "Asilomar and Recombinant DNA: The End of the Beginning," in *Biomedical Politics*, ed. Kathi E. Hanna (National Academies Press, 1991). See their letter of concern, which appeared in *Science* that Fall: Maxine Singer and Dieter Soll, "Guidelines for DNA Hybrid Molecules," *Science* 181, no. 4105 (1973).

[21] Office of Program Planning & Evaluation and Division of Research Grants, "Basic Data Relating to the National Institutes of Health 1975-1976," (National Institutes of Health, 1975), 36, 37.

of the cellular environment. Scientists feared or favored the molecular breach of human bodies which was also conceptually underway in eukaryotic molecular biology. In February 1975, the International Conference at Asilomar resulted in a continuation of the moratorium on some experiments, and although most work involving rDNA was allowed to continue at that time, the new science was quickly becoming embroiled in public controversy.[22] David Botstein, who was on sabbatical at Cold Spring Harbor Laboratory at that time, said that he was shocked by the moratorium and realized after Asilomar "that our decision to work with yeast was going to depend" on the ability to make rDNA technology work.[23]

Within the span of a few short years, several different methodologies emerged to achieve gene cloning. Enriched RNA fragments could be reverse transcribed to obtain pieces of DNA by measuring the rate of hybridization. With DNA fragments, gene expression could be modified by transfecting plasmids, viruses or phage. *E. coli* was the host organism of choice in these early experiments.[24] Other tools in the mid-1970s included the first chemical and synthetic methods for DNA sequencing. Gene cloning was useful only if one could characterize where in the genome a given genetic sequence had come from. Sequencing methods developed in the laboratories of Walter Gilbert at Harvard University and Frederick Sanger at the Medical Research Council in Cambridge, England enabled the analysis of the structure of nucleic acids in small pieces of DNA.[25] These molecular tools were expected to be transformative, but genetic

[22] For a detailed introduction to the public controversy and summary of the efforts to regulate the new gene splicing methods, see S. Krimsky, *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* (MIT Press, 1982).
[23] The technology offered a proof of concept. See Botstein, "A Phage Geneticist Turns to Yeast," 370.
[24] Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."
[25] For these sequencing contributions, Gilbert and Sanger shared the 1980 Nobel Prize in Chemistry with Paul Berg "for his fundamental studies of the biochemistry of nucleic acids, with

engineers were unprepared for increasing pace, volume, and control over their research as it moved onto a public and commercial stage.

In April 1975, U.S. Senator Edward Kennedy held a half-day hearing of the Senate Labor and Public Welfare Committee on science policy issues of rDNA research. The following month, the New York Academy of Sciences and Institute of Society, Ethics and Life Sciences held a two-day conference on the topic, and in December, the NIH review committee recommended practice guidelines that had been stricter than those set at Asilomar. The official guidelines that issued the following year on commercial applications and products of rDNA techniques had influence only over those institutions and projects that NIH sponsored.[26] In 1975, this funding authority extended to many of the nation's academic institutions. Nearly half of all federal R&D support to academic institutions came from NIH, versus one-fifth from the National Science Foundation (NSF), and in the nation's overall spending on health R&D, NIH funded a greater portion than industry (38% to 29% of total support).[27] This would begin to change over the latter half of the decade as the biotech industry bypassed the guidelines of sponsoring agencies and

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particular regard to recombinant-DNA." See "The Nobel Prize in Chemistry (1980)," accessed May 1, 2014, www.nobelprize.org.

[26] In June 1976, the NIH director met with 30 representatives of industry to solicit voluntary compliance with the proposed guidelines but because of the agency's limited authority, private sector firms could and did simply decline to commit to the recombinant rules for proprietary reasons. *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*, 317. See also NIH, "Guidelines for Research Involving Recombinant DNA Molecules," (Federal Register, 1976).

[27] In 1974, the NCI had the largest budget of any NIH institute, and awarded 15% more research grants and nearly 3 times as many R&D contracts (930 contracts vs. the NHLI's 320 contracts) than the next largest institute. See Office of Program Planning & Evaluation and Grants, "Basic Data Relating to the National Institutes of Health 1975-1976," 6, 8, 19.

lobbied for specific protections and incentives. By the mid-1980s, private funding for biomedical R&D surpassed NIH's.[28]

Commercial applications of the new science were of increasing appeal to some members of the University of California, San Francisco biochemistry department. On the national stage the University of California, San Francisco was the top recipient of NIH research grant funding in 1975, but its scientists were also turning to the private sector for support.[29] Rutter and his departmental colleague Howard Goodman had each met with pharmaceutical company Eli Lilly to discuss the possibility of cloning the human insulin gene. Boyer and venture capitalist Bob Swanson co-founded the biotechnology company Genentech in April of 1976. The once-collegial environment which had characterized their work began to grow more internally competitive during this period. A new sense of urgency about the technologies meant that collaborators "began to negotiate outcomes and rewards prior to the experimental results," Rutter recalled.[30] Some blurred the line between university and industry research efforts and property.[31]

In October 1976, a federal committee formed to consider the possibility of rDNA legislation that could extend the applicability of NIH guidelines nationally, regardless of the source of research sponsorship. That same month, the University of California, San Francisco

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[28] R.M. Cook-Deegan, *The Gene Wars: Science, Politics, and the Human Genome* (W.W. Norton & Company, 1996), 307.

[29] The University of Washington in Seattle was the fifth largest recipient of NIH research grant funding. In Office of Program Planning & Evaluation and Grants, "Basic Data Relating to the National Institutes of Health 1975-1976," 31.

[30] Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

[31] The Genentech startup, for example, was still utilizing University of California laboratory space and resources. Tensions over this early arrangement came to a head in 1978, when Axel Ullrich and Pete Seeburg were accused of having taken cDNA clones for human growth hormone to Genentech from John Baxter's freezer at the University. See Penhoet, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders."; Hughes, *Genentech: The Beginnings of Biotech*; Matthew Rimmer, "Genentech and the Stolen Gene: Patent Law and Pioneer Inventions," *Bio-Science Law Review* (2003).

established a biosafety committee to enforce safeguards for genetic engineering.[32] The suggestion for a university biohazards committee had been made previously to the medical school dean by geneticist Brian McCarthy, who had been recruited from Seattle by Rutter.[33] With the threat of national legislation looming, laboratories were preparing to monitor engineering practices closely.

The flexibility which Rutter enjoyed in operational spending since the early days of the department allowed him to move forward rapidly in response to NIH cloning guidelines.[34] When the department learned that it would be necessary to have a P3 facility for the work, for example, they were able to produce the roughly $50,000 it cost to start construction immediately.[35] The department renovated laboratory space to operate under the same secured conditions as were implemented in work with infectious microorganisms. The result was one of the very first university facilities for cloning in the U.S., which also marked a shift in the scale of their science. What had begun as a quest for eukaryotic transcription in a test-tube now, for University of California, San Francisco, occupied the space of two laboratories on the tenth floor of the Health Sciences West building. Use of the new facility and cloning equipment required prior clearance, and was overseen by a small group of faculty including Boyer, Goodman, and

[32] October 5, 1976), Carton 2, Folder 76, Records, 1976-1986 (#AR 86-7), University of California, San Francisco Archives & Special Collections, San Francisco, CA.
[33] Rutter had been on the genetics and microbiology faculty at the University of Washington, Seattle. In Penhoet, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders." See also San Francisco School of Medicine Dean University of California, Brian J. Mccarthy Letter to Julius Krevans, (March 2, 1975), Carton 1, Folder 18, Records, 1936-1987 (#AR 90-56), University of California, San Francisco Archives & Special Collections, San Francisco, CA.
[34] Rutter negotiated an enterprise budget for his department not unlike the university's clinical units which controlled the revenues raised from their group practices. In Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."
[35] P3 was the level of physical containment thought to be proportionate to the risks of the recombinant experiments.

McCarthy. Experiments had to be logged in a sign-out book and all materials needed to be destroyed and disposed of at the experiments' end.[36]

NIH had established these procedural safeguards in an attempt to compromise between what were seen as "the extremes" of no regulation and of no research without proof of safety.[37] The speed at which the genetic engineering practice was changing made this proof difficult to produce, for it seemed to some that the very act of discovery had become subject to a new time scale. According to the Environmental Impact Statement on the NIH recombinant guidelines, "The usual "time gap" (a potential safety valve) between a fundamental discovery in basic science and its application as a technology disappeared in record time with rDNA studies."[38] Molecular biology in the 1970s was no longer "basic science" since it had come to be applied to the homologies of the eukaryotic cell. This reach allowed molecules transplanted or extracted by rDNA technology in the *E. coli* host to threaten another sort of time – that of molecular evolution.[39]

Recombinant Tools in Seattle and Cold Spring Harbor

[36] The logbook became the subject of some controversy in the fall and winter of 1977, when a retroactive log entry was taken by some to be evidence of a cloning cover-up. The ensuing investigation extended to the level of Congressional hearings by the Senate Subcommittee on Science, Technology, and Space, before whom Rutter and Boyer testified on November 8, 1977. For the accusation that the Rutter group had used an uncertified cloning vector, see Nicholas Wade, "Recombinant DNA: NIH Rules Broken in Insulin Gene Project," *Science* 197, no. 4311 (1977).

[37] *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*, 216.

[38] *Final Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules* (National Institutes of Health, 1977).

[39] Sophia Roosth has offered the concept of "biological time travel" in her studies of the de-extinction projects of synthetic biology. See "Biological Time Travel," *Harvard Magazine*, March 5, 2014.

Genetic engineers turned to yeast in the mid-1970s to extract samples of eukaryotic DNA. In 1976, Paul Berg reported that a group at Stanford had successfully inserted yeast DNA into phage vectors and achieved its functional expression in *E. coli* bacteria.[40] *E. coli* had been the first host organism to express rDNA in 1973, and the first to replicate a functional synthetic gene.[41] Now, it appeared to observers, *E. coli* could also handle eukaryotic rDNA and might be made to mass produce "certain valuable eukaryotic proteins… when grown in fermenters."[42] The Stanford group had engineered bacteria to express eukaryotic rDNA, but they had not yet conquered the eukaryotic cell. It would be another two years before Cornell scientists Albert Hinnen, James Hicks, and Gerald Fink published the methods for yeast transformation. The conceptual "transformation" of yeast had already gotten underway by 1970, when Fink assumed instruction of the yeast course at Cold Spring Harbor. The modeling of molecules preceded the physical substitution of yeast rDNA by early genetic engineers. Hicks too was assisting the Cold Spring Harbor course to impart this new conception, and he would soon join the Cold Spring Harbor yeast group to develop mating-type research which conceptually substituted yeast

[40] K. Struhl, J. R. Cameron, and R. W. Davis, "Functional Genetic Expression of Eukaryotic DNA in Escherichia Coli," *Proc Natl Acad Sci U S A* 73, no. 5 (1976): 1471-1475.
[41] See Herbert L Heyneker et al., "Synthetic Lacoperator DNA Is Functional in Vivo," *Nature* 263 (1976): 748-752; K. J. Marians et al., "Cloned Synthetic Lac Operator DNA Is Biologically Active," *Nature* 263, no. 5580 (1976): 744-748.
[42] In John Atkins, "Expression of a Eukaryotic Gene in Escherichia Coli," *Nature* 262, no. 5566 (1976): 256-257. Genentech scientists used this approach to chemically synthesize the first recombinant mammalian protein in bacteria. Together with colleagues at the City of Hope National Medical Center, they achieved expression of the somatostatin gene late in 1977. See Keiichi Itakura et al., "Expression in Escherichia Coli of a Chemically Synthesized Gene for the Hormone Somatostatin," *Science* 198, no. 4321 (1977): 1056-1063. Somatostatin served then as their model for making human insulin. In Hall, *Invisible Frontiers: The Race to Synthesize the Human Gene*.

molecules for those of higher organisms' in models of eukaryotic development and cellular differentiation.[43]

At the University of Washington in Seattle, Benjamin Hall's laboratory was using recombinant techniques to isolate various yeast genes for further study.[44] The Hall laboratory was focused on yeast super-suppressors which had provided evidence of genetic similarities across species.[45] They were also competing with the University of Rochester's Fred Sherman and colleagues for the yeast CYC1 gene, which had been implicated in transcription.[46] Sherman's laboratory had previously contributed to identification of partial CYC1 sequences through the use of frameshift mutations to infer gene sequence from protein sequence.[47] Hall and colleagues

[43] See the previous chapter for more on the research and instruction at Cold Spring Harbor Laboratory.

[44] In one case, eight transfer RNA (tRNA) genes were identified in one experiment. See Maynard V. Olson et al., "Molecular Characterisation of the Tyrosine tRNA Genes of Yeast," *Nature* 267 (1977): 639-641.

[45] "It is generally accepted that the genetic code is, for the most part, universal and it appears that yeast is no exception", Leland Hartwell had declared over yeast super-suppressor genes in 1970. In L. H. Hartwell, "Biochemical Genetics of Yeast," *Annu Rev Genet* 4 (1970): 382. These mutations had been discovered by Berkeley's Robert Mortimer and Seattle's Donald Hawthorne in 1963, and were believed to reactivate the nonsense allele of protein-coding genes to suppress other mutant phenotypes. See chapter 3. Hall's laboratory went after the super-suppressor genes using the technique of DNA/RNA hybridization, which Hall had developed together with microbiologist Sol Spiegelman in the Illinois chemistry department. See Benjamin D. Hall and S. Spiegelman, "Sequence Complementarity of T2-DNA and T2-Specific RNA," *Proceedings of the National Academy of Sciences of the United States of America* 47, no. 2 (1961): 137. Horace Freeland Judson described DNA/RNA hybridization as very significant when it was first developed since it seemed to confirm the messenger hypothesis that the base composition of the code had to be transferred as a specific message. In Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, 455. The tool became increasingly problematic over the course of the 1960s. See Michel Morange, "What History Tells Us Xxxiii. Molecular Hybridization: A Problematic Tool for the Study of Differentiation and Development (1960–1980)," *Journal of Biosciences* (2014): 1-4.

[46] Sherman was introduced in the previous chapter as the co-instructor of the summer yeast course at Cold Spring Harbor.

[47] Stewart and Sherman, "Yeast Frameshift Mutations Identified by Sequence Changes in Iso-1-Cytochrome C," 102-127; Jack W. Szostak et al., "Specific Binding of a Synthetic Oligodeoxyribonucleotide to Yeast Cytochrome C mRNA," *Nature* 265 (1977): 61-63.

used this method to beat Sherman's team to the complete CYC1 gene.[48] Joining the Hall laboratory in these efforts was San Francisco's Howard Goodman, who had left Rutter's department for a sabbatical during the 1977-78 academic year. At that time, Goodman and Rutter had just launched a joint program to clone the insulin gene. The decision to work from Seattle put Goodman in direct competition with his San Francisco colleagues for a time, as he and Hall performed the same kinds of cloning experiments which were underway in Rutter's laboratory.[49]

When in 1977, Hinnen, Hicks, and Fink devised a plan to develop a yeast transformation system, Fink was told that such experiments were not allowable under NIH guidelines and would likely not even be considered by the NIH for another two years. Using his grant sponsorship from NSF as a loophole, Fink sought alternative authorization for the proposed yeast cloning and received approval in October 1977. The NIH, which funded yeast molecular research on the basis of its relevance and practical application to human health and disease, could not accept the limited reach of yeast molecules in 1977, while the NSF, focused on basic research, did not have this predicament. Within several weeks, the Cornell researchers saw that yeast could maintain and transmit bacterial DNA.[50]

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[48] Hall, "Oral History with Ben Hall, Part 2." See also Montgomery et al., "Identification and Isolation of the Yeast Cytochrome C Gene."

[49] Rutter later recalled, "I could never understand how Howard could leave when things were so exciting and uncertain." In Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco." See also Hall, *Invisible Frontiers: The Race to Synthesize the Human Gene*. In Seattle, Goodman, together with Maynard Olson and Hall, discovered intervening sequences (introns) in transfer RNA (tRNA) yeast genes. See H. M. Goodman, M. V. Olson, and B. D. Hall, "Nucleotide Sequence of a Mutant Eukaryotic Gene: The Yeast Tyrosine-Inserting Ochre Suppressor Sup4-O," *Proc Natl Acad Sci U S A* 74, no. 12 (1977). Rutter and colleagues separately published on yeast tRNA splicing. See P Valenzuela et al., "Structure of Yeast Phenylalanine-tRNA Genes: An Intervening DNA Segment within the Region Coding for the tRNA," *Proceedings of the National Academy of Sciences* 75, no. 1 (1978).

[50] In praise of the NSF administrator who had approved the cloning experiments in a time of great uncertainty, Fink claimed that "By sanctioning our experiments, Lewis had accelerated the

Faced with inconsistent policy between federal agencies, the NIH voted in March 1978 to loosen restrictions on yeast research just as Hinnen, Hicks, and Fink's results were going to press in *Proceedings of the National Academy of Sciences (PNAS).* Their yeast transformation experiments mobilized DNA fragments between species to achieve what had been the early vision of gene splicing. To the Cornell scientists, recombinant yeast indicated that, "Genetic exchange by interspecific transformation could lead to the acquisition of blocks of new genes that could contribute to the genetic diversity of the species."[51] Other engineers inserting yeast genes into the bacterial genome noted similarly that such studies might lead to understanding the relevant mechanisms of "prokaryote evolution."[52] In both types of experiments, recombinant yeast and recombinant *E. coli* showed that prokaryotes could be evolutionarily "scaled up" when integrated with the molecules of a higher, safer and more culturally familiar organism. Hinnen, Hicks, and Fink argued that baker's yeast had several advantages over bacteria as a genetic host. "It is not a pathogen under any known circumstances and, because it is a eukaryote, it will probably allow more efficient expression of such eukaryotic genes," they wrote. In addition to the study of DNA inheritance and expression, their work had explicit practical implications. Maximal expression obtained from a eukaryote "would be especially desirable for commercial applications," the researchers recognized. Given the strong biomedical orientation of Hicks and

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genetic engineering of yeast by 2 years", contributing to the development of Hepatitis B vaccine, and saving millions of lives. In Gerald Fink, "Editorial: Bureaucrats Save Lives," *Science* 271 (1996): 1213.

[51] Hinnen, Hicks, and Fink, "Transformation of Yeast," 1933.

[52] See Alfred Walz, Barry Ratzkin, and John Carbon, "Control of Expression of a Cloned Yeast (Saccharomyces Cerevisiae) Gene (Trp5) by a Bacterial Insertion Element (Is2)," *Proceedings of the National Academy of Sciences* 75, no. 12 (1978): 6176.

Fink's yeast work at Cold Spring Harbor, the authors referred specifically to "pharmacologically important" genes like insulin.[53]

The development of a yeast transformation system opened the world of genetic engineering to application in the eukaryotes, both commercially and as a science. In Seattle, Hall claimed that his group was not initially interested in commercial uses of the yeast transformation system. Instead, the attraction was conceptual. They were pursuing what Hinnen, Hicks, and Fink had described as "the link" in yeast between the *in vitro* analysis of DNA and its *in vivo* function. In other words: from the molecularization of the cell to the molecularization of the organism. Yeast possessed a tough cell wall which rendered it difficult to introduce and extract intact cellular constituents. The new method out of Cornell allowed for sequences to be extracted from yeast, cloned into bacteria, and introduced back into the eukaryote from which they originated to offer proof of transformation.[54] These single gene knock-outs of yeast were a way of deriving gene function by mutation and offered engineers a targeted method of altering eukaryotic control sequences.[55]

A second report of yeast transformation followed closely on the heels of the first and was reported in 1978 by molecular biologist Jean Beggs at the University of Edinburgh. Beggs saw the possibility of "genetic manipulation of commercially important yeasts" with the new

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[53] Hinnen, Hicks, and Fink, "Transformation of Yeast," 1932. The race for the insulin gene was well underway by spring of 1978. The Rutter-Goodman team had published on successful insertion of the rat insulin gene into *E. coli* in May 1977, and Gilbert's group at Harvard was refining this expression system so that bacteria might secrete the protein for easier extraction. Genentech scientists were pursuing chemical synthesis of the gene, and contracts with pharmaceutical manufacturer Eli Lilly fanned the flames of their competition.

[54] Their experiments had entailed removal of the yeast cell wall using an enzyme from snails' gut, the incorporations of bacterial plasmid DNA by osmotic shocking of the yeast, and confirmation of transformation in yeast culture.

[55] This has been described as the "reverse" of classical genetics in that intentional manipulation of the genome was followed "upward" to observe phenotype. In Botstein and Fink, "Yeast: An Experimental Organism for Modern Biology," 1441.

technology due to the potential genetic diversification of the species.[56] Rather than recombinant proteins, it was yeast variety which appeared commercially valuable. Edinburgh zoology student Kim Nasmyth saw yeast transformation as potentially useful for the study of yeast gene function, but thought it remained to be seen whether the genes of higher eukaryotes could also function in the yeast environment.[57] Nasmyth was on his way to Seattle to apply the transformation system to a number of yeast genes as a postdoctoral researcher in the Hall laboratory. There he would find colleagues already counting on the physical substitution of yeast DNA to serve as a proof of concept of the exchange of yeast and human molecules.

Yeast as a Wholesome and Scalable Resource

Nasmyth had warned that rDNA might be an even "greater biohazard" now since it had extended into yeast, while Hinnen, Hicks and Fink had dismissed such safety concerns believing yeast's long history of use had shown it to be harmless. On the national stage in 1978, there seemed to be a quelling of some of the initial fears over the new technology as studies began to show that perhaps genetic recombination was not as novel or unique as had been thought. Recombination could and did regularly occur between lower and higher life forms without scientists' intervention. A federal review committee had decided to recommend legislative extension of the NIH guidelines but by July 1978, it was looking like none of the proposed bills would make it through Congress. As an alternative, the NIH and Department of Health, Education and Welfare began developing voluntary standards which would accommodate public

[56] Beggs, "Transformation of Yeast by a Replicating Hybrid Plasmid," 104.
[57] Nasmyth, "Eukaryotic Gene Cloning and Expression in Yeast," 742.

involvement.[58] The new guidelines were issued in December of that year and allowed most recombinant experiments to be done in lower containment levels. At the University of Washington, for example, yeast recombinant experiments could be done under less restrictive containment than the microbiology department's P3 laboratory.[59] The NIH had also certified several mutant yeast strains as highly-contained host vector (HV2) systems. In addition to physical containment of the laboratory, the use of these "crippled" organisms, which could not survive outside of experimental conditions, was thought to ensure biological containment. Certain "built-in environmental limitations" could be engineered into the organism just like any other property.[60] The NIH-certified yeast mutants, known as the sterile host yeasts or "SHY" strains, were presumed self-contained because they were unable to mate and pass cloned DNA fragments into the robust "wild" strains.[61] Students of the Cold Spring Harbor yeast course used one of these approved HV2 yeast host strains, SHY2, to perform yeast transformation experiments.[62] However, scientists at MIT and Stanford argued that these HV2 precautions were unnecessary because, "No members of the genus *Saccharomyces* colonizes man or animals and

[58] The Department of Health, Education and Welfare was renamed Health and Human Services (HHS) in 1979.

[59] Gustav Ammerer, Email to the Author, June 26, 2014. See also S. Krimsky and D. Ozonoff, "Recombinant DNA Research: The Scope and Limits of Regulation," *American Journal of Public Health* 69, no. 12 (1979): 1257.

[60] In 1977, Rutter responded to the biosafety concerns of several high school students, writing that, "Scientists have gone to considerable length to construct… feebled microorganisms which cannot live outside the laboratory. There has not been a single recorded incident of a hazard using recombinant DNA since the experiments began" In William J. Rutter, Correspondence: High School Students Information Requests, (November 28, 1977), Box 1 of 13, Subgroup I, Series I, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[61] See David Botstein et al., "Sterile Host Yeasts (SHY): A Eukaryotic System of Biological Containment for Recombinant DNA Experiments," *Gene* 8, no. 1 (1979): 21.

[62] Fred Sherman, Gerald Fink, and Jim Hicks, Laboratory Manual for a Course: Methods in Yeast Genetics, (1979), Cold Spring Harbor Laboratory Meetings and Courses Department Collection, 1890-2010, Cold Spring Harbor Laboratory Archives, New York, 90.

none causes any disease."[63] Yeast was presumed much safer than *E. coli* in this respect. Later, the Nobel prize-winning yeast molecular biologist Randy Schekman dismissed the rDNA scare saying that he thought scientists had been overly cautious.[64] As evidence of the technology's safety, he noted, "the research was in baker's yeast! Give me a break."[65] While NIH-funded facilities experienced the loosening of physical containment restrictions and the newly approved SHY strains, private research was brought under more restrictive compliance as manufacturers were subject to the Food and Drug Administration (FDA) approval process. Commercialization was built-in as a necessary part of the federal research control strategy.[66]

The yeast model organism had already found other uses specifically as a safer alternative to pathogenic bacteria, in particular on the large scale of industrial production. In 1974, for example, scientists of the U.S. Department of Food Science and Nutrition turned to yeast to predict the deactivation of cultures over time as a function of high temperature exposure. Several serious outbreaks of foodborne disease at the time had resulted from spray-dried foods. While yeast was not a suspected contaminant in the outbreaks, it was a single-celled organism that

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[63] In Botstein et al., "Sterile Host Yeasts (SHY): A Eukaryotic System of Biological Containment for Recombinant DNA Experiments," 18. This claim did not address several studies which had reported on human diseases caused by the organism from 1970. See Paul D Stein, Alan T Folkens, and Keith A Hruska, "Saccharomyces Fungemia," *CHEST Journal* 58, no. 2 (1970): 173-175; E. Rubenstein et al., "Fungal Endocarditis: Analysis of 24 Cases and Review of the Literature," *Medicine* 54 (1975): 331-344; Douglas P Jensen and David L Smith, "Fever of Unknown Origin Secondary to Brewer's Yeast Ingestion," *Archives of internal medicine* 136, no. 3 (1976): 332-333; S. Albaret et al., "Le Traitment Des Septicemies a' Levures.," *Anesthesie, Analgesic et Reanimation* 36 (1979): 13-17.

[64] Schekman was awarded the prize for genetic analysis of the yeast secretion pathway, which he identified as related to the process in mammalian cells. He served as a consultant to the biotech industry on the expression and secretion of human proteins, including on the hepatitis B vaccine. See William J. Rutter, interview by Sally Smith Hughes, 2015, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," Berkeley, CA, Oral History Center, The Bancroft Library, University of California, Berkeley, 35.

[65] Schekman, "Randy Wayne Schekman: Cell Biologist and UC Berkeley Nobel Laureate," 67.

[66] *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*.

could be grown up quickly and at low cost in order to perform the temperature analysis. Moreover, for the benefit of scientists involved, yeast was presumed to be safe in very large quantities. “Since our laboratories were not isolated so that pathogenic organisms could be purposely dried without causing problems,” the scientists explained, “a vegetative yeast was chosen as the model cell organism. This would thus serve the purpose of a scale-up of the model predicted.”[67]

It had long been established that yeast could reproduce quickly and grow to large quantities. Seattle’s Benjamin Hall recalled that because of the yeast-making industry, “you weren’t starting out at zero in terms of fermentation technology.”[68] It was important to know how yeast cells behaved in culture in order to deal with them on an engineering scale. Control over the fermentation environment was necessary for precise repetition of the process using the same amounts of raw materials, broth and microorganism to achieve consistent results.[69] It also ensured that foreign microorganisms did not invade and contaminate the process or degrade the final product. Microbial competition for the nutrient medium could mean a loss of yeast’s productivity, and the presence of contaminants would limit its reuse and make final extraction of the product more difficult. If a contaminant were to fully outgrow the desired yeast it would ultimately mean much lost time and expense.

In brewing, yeast served a technological function that could be produced under a specific set of conditions. While few basic needs were required for yeast’s growth and maintenance, and the organism was considered generally non-pathogenic and safe, large-scale fermentation

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[67] Spray drying was a method of atomizing liquid materials or mixtures into drops which could be rapidly dried with a hot gas and preserved in powdered form. Hector Elizondo and T. P. Labuza, "Death Kinetics of Yeast in Spray Drying," *Biotechnology and Bioengineering* 16, no. 9 (1974): 1246 and 1258.
[68] Hall, "Oral History with Ben Hall, Part 2."
[69] *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*, 52.

processes required, for instance, pure cultures, sterilized vessels, nutrient mediums and process materials, and the maintenance of these aseptic conditions throughout fermentation. The final product could then be purified from the cells' secretions or extracted directly by perforating and killing the cells. The amount of yeast usually quadrupled during the fermentation process and could often be reused. Excess could be turned into extracts like the savory food spread Marmite, or used as flavorings or animal feed.

The economic value of yeast protein production was well-known in the agricultural industry, which continued to look to the organism for new profits. In 1974, for example, a study that fed yeast to Wistar rats determined that concentrate could be more useful to the food industry than intact yeast as a protein source, because "a native tasteless protein [which was] given a meat texture" could overcome the problems of "the typical yeast smell, high content of nucleic acids, [and] nonaccessibility of protein in cells." The authors noted that the "economics of the process are judged according to the amount of protein produced."[70]

To process knowledge developed in the agricultural industry, there could be added the familiar use of yeast in large quantities as an experimental organism. Rutter's laboratory, for example, had from the mid-1970s used yeast to purify eukaryotic RNA polymerases with hope that large enough quantities of the enzyme would be useful for the *in vivo* characterization of DNA and some RNA molecules.[71] "Yeast is one of the most suitable sources for large scale purification of eukaryotic RNA polymerases since it is readily available at reasonable cost in

[70] F. Machek et al., "Production of Native Protein from Yeasts," *Biotechnol Bioeng Symp*, no. 4-2 (1974): 980.

[71] While in Seattle, Rutter and graduate student Robert Roeder had identified three eukaryotic RNA polymerases believed to control the range of transcriptional activity in higher organisms. That eukaryotes had multiple RNA polymerases as opposed to the single RNA polymerase in the prokaryotes was taken as evidence of the complexity of the eukaryotic cell. Their research is described in chapter 3.

bulk amounts, [and] growth conditions can easily be manipulated," reported Pablo Valenzuela, a postdoctoral researcher in the Rutter laboratory.[72] With their starting material provided free of charge from the Oakland-based Red Star Yeast company in California, the group performed a series of manipulations to extract yeast RNA polymerase.[73] Valenzuela and colleagues predicted that the rapid availability in yeast of large quantities of molecularly-characterized enzymes would make feasible "an experimental onslaught" on the regulation of specific gene transcription.[74]

In addition to being scalable, yeast had also been valued as a resource with a degree of benefit to human and animal health and nutrition, and was believed to function with some therapeutic value as a rich source of protein, fiber, B vitamins and folic acid. For example, large-scale production of yeast had enabled its use as a protein supply for sixty percent of Germany's animal feed needs during the First World War.[75] During U.S. Prohibition, Fleischmann's Yeast began its dietary yeast campaign, and Joseph Goldberger advised the Red Cross to add brewer's yeast to human food rations for the prevention and treatment of pellagra.[76] At mid-century,

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[72] P. Valenzuela et al., "Yeast DNA-Dependent RNA Polymerase I. A Rapid Procedure for the Large Scale Purification of Homogeneous Enzyme," *Journal of Biological Chemistry* 251, no. 5 (1976): 1464.

[73] They harvested enzymes from yeast culture which had reached its maximum density and was saturated. This period is known as the late log or exponential phase of cell division because cells cannot divide further. Yeast's scalability is dependent upon careful monitoring of the rate of cell growth since after the saturation point, cells begin to die. See a description in Victoria Lundblad and Douglas A. Treco, "Basic Techniques of Yeast Genetics," in *Current Protocols in Molecular Biology* (John Wiley & Sons, Inc., 2000).

[74] P. Valenzuela et al., "Molecular Structure of Yeast RNA Polymerase III: Demonstration of the Tripartite Transcriptive System in Lower Eukaryotes," *Proc Natl Acad Sci U S A* 73, no. 4 (1976): 1028.

[75] Braude, "Dried Yeast as Fodder for Livestock."

[76] This included the mass marketing of yeast as a dietary supplement during an hour-long Fleischmann's radio program beginning in September 1929. See T.D. Taylor, *The Sounds of Capitalism: Advertising, Music, and the Conquest of Culture* (University of Chicago Press,

researchers in Mexico were administering yeast in high doses to observe its "favorable therapeutic action" against bacterial growth of salmonella and shigella in the human gut.[77]

Although yeast possessed these connotations for safety, industrial scalability, and general health, it could not become a technology for biomedical production until the start of the 1980s when Seattle's yeast geneticists leveraged the conceptual groundwork of molecular modeling. The Hall laboratory remade yeast with biomedical and commercial intent as a patented promoter of applied eukaryotic molecular biology, and yeast became a therapeutic cell factory.

The Seattle Promoter

Nasmyth and colleagues in the University of Washington laboratories of Hall and Ted Young cloned the ADH1 yeast gene for alcohol dehydrogenase in January of 1980.[78] Young had provided the yeast cloning system, while Hall had an extensive collection of yeast mutants. Another of Hall's postdocs, Gustav Ammerer, wanted to dissect the regulatory sequences of the ADH1 yeast gene using the new transformation system. He was looking for where in the gene sequence a signal resided for starting the RNA molecule. The concept of eukaryotic promoters was unknown at the time but to study the origin of this signal, Ammerer fused the coding region which had been identified in the CYC1 gene to the regulatory region of ADH1. "Nobody else was doing this," Hall recalled. "We had the idea to do this, to take some higher organism coding

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2012), 64. On Goldberger, see Elmore and Feinstein, "Joseph Goldberger: An Unsung Hero of American Clinical Epidemiology," 372-375.

[77] A. Monnier and C. Trevino, "[Therapeutic Uses of Yeasts. II. Clinical Trials]," *Medicina (Mex)* 37, no. 771 (1957): 193. This therapeutic use was disputed and another study the following decade showed that excess consumption of yeast had some effect on rat lymph nodes. See H. Wolochow, G. J. Hildebrand, and C. Lamanna, "Translocation of Microorganisms across the Intestinal Wall of the Rat: Effect of Microbial Size and Concentration," *Journal of Infectious Diseases* 116, no. 4 (1966): 523-528.

[78] V. M. Williamson et al., "Isolation of the Structural Gene for Alcohol Dehydrogenase by Genetic Complementation in Yeast," *Nature* 283, no. 5743 (1980): 214-216.

region, hook it to a piece of the ADH1 regulatory region, and transform it into yeast; and see if we could make that non-yeast protein."[79] When the hybrid was seen to be functional, the group thought to try the coding regions of higher organisms. Nasmyth and Hall, together with Steve Henikoff and Kelly Tatchell, next used yeast transformation to isolate and functionally transcribe a *Drosophila* gene that August. The finding showed similarities between eukaryotic insects and fungi, and the researchers anticipated that further inter-kingdom comparisons would be possible.[80]

Ammerer had joined Seattle's "famous yeast community" from Vienna, where he had been investigating yeast regulatory phenomena. As a doctoral student, Ammerer had seen the advantages of working with yeast in that it was easy to process and grow, with few bacterial contaminations, phage infections or fermentation problems.[81] When the opportunity to work with Hall arose, it was the pursuit of his mountaineering hobby and a romance with Austrian colleague Andrea Barta, newly-settled at University of California, San Francisco, that brought Ammerer to the west coast at the University of Washington in Seattle. In 1980, Barta was doing her postdoctoral research in the laboratory of John Baxter on rat growth hormone. She sent Ammerer a clone and assay kit from San Francisco. Ammerer was able to connect the yeast ADH1 regulatory region to the rat growth hormone fragment, but to his disappointment he could not detect the protein. At the time, his collaborators thought that some additional structural

[79] In Hall, "Oral History with Ben Hall, Part 2."
[80] S. Henikoff et al., "Isolation of a Gene from Drosophila by Complementation in Yeast," *Nature* 289, no. 5793 (1981).
[81] Ammerer recalled that in Vienna he was ahead of "a lot of biologists [at the time, who] still did not realize that baker's yeast was not behaving like a bacterial system." In Ammerer, Email to the Author, June 26, 2014.

determinants were controlling the level at which the rat gene could be expressed.[82] They turned instead to the pursuit of other proteins.

In 1980, the same year that Hall succeeded Roman as chair of the genetics department, his group shifted from the focused study of yeast gene transcription to a pursuit of yeast's protein expressions.[83] It wasn't obvious that the yeast experiments should necessarily be for commercial applications nor that the academic laboratories should be involved with this aspect of the yeast transformation system, but the question of *how* genes expressed their molecular instructions had become inseparable from the issue of *what* they expressed. Eukaryotic molecular biology had moved away from a focus on the gene to other molecular functioning of the cell.

Hall recalled that he was less excited about the gene products than about the yeast technology, but that did not mean he overlooked the commercial value of his yeast promoter. Ammerer, too, realized that their work could have distinct scientific and applied purposes. At Genentech, Ron Hitzeman and Frank Hagie were working on a similar system to express the yeast phosphoglycerate kinase (PGK) *gene*, but they had not yet found where it could be cleaved and extracted. With several months of lead time, Hall and Ammerer had developed a promoter and were looking like excellent potential partners to the Genentech researchers. Hitzeman had

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[82] Science studies scholars have written about the ways scientists make sense of experimental failures so that they can be made to "work" in retrospect. See David Gooding, T. J. Pinch, and Simon Schaffer, *The Uses of Experiment: Studies in the Natural Sciences* (New York: Cambridge University Press, 1989). Hall presumed that the experiment had actually worked but that they had just used a defective assay kit. In Hall, "Oral History with Ben Hall, Part 2." See also Ammerer, Email to the Author, June 26, 2014; G Ammerer et al., "The Functional Expression of Mammalian Genes in Yeast," in *Recombinant DNA: Proceedings of the Third Cleveland Symposium on Macromolecules*, ed. A.G. Walton (Amsterdam: Elsevier Scientific Publishing Company, 1981).

[83] On Hall's succession and Roman's retirement see Herschel Roman, General Correspondence, 1941-1989, (August 18, 1981), Box 1, Folder 7, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington; Herschel Roman, General Correspondence, 1941-1989, (February 22, 1982), Box 1, Folder 7, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.

met Ammerer while the latter was touring Genentech during a visit to San Francisco to see Barta. When Hitzeman reached out to Hall, the senior investigator also made the trip to Genentech for a meeting.

Genentech had contracted with Hoffmann-La Roche Corporation to work on alpha interferon, a human protein perceived to have great utility as a potential virus inhibitor or cancer therapy. Interferon was an early model for scaling up the new technology and would prove a highly-competitive area of commercial development.[84] Biologically-active interferon had already been produced in *E. coli* in January 1980 by Charles Weissmann, co-founder of the Geneva-based biotech company Biogen. The initial bacterial expression had several problems, however. The protein yield was low, and the product was larger than the human interferon molecule and did not contain some of its sugars. "Increasing the level of bacterial production and tailoring the protein are just matters of manipulating the DNA molecule, and the techniques for that are well known," argued Gilbert, another Biogen co-founder, in a public announcement.[85] The scientists were confident they could relocate the gene within the plasmid or fuse it to a bacterial gene to enhance expression and improve productivity. Privately, there was a lot more uncertainty, recalled Hugh D'Andrade, a senior administrator at Schering-Plough who oversaw the company's collaboration with Biogen on the interferon project:

> We agonized over glycosolation; we agonized over methionines, plus or minus; we agonized over containment issues; cost. We didn't know what it would cost to ferment large quantities. Yields. Our first estimate of the size of the plant we have to build for interferon was extraordinary. The cost was staggering. But we… [reworked the bacteria system and] got a very significant yield increase. It was at least a full order of magnitude. So we built a plant a tenth of the size of the one we had on the design table.[86]

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[84] "Interferon Medley: Yeast, Genes, Hybrids," *Science News* 119, no. 10 (1981): 148-149.
[85] "Interferon: Gene-Splicing Triumph," *Science News* 117, no. 4 (1980): 52.
[86] Hugh A. D'Andrade, interview by Sally Smith Hughes, 1998, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

In the early development of bacterial cloning, the presence of a protein had been a way of confirming the identity of a clone.[87] By the start of the 1980s, greater quantity became the new indicator of success. Slight changes at the level of the cell could have large consequences when the processes scaled up. The homology and quantity of molecules per cell was directly related to manufacturing costs at a later stage of production, and it was essential that these be maximized to ensure profitability.[88]

Keenly aware of their competitors' progress in bacteria, Hitzeman and Hagie sought to use Hall's promoter for yeast transformation of the interferon coding region. In early 1981, Hall and Ammerer were brought into the Genentech-Roche arrangement. Ammerer sent multiple promoter constructs to be tested at Genentech, before heading off to join friends for a winter mountaineering expedition of the Pakistan Karakoram. When Ammerer returned to Seattle, he learned that yeast had successfully built the human protein interferon.[89]

Late in February 1981, Genentech's director of molecular biology Dave Goeddel made a public announcement of the results. Even from their preliminary work it appeared that yeast could produce more interferon than bacteria at a lower cost. Although by this time bacterial systems could match the production level of traditional interferon preparation from white blood cells, yeast produced more and seemed better suited to high-volume production, according to Goeddel, because the techniques to grow it commercially had already been worked out in bread,

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[87] This was the expression screening of cloning. Rutter explained, "The first cloning was to focus on the DNA itself. Of course, once you had the DNA, then the next challenge was to express it and measure the protein." In Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

[88] Ammerer and Hall later identified the problem of unequal protein production across different generations of yeast cells. The loss was believed to be a consequence of unequal segregation of plasmids to daughter cells during mitotic nuclear division. In Ammerer et al., "The Functional Expression of Mammalian Genes in Yeast," 191.

[89] Ammerer, Email to the Author, June 26, 2014; R. A. Hitzeman et al., "Expression of a Human Gene for Interferon in Yeast," *Nature* 293, no. 5835 (1981): 717-722.

beer and wine production.[90] The justification resonated intuitively with investors. Following Goeddel's announcement, the company's stock shot up so quickly that trading was halted.

Despite this display of public confidence, a pervasive uncertainty continued on the part of the commercial strategists. Readers of the *New York Times* who saw Genentech's trading news would have also read that article's strange conclusion. Although Genentech expected it would have no trouble producing interferon commercially using yeast, the company had not yet decided whether to use yeast or bacteria.[91] Yeast was safe and scalable and thus culturally favorable, but whether it was commercially viable was another matter given the uncertainties of the clinical testing which remained to be done, the nuances of intellectual property law, the expense of large-scale manufacturing facilities, pricing and other considerations.[92]

As the Genentech team deliberated, Hall began to envision other uses for his technology. As part of the interferon experiments, Ammerer had tested where in the sequence of the coding and promoter regions their connection could be made with greatest sensitivity. To their surprise, it turned out the fusion worked well in a majority of places - the promoter was not particularly sensitive. This led them to develop a general yeast expression vector, comprising not only a promoter, but a structural gene, and associated controls over its expression. They patented this technology for the expression of other genes.[93] Before entering into the arrangement with Genentech, Hall had obtained a written agreement with the company not to use the promoter for

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[90] "Interferon Medley: Yeast, Genes, Hybrids," 148-149.
[91] "Genentech Reports Interferon-Yeast Tie," *The New York Times*, February 27, 1981, D3.
[92] "Any industrial fermentation must take into account certain economic criteria: the cost of starting materials, energy, and purification; the sale price of the final product; and the availability of competing substances produced by other means. If genetic engineering approaches do not provide economic advantages over traditional fermentations, they will not be implemented." In William E. Timberlake, *Molecular Genetics of Filamentous Fungi: Proceedings of a UCLA Symposium Held in Keystone, Colorado, April 13-19, 1985*, UCLA Symposia on Molecular and Cellular Biology (New York: A.R. Liss, 1985), 361.
[93] Hall, "Oral History with Ben Hall, Part 2."

other genes without his prior consent. When Genentech later sent over a more extensive consulting proposal, Hall refused to sign on the advice of a lawyer because, he recalled, it would have given them rights over future work his laboratory might conduct.[94] Hall later claimed that he entered into the interferon collaboration with Genentech without any commercial idea in mind, but that "when the experiments worked, things changed in a hurry."[95]

On the University of Washington campus, examples of technology transfer of intellectual property rights from the academy to the private sector were extremely few at this time. Work on the artificial kidney and some medical devices had come out of the medical school, but there had been no previous commercialization of genetics. Not long before, U.S. president Jimmy Carter had signed into law the Patent and Trademark Law Amendments Act of 1980, which allowed universities to retain ownership of inventions made under federal funding and to license these inventions to industry. Prior to this law, which came to be known as the Bayh-Dole Act, federally-funded grants and contracts obligated inventors to assign their sponsored inventions to the federal government, but very few licensing arrangement were ever made on this property. The U.S. Supreme Court had decided *Diamond v. Chakrabarty* in June 1980, allowing for a "live, human-made micro-organism" to be legally patentable as "a nonnaturally occurring manufacture or composition of matter."[96] Hall recalled that his colleagues in the department

[94] Benjamin D. Hall, interview by Mark Jones, August 29, 2013, "Oral History with Ben Hall," San Francisco, CA, Life Sciences Foundation.
[95] Hall, "A Conversation with Industry Pioneer Dr. Benjamin Hall."
[96] *Diamond V. Chakrabarty*, 447 U.S. Supreme Court 303 (1980). In response, Cold Spring Harbor Laboratory hosted a "patenting life forms" conference in October 1981, bringing in patent lawyers to discuss with scientists the commercialization of molecular biology. Jim Hicks presented on the life cycle of microbial hosts "with emphasis on yeast – the most complex." In *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1981).

were suspicious and had a very negative impression of commercial work, but he thought it important to secure the intellectual property rights for the University of Washington.[97]

Despite contention in his own department, it was obvious to Hall that he should apply for broad patents on the yeast expression system in the U.S. and Europe, to be jointly owned by Genentech and the University of Washington's new intellectual property management foundation.[98] He began to pursue additional avenues of commercial development as well. On June 22, 1981, together with the University of Washington's Earl Davie, the University of British Columbia's Michael Smith, and the venture capital group Cable and Howse, Hall founded a Seattle-based biotechnology company to begin working on additional recombinant

[97] Hall met several times with the faculty and circulated a memo inviting individuals to express their misgivings to him personally. See Benjamin D. Hall, General Correspondence, 1941-1989, (June 9, 1982), Box 1, Folder 7, Herschel Roman papers (#2955-002), University of Washington Libraries Special Collections, Seattle, Washington.

[98] The patents entitled 'Expression of polypeptides in yeast' were filed in Europe on February 24, 1982 with a priority date of one year prior, and in the U.S. on February 25, 1981. See R.A. Hitzeman et al. Expression of Polypeptides in Yeast. 1987; R.A. Hitzeman et al. Expression of Polypeptides in Yeast. 1986. In the early 1990s, challenges to his European patent ultimately caused it to be overturned. Hall noted the irony that evidence revealed in this dispute made the U.S. patent claim even more solid. The litigation over his U.S. patent went on for so long that it did not issue until April 8, 1997, a time when many of the developments using the technology were finally coming to market. The patent was valid until 2014. In Hall, "Oral History with Ben Hall, Part 2." This delay was "a stroke of good luck, really," said Hall. As of 2009, his portion of the patent royalties had yielded $400 million to support the University of Washington, the investors, and the genetics department. In Hall, "A Conversation with Industry Pioneer Dr. Benjamin Hall." Luke Timmerman has described how the U.S. patent was licensed to more than 50 companies for such varied applications as the production of enzymes for detergents and proteins to make cheese creamier. It also covered Novo Nordisk's insulin, and one of the world's best-selling vaccines, Merck's Gardasil. In Luke Timmerman, "Uw's Gardasil Connection Generates Windfall for Research, Tech Transfer," *Xconomy,* February 23, 2009. Licensees also included Smith Kline Beecham Biologicals, Immunex, and American Cyanamid. In Deborah L. Illman, "Pathbreakers: 1981 - a Triumph of Biotechnology," in *A Century of Excellence in Science and Technology at the University of Washington*, ed. Alvin L. Kwiram (Seattle, Washington: University of Washington Office of Research, 1996).

proteins.[99] They named it Zymos, the Greek word for yeast.[100] The same day that Zymos legally incorporated, the Third Cleveland Symposium on Macromolecules was getting started in Cleveland, Ohio. Hall was in attendance to deliver a talk on "The Functional Expression of Mammalian Genes in Yeast" co-authored by Seattle's Ammerer, San Francisco's Barta, and Genentech's Hitzeman and Hagie.[101] The prepared paper read:

> Experiments on the expression of mammalian genes in yeast relate to three subjects of current interest to molecular geneticists. These are: the comparative study of mechanisms and functional sites involved in gene activity, the possibility of using functional complementation of yeast auxotrophic mutants to clone corresponding mammalian genes and the use of yeast as a host cell for expression of mammalian genes which code for commercially useful proteins.[102]

Commercial utility was now listed explicitly among Seattle's interests. The eukaryotic cell was no longer just a resource for production, but the very means of that production and, like any good leaven, it could scale exponentially. Many adopted the metaphor of yeast as a cell

[99] Smith had been part of a team to develop oligonucleotide-directed site-directed mutagenesis in 1978. This synthetic DNA technique allowed determination the effect of a single mutant gene upon a protein molecule, and would lead to the making of Polymerase Chain Reaction (PCR), site-directed mutagenesis and synthetic biology. He shared the Nobel Prize in Chemistry for this contribution with PCR-inventor Kary Mullis in 1993. See P. Rabinow, *Making PCR: A Story of Biotechnology* (University of Chicago Press, 1996).

[100] After the interferon success, Ammerer went to Zymos to start work on human insulin. This work led to a collaboration with Novo of Denmark that following summer. In Hall, "Oral History with Ben Hall, Part 2." Under their agreement dated August 6, 1982, Zymos was to receive part of the cost reduction realized by Novo (later Novo Nordisk) using recombinant methods. See "Zymos Corporation and Novo Industri a/S: Insulin Agreement," in *Exhibit 10.18* (Washington, D.C.: Securities and Exchange Commission, 1982). Rather than make these payments in 1988, Novo Nordisk bought the company outright. See "Zymogenetics, Inc.: Registration Statement," (Washington, DC: Securities and Exchange Commission, 2001). The company had been renamed ZymoGenetics on January 8, 1985 to avoid charges of trademark infringement by the custom integrated circuit manufacturer of silicon chips, Zymos Corporation, of Sunnyvale, California. After its acquisition by Novo Nordisk, it was spun off again as an independent company in 2000, and acquired again by Bristol-Myers Squibb in 2010.

[101] Hall, "Oral History with Ben Hall, Part 2."

[102] Ammerer et al., "The Functional Expression of Mammalian Genes in Yeast," 185-186.

factory, one designed expressly for the manufacturing of "mammalian" molecules.[103] There was one mammal in particular which commanded biomedical research support, had purchasing power, and wanted to reap therapeutic benefits from science.

A Recombinant Vaccine for Hepatitis B

The University of Washington's yeast promotor was not the only technology in development to manufacture therapeutic proteins at the start of the 1980s. A number of other expression systems were also being tested. The case of hepatitis B vaccine offers insight as to how genetic engineers outside of Seattle came to favor yeast cell factories for certain projects. The Seattle promoter stimulated commercial aims for applied eukaryotic molecular biology at the level of the cell, and yeast model organism research laid the groundwork for these cell factories to be seen safe, efficacious, and familiar. Competing expression systems in *E. coli*, mouse cells, and Chinese hamster ovary (CHO) cells were also under development.

In William Rutter's laboratory at the University of California, San Francisco, the idea for a recombinant vaccine against hepatitis B virus (HBV) came on the heels of their successful bacterial cloning of the rat insulin gene in 1977. That fall, Rutter contacted Merck, Sharpe, and Dohme president Roy Vagelos to discuss his pending pharmaceutical deal with Eli Lilly for human insulin development. He learned that Merck had no interest in insulin but was interested in other potential uses of rDNA technology. When Rutter proposed a vaccine, Vagelos told him about Merck's HBV vaccine program with American physician Baruch Blumberg.

[103] This metaphor has since been developed in great detail down to the level of specific factory roles for organelles of the cell; for example, the nucleus as CEO, the cytoplasm as factory floor, and ribosomes as workers in the assembly line. "Science Netlinks: Comparing a Cell to a Factory, Answer Key," accessed May 13, 2014, http://sciencenetlinks.com/student-teacher-sheets/comparing-cell-factory-answer-key/.

Blumberg had isolated an "Australian antigen" from the blood of an Australian aborigine in 1963 and by comparing it to blood samples of hemophiliac and leukemia patients had later shown it to be hepatitis B surface antigen (HBsAg). HBV was a virus which had been linked to the development of acute hepatitis with jaundice, cirrhosis, and hepatocellular carcinoma. In the late 1970s, Blumberg was working to produce an HBV vaccine for Merck by extracting viral particles from the blood of infected individuals to stimulate immunogenicity. Because the virus could not be persuaded to grow in the laboratory in tissue culture, Blumberg's approach was to use only the surface antigen without the DNA core.[104] The resulting subunit vaccine was expected to be safer than other vaccine-types containing whole inactivated or attenuated infectious agents.[105]

Rutter saw HBsAg as a good research problem because hepatitis B was the smallest known human virus at only 3,200 DNA bases and it was a major health problem on a global scale.[106] In terms of engineering technology, he had also become concerned with the idiosyncrasies of gene expression across different biological systems, a problem he later referred to as the "microheterogeneity of proteins synthesized in heterologous systems."[107] He thought that if a gene for the virus' surface antigen could be found and cloned into *E. coli*, not only

[104] Blumberg was awarded the 1976 Nobel Prize in Medicine for this work.
[105] In J.D. Watson, *Recombinant DNA* (W. H. Freeman, 1992), 458.
[106] In 1981, it was estimated that Hepatitis B affected more than half a billion people throughout the world. In "Yeast Engineered to Produce Hepatitis B Coat," *Science News* 120, no. 6 (1981). See also S. Krugman, "The Newly Licensed Hepatitis B Vaccine: Characteristics and Indications for Use," *JAMA* 247, no. 14 (1982).
[107] In William J. Rutter, Notes on Faculty Research Lecturer Award, (May 20, 1982), Box 2 of 13, Subgroup 11, Series II, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA. Later Rutter recalled that, "Even though the genetic code was general, translation mechanisms in different systems might not have uniform high fidelity." A vaccine seemed likely to avoid these errors of translation. In Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

would a resulting subunit vaccine have no chance of producing infection, but it would produce large quantities readily. Moreover, the recombinant version would avoid the difficulties and expense associated with production using the infectious blood donations of healthy carriers.[108] Rutter agreed that his and Goodman's laboratories would consider producing a recombinant alternative for Merck.

Although the Rutter laboratory was stretched thin at this time, postdoctoral researcher Pablo Valenzuela agreed to support a three-year cooperative agreement with Merck beginning on August 1, 1978. The University would supply Merck's Virus and Cell Biology research team with the expertise to culture recombinant microorganisms and to isolate and purify the translation products for immunogenic evaluation.[109] In exchange, the company would fund the University's project at $186,000 in the first year for the isolation, analysis and cloning of HBV DNA fragments obtained either from Dane particles in the human blood or shed from human hepatoma-derived Alexander cells.[110]

At the time, University of California scientists were prohibited by NIH guidelines from doing certain recombinant experiments so even as the partners signed their agreement in the fall

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[108] See William J. Rutter, "Biotechnology at 25: Perspectives on History, Science, and Society" (March 13, 1999).

[109] William J. Rutter, Research, Merck, Correspondence (3), 1977-1980, (September 1, 1978), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA. The next month, Merck would establish a separate consulting agreement with Rutter for general rDNA advice as well. In William J. Rutter, Research, Merck, Correspondence (2), 1977-1978, (August 28, 1978), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[110] Dane particles, named for D.S. Dane of the Bland-Sutton Institute in London who had identified the complete virus in 1970, were isolated from human blood, while Alexander cells were a liver tumor cell line originating with a Mozambican male and collected by South Africa's Jennifer Alexander. In William J. Rutter, Research, Merck, Correspondence (5), 1981-1987, (October 29, 1980), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

of 1978, they knew they would be subject to what Rutter later called "the long wait" and "terror on the homefront." His work was frequently criticized in the press at this time, and he watched as competitors began the experiments he was banned from performing.[111] At the Pasteur Institute in France, for example, researchers in the Genetic Recombination and Expression Unit led by biochemist Pierre Tiollais were first to clone the entire HBV genome into *E. coli* from Dane particles in December of 1978.[112] Adding insult to injury for Rutter, Tiollais' graduate student Patrick Charnay had learned the cloning technology from Goodman at the University of California, San Francisco.[113]

When, in January 1979, revised guidelines eased restrictions on *E. coli* cloning experiments at NIH-funded institutions, the University of California, San Francisco biosafety committee approved Rutter and Goodman's collaboration with Merck on the condition that all study personnel be tested for baseline HBV exposure and be offered immune serum globulin injections by the employee health service.[114] With Valenzuela as the University of California, San Francisco lead and Merck microbiologist Jerome Birnbaum serving as a go-between, the collaborators began efforts to clone and sequence the virus.[115] Rutter later reflected that this was

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[111] Rutter, Notes on Faculty Research Lecturer Award, (May 20, 1982), Box 2 of 13, Subgroup 11, Series II, William Rutter Papers MSS 94-54.
[112] A. Fritsch et al., "[Cloning of the Hepatitis B Virus Genome in Escherichia Coli]," *C R Acad Sci Hebd Seances Acad Sci D* 287, no. 16 (1978).
[113] Charnay and Tiollais were collaborating on the biological characterization of HBV with University of California, San Francisco Blood Bank director Girish Vyas, who had spent a year at the Pasteur Institute. The outcome of this collaboration was Pierre Tiollais, Patrick Charnay, and Girish N Vyas, "Biology of Hepatitis B Virus," *Science* 213, no. 4506 (1981). Tiollais had also spent three months at Cold Spring Harbor Laboratory in the early 1970s learning how to cleave DNA fragments with restriction enzymes.
[114] William J. Rutter, Research, Merck, Correspondence (4), 1979-1983, (January 19, 1979), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.
[115] P.R. Vagelos and L. Galambos, *Medicine, Science and Merck* (Cambridge University Press, 2004), 242.

the one time he felt truly happy to have a P3 facility for his work, because HBV was a real danger. The initial quantity of virus that Merck sent to his laboratory could have infected the entire global population.[116]

With at least six other groups also working on HBV, Merck wanted the University of California, San Francisco experiments kept highly confidential, even from members of NIH.[117] That spring, with backing from Gilbert at Biogen, a competing team out of the University of Edinburgh reported that they had transferred gene fragments of HBV into bacteria where they were cloned and propagated. The group believed that it would soon be possible to produce large quantities of HBV DNA needed for detailed structural and sequence analysis of the virus and its genome. Greater availability of cloned, purified single molecules might also advance diagnostics and support possible production of a vaccine.[118]

That summer, Valenzuela, Rutter, Goodman, postdoc Patrick Gray, and research biochemists Margarita Quiroga and Josephina Zaldivar also achieved HBV DNA cloning in bacteria. Starting from a small fragment of DNA, they spent four months looking for the gene for HBsAg and ended up sequencing almost half of the total virus in the process. Rutter returned from the annual Cold Harbor Spring yeast conference in August 1979 to see his group's results

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[116] Rutter estimated that 4mg of Dane particles was enough to provide every individual in the world with 10^6 virus. In Rutter, Notes on Faculty Research Lecturer Award, (May 20, 1982), Box 2 of 13, Subgroup 11, Series II, William Rutter Papers MSS 94-54.

[117] Merck requested that Rutter not disclose extraneous detail of their experiments to the NIH for proprietary reasons. Rutter tried to retrieve his memorandum of understanding with the company, but this had already been sent to NIH after review by the University of California, San Francisco biosafety committee. He assured Merck that it contained minimal detail and advised that there were few real secrets in the field any longer. William J. Rutter, Research, Merck, Muas, Misc. (1), 1978-1981 (March 22, 1979), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[118] "Biology," *Science News* 115, no. 21 (1979): 344; C. J. Burrell et al., "Expression in Escherichia Coli of Hepatitis B Virus DNA Sequences Cloned in Plasmid Pbr322," *Nature* 279, no. 5708 (1979): 43-47.

printed up in *Nature*. They had the gene coding for the major protein of HBsAg.[119] After his group's cloning milestone, Rutter was contacted by Merck Senior Vice President Maurice Hilleman about the possibility of future vaccine projects together. Competition in the HBV arena had driven home the importance of an early start and while he was open to the idea of further collaboration, Rutter warned, "The word is more or less out that this approach will be fruitful and the technology is much more widespread than a year ago. Therefore, we must mount a concerted effort in systems where we have a real chance of coming in first."[120] HBV showed how close the competition could become. A month after the University of California, San Francisco announcement, Charnay, Tiollais and colleagues reported that they too had found the HBV nucleotide sequence corresponding to HBsAg.[121]

Rutter continued to receive and comply with U.S. and international requests during this period asking to trade unpublished findings, access reprints, or be sent specific materials such as eukaryote polymerase. He protected his privileged access to Merck's hepatitis virus, however. "As you can appreciate, we are also carrying out such transformation experiments and, therefore, are not giving out the virus for identical work," he wrote to one Texas virologist who inquired.[122] By the end of their first year of Merck's sponsorship, the University of California, San Francisco

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[119] P. Valenzuela et al., "Nucleotide Sequence of the Gene Coding for the Major Protein of Hepatitis B Virus Surface Antigen," *Nature* 280, no. 5725 (1979): 815-819. See also Rutter, Notes on Faculty Research Lecturer Award, (May 20, 1982), Box 2 of 13, Subgroup 11, Series II, William Rutter Papers MSS 94-54; Arnold H. Levinson, "Making Microbes," *UCSF Magazine*, October, 1981.

[120] William J. Rutter, Research, Merck, Correspondence (3), 1977-1980, (June 18, 1979), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[121] Patrick Charnay et al., "Localization on the Viral Genome and Nucleotide Sequence of the Gene Coding for the Two Major Polypeptides of the Hepatitis B Surface Antigen (Hbs Ag)," *Nucleic Acids Research* 7, no. 2 (1979).

[122] William J. Rutter, Correspondence K 1970-1991, (October 2, 1979), Box 1 of 13, Subgroup I, Series I, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

researchers had nearly completed sequencing of the entire viral genome. The company renewed their agreement at a twenty-one percent increase in the second year. The team's next major effort would be to insert DNA fragments into both bacterial and yeast hosts to compare expression, for although they had isolated the HBsAg gene and cloned it in *E. coli*, Rutter's team faced challenges with the amount of antigen they produced.[123] So far, it had been wholly insignificant for therapeutic use.

Rutter's team was not alone in attaining an almost negligible yield of HBsAg from bacteria. Scientists from Genentech and the Merieux Institute had achieved HBV bacterial expression, but, as Genentech's Dennis Kleid recalled, the bacteria soon stopped growing. "They would just quit. *E. coli* just hated that protein… As it was being made, it was poking itself into the membrane of the *E. coli*, and the bacteria couldn't divide anymore."[124] The Edinburgh group, too, reported difficulties with HBsAg in December 1979. The Scottish researchers had teamed up with Biogen and colleagues at the University of Heidelberg to express multiple regions of HBV DNA in *E. coli*, including the surface antigen and viral core. When injected into rabbits, the cloned core antigen (HBcAg) appeared to induce antibody production, giving evidence for the feasibility of vaccine production from viral antigens synthesized in microbial cells. But the core was infectious, and the group could not detect bacterial synthesis of HBsAg.[125]

As an alternative, Tiollais joined colleagues at the French National Center of Scientific Research to transform mouse cells with tandem repeats of the entire HBV genome. This

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[123] Rutter, Research, Merck, Correspondence (3), 1977-1980, (June 18, 1979), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54.
[124] Dennis G. Kleid, interview by Sally Smith Hughes, 2002, "Scientist and Patent Agent at Genentech," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.
[125] M. Pasek et al., "Hepatitis B Virus Genes and Their Expression in E. Coli," *Nature* 282, no. 5739 (1979).

"mediated gene transfer technique" allowed the scientists to study the functional capacity of cloned viral DNA after introduction in mammalian cell culture. They demonstrated that highly immunogenic particles of HBsAg could be expressed in eukaryotic cells which were not from the human liver.[126] The excreted product appeared very similar to human HBsAg and the mouse cells remained intact following protein expression, however, the risk of vaccine-induced HBV infection still remained because the cells contained the entire viral genome.[127]

In their own studies, the University of California, San Francisco group observed that, unlike isolated HBsAg particles taken from human sera, the bacteria-made particles were not fully assembled and may not have functioned as antigens. "We are uncertain of the reasons for degradation but it is known the bacteria have extremely efficient systems for degrading certain peptides," Rutter informed Hilleman.[128] It appeared that *E. coli* were making, then unmaking, the recombinant product. They needed homologous structure in order to produce the human immune response. As year three of the Merck contract began in September of 1980, Rutter struggled to supply Merck with enough material to evaluate in animal trials. Valenzuela had succeeded in expressing the correct gene but his subunit of the virus did not fold properly, in a manner essential to its specificity. This form of HBsAg, they determined, was a poor "molecular facsimile" to that found in the human blood.[129]

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[126] C. Pourcel et al., "Transcription of the Hepatitis B Surface Antigen Gene in Mouse Cells Transformed with Cloned Viral DNA," *J Virol* 42, no. 1 (1982): 100-105.
[127] Marie-Francoise Dubois et al., "Excretion of Hepatitis B Surface Antigen Particles from Mouse Cells Transformed with Cloned Viral DNA," *Proceedings of the National Academy of Sciences* 77, no. 8 (1980): 4553.
[128] William J. Rutter, Research, Merck, Correspondence (4), 1979-1983, (March 14, 1980), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.
[129] This phrase was taken from Rutter's description of what the ideal recombinant antigen should be. In Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 47.

The "Essential Ingredients" for Commercial Production

Rutter maintained a public optimism despite the early challenges, and estimated for *Science* writer Thomas Maugh in October of 1980 that, depending on the FDA approval process, bacteria could produce a commercial rDNA vaccine within five years.[130] The projection came just two weeks after Genentech's initial public offering stirred Wall Street with a huge escalation of value.[131] A growing push to commercialize already characterized other projects in Rutter's laboratory. Postdoc Michael Urdea had just left the University of California, San Francisco to co-found with Rutter and financier C.K. Chang the synthetic DNA company BioPolymers in Emeryville.[132] While this venture would be absorbed by Hana-Biologics early in the new year, a frenzy of financial speculation meant that it was important for Rutter to project confidence with an eye to future investments.

An impact assessment of applied genetics in 1981 by the U.S. Congressional Office of Technology projected that, "The first major commercial effects of the application of genetic engineering will be in the pharmaceutical, chemical, and food processing industries" rather than the more speculative energy or environmental applications.[133] In the early 1980s, genetic engineering was producing fewer anxieties about uncontrolled recombinant organisms and more interest as an economic engine that could drive the country out of stagflation on a wave of new

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[130] Rutter, Research, Merck, Correspondence (5), 1981-1987, (October 29, 1980), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54.
[131] "A minute after the opening bell, the share price skyrocketed from $35 to $80—the fastest first-day gain in Wall Street history." In Hughes, *Genentech: The Beginnings of Biotech*, 158.
[132] Urdea was an expert in DNA synthesis, and as he recalled, "the notion just came about that perhaps what we could do is sell DNA, and make some money, while also doing some improvements in the DNA synthetic methods with the money we might earn." In Michael S. Urdea, interview by Sally Smith Hughes, 1992, "Nucleic Acid Chemistry at Chiron Corporation," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.
[133] *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*.

investments. The Bay Area was particularly attractive for venture capitalists because of the recent success of computer-related investments in Silicon Valley.[134] These politics reflected the decline of a collective environmentalism in the U.S. and the pro-business ideology which delivered Ronald Reagan the presidency.

One of the biggest threats to the commercial viability of recombinant vaccine production was Merck's own HBV blood-derived vaccine, which was already in large-scale production in anticipation of government licensing. The lead clinical researcher for the blood vaccine dismissed rumors of a rivalry on the basis that there was no contest. In contradiction to Rutter's estimate, he estimated that it would be not five years but another seven to ten years before a recombinant alternative would be available.[135] The researcher, New York Blood Center epidemiologist Wolf Szmuness, had led a two-year double-blind clinical trial indicating that the blood-derived vaccine provided excellent protection against HBV with no adverse side effects.[136] It was currently undergoing additional testing in high-risk groups, and Merck anticipated the vaccine's introduction in 1982.[137] The company made an eight million dollar investment to upgrade their vaccine production facilities and was able to triple the antigen recovery rate. The inactivated blood HBV vaccine Heptavax-B received approval from the FDA's Division of Biologics Standard on November 16, 1981, putting Merck ahead of schedule on its own forecasts. However, the blood vaccine still had the longest cycle time for production and testing

[134] In Penhoet, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders."
[135] This was one-year into Rutter's five-year estimate. William J. Rutter, Research Project - Hepatitis 1972-1981, (August 4, 1981), Box 2 of 13, Subgroup 11, Series IIIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.
[136] Wolf Szmuness et al., "Hepatitis B Vaccine," *New England Journal of Medicine* 303, no. 15 (1980): 833-841.
[137] "Hepatitis Vaccine Found," *Science News* 118, no. 15 (1980): 231.

of any vaccine then manufactured – a total of sixty-five weeks.[138] Later priced at one hundred dollars for just three doses, it was also the most expensive vaccine ever produced, which meant that it was not taken up in many of the countries where it was most needed.[139]

The blood-derived vaccine was soon associated with a risk perceived to be even greater than the use of rDNA, however, and the University of California, San Francisco researchers were driven to overcome their problems with recombinant bacterial production. Readers of *The San Francisco Chronicle* on June 4, 1981, would have seen a story about the planned yeast-based and mammalian cell production of a recombinant hepatitis vaccine.[140] Two days later, the same reporter would write about a "mysterious outbreak of a sometimes fatal pneumonia among gay men" in San Francisco and other cities, which had just been reported by the U.S. Centers for Disease Control and Prevention.[141] While it would be some time before investigators would sort out the link between AIDS and *human immunodeficiency virus* (HIV), including blood-borne transmission of the virus, the experimental blood vaccine suddenly looked quite risky.[142] At one

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[138] L. Galambos and J.E. Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995* (Cambridge University Press, 1997), 193. See also "FDA Approves Hepatitis B Vaccine," *Science* 214 (1981): 1113.

[139] In Galambos and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*, 195. Merck initially pursued a strategy of licensing the blood-derived vaccine technology to regional manufacturers. In the fall of 1983, for example, Singapore Biotech signed a deal to eventually manufacture their own government-subsidized product and administer it in Southeast Asia through government immunization programs. See Tazewell Wilson, "Engineering Tomorrow's Vaccines," *Nature Biotechnology* 2, no. 1 (1984): 28-39.

[140] David Perlman, "'Cloning' a Vaccine for Hepatitis," *The San Francisco Chronicle*, June 4, 1981.

[141] David Perlman, "Aids at 20 / an 'Interesting Medical Oddity' / First Report of Aids 20 Years Ago Offered No Hints of Epidemic to Come," *The San Francisco Chronicle*, May 30, 2001. See also Michael S Gottlieb et al., "Pneumocystis Pneumonia--Los Angeles," *MMWR. Morbidity and Mortality Weekly Report* 30, no. 21 (1981): 250-252.

[142] "[T]he discovery of HIV did totally transform the project. It completely eliminated the other [Hilleman's] way of doing it, and of course exacerbated the need for such a vaccine…" In Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 20.

point, Merck's clinical trials were suspected as a potential source of the epidemic among gay men in New York as the high-risk population enrolled in HBV clinical trials was also the population among which some of the earliest cases AIDS cases were detected.[143] The absence of any contaminating viruses had been a major theoretical benefit of yeast over tissue culture cells in a recombinant vaccine. That was "one of the crazy benefits of such a plague on mankind," Rutter later reflected. "That it, in fact, contributed to the rapid development of this vaccine and subsequently its promulgation broadly."[144]

Another threat to the commercial viability of a recombinant vaccine from the Rutter laboratory was the possibility the use of other methods and materials would allow a different laboratory to get there first. At the First Annual Congress for Recombinant DNA Research held in San Francisco during the last days of February 1981, the Tiollais' group presented a poster on the recombinant synthesis of HBsAg in both *E. coli* and mouse cells. They showed that mouse cells had the exciting ability to secrete eukaryotic HBsAg without the need to rupture cells to extract it.[145] Rutter reported on his group's efforts to produce "significant quantities" of both HBsAg and HBcAg in a bacterial system. This latest attempt to express two proteins in tandem was hoped to have higher yield – but this still looked to be insufficient for commercial use.[146]

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[143] This spurious relationship formed the basis of a discredited theory about the man-made origins of AIDS. For the flavor of this purported conspiracy, see A. Cantwell, *Aids and the Doctors of Death: An Inquiry into the Origin of the Aids Epidemic* (Aries Rising Press, 1988).
[144] In Rutter, "Biotechnology at 25: Perspectives on History, Science, and Society." Ammerer concurred: "I had some doubts about whether for example HB [hepatitis B surface antigen] expression in yeast could be competitive. It is only later, when the extent of possible retroviral dangers became apparent that yeast also was considered a safer alternative" than the blood version. In Ammerer, Email to the Author, June 26, 2014.
[145] "Abstracts from the First Annual Congress on Recombinant DNA Research," *DNA* 1, no. 1 (1981): 71-98.
[146] "Progress against Hepatitis B Virus," *Science News* 119, no. 12 (1981): 180-181.

In the companion article published later that spring, the University of California, San Francisco group explained that the level of polypeptide they were able to synthesize in bacteria varied widely and was in some cases not detected – perhaps due to subtle variations in cellular growth conditions or shifting product stability. They hypothesized bacterial degradation of the product as well as the transcription or translation inefficiencies of a poorly-disciplined production line. They assumed a "substantial" level of antigen could be produced vis-à-vis an additive effect, arguing that "rDNA can in principle provide a limitless source of vaccine."[147] The low-yield bacterial system could be overcome by extensive production on the part of the microbes, they argued publically. Privately, however, Rutter was ready to change strategies. The use of bacterial expression systems had proven a highly frustrating experience.[148] Interferon competitors Weissmann and Goeddel had also been at the Congress to report on their individual cloning successes, and Goeddel had described Genentech's use of Ben Hall's ADH1 promoter.[149] Later that week, Rutter called his former colleague in Seattle to discuss the use of his and Ammerer's yeast promoter for the Merck HBV project. It was possible that the human molecules of HBsAg had a better chance of being constituted within eukaryotic membranes, Rutter thought.[150] He invited Hall and Ammerer to collaborate.[151]

While the Rutter laboratory had extensive experience with yeast, they lacked "a strong yeast promoter that could be used to drive [expression] on a commercial scale." Since eukaryotic yeast shared structural homologies with mammalian cells, Rutter hoped that the right promoter

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[147] In Jeffrey C Edman et al., "Synthesis of Hepatitis B Surface and Core Antigens in E. Coli," *Nature* 291, no. 5815 (1981): 503-506.
[148] Ammerer, Email to the Author, June 26, 2014.
[149] Harold M. Schmeck, "Scientists Present Results of New Genetic Research," *The New York Times*, March 2, 1981.
[150] Rutter, "Biotechnology at 25: Perspectives on History, Science, and Society."
[151] "Ben Hall Hep B: 1981 - a Triumph of Biotechnology," news release, (University of Washington Office of Research), November, 1996.

could make yeast into a vaccine "factory." Later, Rutter argued that, "there were lots of other alternatives to get there; [Hall] provided the one that actually was available."[152] He had already reached out to yeast geneticist Ira Herskowitz at the University of California, San Francisco to see if he had any interest in the project, but Herskowitz was "more on the hesitant side about business in general.[153] Other investigators studying yeast expression was already affiliated with competing laboratories. Hall's promoter was resulting in high levels of protein expression as a consequence of a previously-negotiated commercialization strategy in the yeast organism. After years of interrogating an industrial organism that could make eukaryotic molecules, the Seattle scientists had already shifted the focus of their research from the mechanistic study of gene expression to a study of what gene expression produced. In that practical question of applied eukaryotic molecular biology, the Hall laboratory had found the potential to pursue proteins of known commercial value with an emphasis on yield. This meant that when Rutter needed "the right tool for the job," Hall and Ammerer were already making it.[154]

Hall and Ammerer, however, needed convincing that this was the right job for their yeast promoter. GlaxoSmithKline was also interested in collaborating, and Genentech wanted to explore further projects together. After the call with Rutter, Hall contacted Merck president Vagelos to set up a meeting in San Francisco. There, he met representatives from all three companies on the same day to explore which was offering the best deal. The answer was Merck,

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[152] In Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 61.
[153] Herskowitz also turned down a consulting role at Chiron. See ibid., 18, 33, and 49. In 1983, he explained to a microbiologist at the University of Tennessee, "I consult for no companies. I am a financially disinterested party to all of this stuff, interested only in learning about yeast." In Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25). Herskowitz's yeast mating type research is described in the previous chapter.
[154] Clarke and Fujimura, *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences*.

which would pay Hall for use of his promoter while the Rutter laboratory performed the work.[155] Late in March 1981, Merck began to fund the collaboration as an equal 50-50 partnership between Seattle and San Francisco.[156] They would measure the success of recombinant production in the yield of eukaryotic molecules.[157]

Their progress was threatened almost immediately as the University of California, San Francisco biochemistry department began to show signs of unraveling.[158] That spring, Goodman accepted an offer from Massachusetts General Hospital to lead a new department of molecular biology.[159] Members of the Rutter laboratory were regularly receiving attractive offers from industry. Because of his position on Amgen's scientific advisory board, Rutter had been asked to make suggestions for the company's new research director. He recommended Edward Penhoet, a former laboratory member who had travelled with him from Illinois to the University of Washington, had done a sabbatical with McCarthy at the University of California, San Francisco, and was now at the University of California, Berkeley. When Penhoet turned down the offer,

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[155] Hall, "Oral History with Ben Hall."

[156] It was a "very tough negotiation" involving their attorneys, Rutter recalled, "but we finally could get on with it." In Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 18.

[157] Yeast had cultural resonance at this time as an agent of high-volume yield. In 1985, for example, the political action committee EMILY's List, which in 1985 adopted the acronym-slogan "Early Money Is Like Yeast (it makes the dough rise) to raise seed money for female pro-choice Democratic politicians." See J.P. Pimlott, *Women and the Democratic Party: The Evolution of Emily's List* (Cambria Press, 2010).

[158] "Bill concluded that he couldn't continue to be competitive on several projects that he was pursuing in the University of California, particularly the hepatitis B project because all of the people who worked for him …were being offered compelling positions in the budding industry." In Penhoet, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders."

[159] The department had been Goodman's brainchild, to be funded at $70 million for ten years by the German pharmaceutical company Heochst AG as an arm of Harvard Medical School's genetics department. See B. J. Culliton, "The Hoechst Department of Mass General," *Science* 216, no. 4551 (1982): 1200-1203.

Amgen tried to recruit Valenzuela from the University of California, San Francisco.[160] Rutter talked to Amgen chairman George Rathmann about the possibility of forming his own San Francisco-based branch of the company as a way of keeping his laboratory together. Rutter sat down with Valenzuela and Penhoet to consider plans for an Amgen North, but ultimately the group abandoned the idea with a preference for starting their own company.[161]

Rutter believed that independence from the university would be a more effective means of developing the clinical utility of his research, as he believed the private sector could offer greater resources for innovation and competition. As the University of Washington and University of California, San Francisco groups discussed the details of joining the HBsAg gene to the ADH1 promoter, he, Valenzuela and Penhoet worked up a business plan for Chiron Corporation in April of 1981, which positioned Rutter as chairman, Valenzuela as director of research, and Penhoet as CEO. Between them, they had trained many students over the years and had a large network of talent to recruit from. The company would focus on developing vaccines, diagnostics, and therapeutics like insulin, and would partner with major pharmaceutical companies or form joint ventures with others to handle the marketing. They would focus first on a vaccine for hepatitis and avoid the overcrowded interferon market.[162] The founders had no patents to get started, and did not make any specific deals with their universities on the technology transfer, but later Rutter would donate some stock to University of California, San

[160] Penhoet, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders."
[161] George B. Rathmann, interview by Sally Smith Hughes, 2003, "Chairman, CEO, and President of Amgen, 1980-1988," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.
[162] Penhoet recalled that there was a finite list of proteins expected to be useful as therapeutics, and everybody was working on them. “If you looked at Amgen’s list, it was the same as Chiron’s list, same as Genentech’s list.” Chiron was too far behind on interferon. In Penhoet, "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders."

Francisco and Penhoet to University of California, Berkeley. The company incorporated the next month with support from Hana-Biologics, and opened an office in Emeryville, California on June 1. More than a decade after making the transition into industry, Rutter defended his commercial objectives; “[T]he lure of being both rich and famous is pretty intense. It’s not as crass as it sounds; new scientific information frequently can be coupled to a commercial goal,” he said.[163] His highest ideals spoke to the “possibility of helping his fellows live a more comfortable life,” but he believed also that projects offering tangible benefit to intervene in disease were inevitably commercial if successful.[164]

Merck worked up a new HBV agreement between Rutter’s team at the University of California, San Francisco, Hall’s laboratory at the University of Washington, Merck’s Virus and Cell Biology team, and Chiron. The contract provided credibility for the new company’s fundraising.[165] If the University of California, San Francisco lacked the capital, structure and authority to properly transfer their results from discovery into an actual product, Chiron with Merck’s backing would not. Like the transition from bacteria into yeast, the researchers had

[163] Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco." Others have shown how biotech startups reflect the reconfiguration of public knowledge ownership the late 1970s and 1980s. Intellectual property rights helped to redefine the public interest in terms of economic growth. In Yi, "Who Owns What? Private Ownership and the Public Interest in Recombinant DNA Technology in the 1970s," 473.

[164] Rutter, Notes on Faculty Research Lecturer Award, (May 20, 1982), Box 2 of 13, Subgroup 11, Series II, William Rutter Papers MSS 94-54.

[165] Rutter later reflected that, “Venture capital companies are both a strength and weakness of our capitalist system. They provide funding, but they are interested for the most part in selling to the public market and getting out and doing another deal instead of building something over a longer period of time.” His goal for Chiron was to have a more sustainable enterprise. In Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

found a commercial partner to provide the industrial-scale means of production.[166] Merck - and yeast - indicated that Chiron meant business.

Chiron had "the essential ingredients" to become successful, argued Rutter's former postdoc and BioPolymers co-founder, Michael Urdea who had joined the new company. "[A]nd they were unique ingredients," he said, referring to "the yeast knowledge."[167] It was an argument repeated in December of that year by Collaborative Research, Inc., which planned to go public with backing from Dow Chemical Company. "Collaborative's concentration on yeast at a time when most other companies have focused on bacteria like *E. Coli* could prove to be a major competitive advantage in the long run, if yeast turn out to be a better host for the production of useful drugs and chemicals," the *New York Times* reported.[168] The following year, a report from the Institute of Biology declared that yeast appeared to be "the preferred organism for the production of pharmaceutical products by genetic engineering." The authors found that, "Yeast technology has an impressive past but looks to have an even brighter future."[169]

At Chiron's founding, it was still not clear that yeast could process human HBsAg. The team had a promoter but still had to obtain expression from the eukaryotic cell. Cornell scientists had recently moved nitrogen-fixing bacterial genes into yeast and back again into bacteria where they

[166] Brian Elliot, *Chiron Corporation*, ed. Steven C. Wheelwright (Boston, MA: Harvard Business School Publishing, 1993), 4.
[167] Urdea, "Nucleic Acid Chemistry at Chiron Corporation." In his study of British microbial studies in the early twentieth century, Keith Vernon has identified institutionalization as the mark of the development of a new practice. Vernon contrasted the practical organization of industry with specialty formation in academia. See Keith Vernon, "Microbes at Work. Micro-Organisms, the D.S.I.R. And Industry in Britain, 1900--1936," *Annals of Science* 51, no. 6 (1994): 612.
[168] Barnaby J. Feder, "Uncertain Demand Awaits New Issue of Collaborative," *The New York Times*, December 10, 1981, D5.
[169] David R. Berry, *Biology of Yeast*, The Institute of Biology's Studies in Biology, (London: E. Arnold, 1982), 57.

continued to work, but these genes had not yet "been persuaded to act" in the yeast.[170] It was possible that yeast would reject HBsAg. Because yeast was a eukaryote, it was hoped that it might be able to better mimic the human antigen. *E. coli* expression systems had yielded minimal expression or were altered to increase secretion but then these particles lacked value as antigens. In order to stimulate antibody reaction, yeast would need to fold the particles in the same manner as human HBsAg.[171]

Ammerer recalled the "slightly schizophrenic" three-week period in which, by day, he continued to work with Genentech to enhance interferon expression in the yeast system by including a transcription terminator, while, by night, he worked with the University of California, San Francisco-Chiron group to construct plasmids and yeast strains for HBsAg expression.[172] For the HBsAg project, this meant fusing the ADH1 promoter to the viral gene Valenzuela had isolated, and transferring the resulting hybrids into yeast cells. Once this was done, Ammerer headed back to the University of Washington, and left Valenzuela to grow up the strains at Chiron. On June 3, 1981, as the Pasteur Institute made plans to market another blood-derived HBV vaccine in Europe, Ammerer's strains tested positive for HBsAg. Moreover, Valenzuela reported to the University of Washington group that the resulting particles were clumping together to resemble the form of antigen found in the human blood. Yeast's protein product was appearing attractively human-like. Rutter later described their excitement over the visual confirmation of homology:

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[170] "Nitrogen Fixing," *The New York Times*, February 17, 1981, C3.
[171] "The general idea was to use recombinant DNA technologies to produce proteins which self-organized to form a three dimensional structural homolog of the virus in such a way that the human immunological response to this structure would be sufficiently strong in breadth of antibodies produced and T-cell responses to neutralize the infectious agent." In Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 47.
[172] Ammerer, Email to the Author, June 26, 2014.

> …we also could see particles in the microscope! These were amazing results—the first complicated structure naturally made in humans but produced by genetic engineering in a foreign— microbial—cell!… I specifically remember the [earlier] conversations with Ben… saying that we would really know what we have only when we see the electron micrographs. Sure enough, there were particles, beautiful particles….[173]

That August at the International Conference of Virology in Strasbourg, Rutter outlined the progress that he, Hall, Ammerer, and Valenzuela had made along with University of California, San Francisco biochemist Angelica Medina. While bacterial systems using powerful promoters failed to produce high-level yields, yeast initially delivered more than 10,000 molecules of HBsAg per cell. *Science News* coverage of the event reported that "a second generation of genetic engineering" had dawned, in which scientists moved genes of interest "from their bacterial 'foster homes' into a slightly more complex organism, a yeast… [which] does have skills bacteria lack."[174] Previous engineering attempts had yielded proteins alone, such as insulin or interferon, but the current experiment marked a milestone for they showed that the fungal factory could make intricate biochemical structures ordinarily associated with more complex cells even though the yeast host was "far removed on an evolutionary scale from the normal host (man)."[175] While Valenzuela warned that further experiments were needed to confirm that the product contained the appropriate sugar and fat-like molecules which resembled the immunizing particle found in the blood of hepatitis B patients, yeast's antigen ought to be recognized by the human body.[176] "We were delighted that a particle like this could be formed in

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[173] In Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 19.
[174] In "Yeast Engineered to Produce Hepatitis B Coat." Other coverage of the event reported the yeast was a step up in complexity, but one that might "prove as valuable in genetic engineering research as the more commonly used bacteria." In "A Vaccine-Making Yeast," *The New York Times*, August 4, 1981.
[175] In W.J. Rutter et al. Synthesis of Human Virus Antigens by Yeast. 1990. See also Rutter, Research Project - Hepatitis 1972-1981, (August 4, 1981), Box 2 of 13, Subgroup 11, Series IIIa, William Rutter Papers MSS 94-54.
[176] While HBsAg required this posttranslational modification which could not be performed by bacteria, many other recombinant products did not require this complex expression. Prokaryotic

a totally different genetic system," Rutter recalled.[177] Unlike *E. coli*, yeast produced no endotoxins during fermentation, so its HBsAg yield was expected to be more pure, and unlike mammalian cells, yeast provided a "clean" interior with relatively few other proteins to complicate extraction. The new product looked so hopeful that Rutter predicted trials before 1982.[178]

Engineering the Cell for Economies of Scale

In August 1981, Rutter, Valenzuela, Hall and Ammerer jointly filed a patent application, "Synthesis of human virus antigens by yeast." The application claimed that they had endowed a microorganism with genetic capability to produce human-like HBsAg to permit "large-scale production with economies of scale."[179] These "economies" could be achieved because the "uniform product [was] obtainable at an advantageous cost per unit [which was] expected to decrease with increasing production volume."[180] Yeast was a resource which scaled up easily, but it was also a technology for achieving economies of scale since the commercial interests of industrial microbiology were already firmly apparent in microbial genetic engineering. This was not true universally across other genetic engineering practices, as a priority dispute over the first

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systems were preferred for other small proteins like human growth hormone, for example, which did not need to be glycolized.

[177] Rutter, "Biotechnology at 25: Perspectives on History, Science, and Society."

[178] These milestones were summarized in a book focused on the contributions of women in technology, which reported University of California, San Francisco biochemist Angelica Medina was part of the collaborative team to produce the HBV immunizing particles. In A. Stanley, *Mothers and Daughters of Invention: Notes for a Revised History of Technology* (Rutgers University Press, 1995), 203. See also a review of the benefits of yeast expression over *E. coli* and mammalian systems as a way to avoid, respectively, toxic cell wall pyrogens and oncogenic or viral DNA in Michael A Romanos, Carol A Scorer, and Jeffrey J Clare, "Foreign Gene Expression in Yeast: A Review," *Yeast* 8, no. 6 (1992): 423.

[179] Rutter et al. Synthesis of Human Virus Antigens by Yeast.

[180] W.J. Rutter et al. Hepatitis B Virus Surface Antigen; Hepatitis B Vaccine. 1988.

eukaryote expression of HBsAg makes clear. Researchers Charles Chany and Marie-Francoise Dubois of the French National Institute of Health and Medical Research had a different view of what constituted experimental success, and this led them to make conflicting claims with Rutter's group over the production of HBsAg. At stake was whether "engineering" necessarily required plans for commercialization of the recombinant product as was the case with Hall's "promoter."

As Rutter was well-aware, the French team had published and presented with Tiollais at the rDNA research congress in San Francisco on the isolation and expression of the gene for HBsAg in both bacteria and mouse cells.[181] When Rutter's yeast-based production was profiled in the December 1981 issue of *Science* as "the most promising route" for a recombinant alternative to Merck's forthcoming blood vaccine, Chany and Dubois objected, copying Rutter and the editor of *PNAS* on a letter to the *Science* board. Taking issue with Rutter's quote that this marked "the first time that genetic engineering techniques have been used for production of a complex, biochemical structure that probably combines protein, sugar, and fat-like molecules," they wrote, "We are somewhat surprised by Dr. Rutter's statement about the HBsAg particles being expressed for the first time by his team in eukaryotic cells."[182] Given the prior expression of HBsAg in mouse cells, they found it "difficult to understand Dr. Rutter's misquotation since he has probably benefitted from the information published [previously]."

[181] Rutter had sent the group a preprint of Valenzuela's work on the complete HBV nucleotide sequence. See Dubois et al., "Excretion of Hepatitis B Surface Antigen Particles from Mouse Cells Transformed with Cloned Viral DNA."; "Abstracts from the First Annual Congress on Recombinant DNA Research."

[182] William J. Rutter, Research, Merck, Correspondence (5), 1981-1987, (February 2, 1982), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

Rutter's statement had its origins in a University of California, San Francisco press release which was misrepresented by the *Science* article. Other media outlets more clearly emphasized that he was claiming the first recombinant HBsAg expression *in microorganisms*.[183] Rutter responded to the letter that he had not made claims to the first eukaryotic production since clearly human blood cells and other recombinant mammalian cell lines also produced the particle. He thought Chany and Dubois's mouse cell system was not particularly attractive for recombinant production of a vaccine since the yield was no higher than blood-based production, the antigen contained the DNA core, and the risk of infection remained. "Our experiments were quite different in scientific purpose, strategy and in their consequences," Rutter wrote, because they isolated the surface antigen coding sequences, designed a yeast vector for expression, and employed a yeast promoter to activate translation. This, he wrote, was the meaning of "engineering" in laboratory jargon.[184]

For Chany and Dubois, however, the meaning of genetic engineering was "a debatable matter." It was true they had not isolated a single gene in advance of cloning, and had instead extracted the antigen after expression of the whole viral genome. Yet, "[t]he important fact is that by the use of genetic engineering techniques we obtained eukaryotic cells constitutively producing HBsAg particles," they argued. For Rutter, the work was nonspecific, and therefore not as valuable. He believed that genetic engineering necessitated the upfront specification of that commercially useful portion of the genome - the antigen's gene sequence - so that what was

[183] For example the October 1981 volume of the University of California, San Francisco magazine makes clear that: "it is the first time that *microbes* have been instructed to synthesize an elaborate biochemical structure usually made only by cells of higher organisms." Levinson, "Making Microbes," 4, emphasis added.
[184] Rutter, Research, Merck, Correspondence (5), 1981-1987, (February 2, 1982), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54.

engineered was a specific means of production.[185] Cell factories were proprietary because they were built to certain specifications which allowed gene products to scale without further intervention.[186] Rutter continued protesting. "Now with respect to the allegation that I 'benefitted' from the information published in this paper, I want to state unequivocally and emphatically that I did not benefit financially from this report… Chiron does not intend to go public in the foreseeable future."[187] Chany and Dubois found this response bewildering, writing again that they had been "unaware of [Rutter's] relationship with industry." Of Rutter's commercial interest in genetic engineering, they made clear, "this matter is of no interest here."[188] But this difference in commercial interests was at the heart of their dispute.

Engineering the cell for economies of scale was how Rutter understood his laboratory's contributions. If, as they believed, the goal of genetic engineering was to produce an antigen for commercial quantities of vaccine, then cell factories constituted intellectual property. If the goal was to "study the regulation of HBV gene expression" in eukaryotes, as the French scientists claimed, then engineering offered new experimental models with possible practical potential.[189]

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[185] As Chiron's chief patent attorney later argued in defense of the companies Hepatitis C virus-related patents, technology had no value if it was impossible to infringe. In Jon Cohen, "Chiron Stakes out Its Territory," *Science* 285 (1999): 26-30.

[186] Like Rutter, Genentech scientists echoed the commercial importance of the cell factory: "Genentech was interested in making a product; we didn't feel that just sequencing the gene was really patentable since a group from France was also right in there with the hepatitis virus sequence." In Kleid, "Scientist and Patent Agent at Genentech."

[187] Chiron would go public the following summer.

[188] Rutter, Research, Merck, Correspondence (5), 1981-1987, (February 2, 1982), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54.

[189] They explained, "In the absence of a cell culture system able to propagate HBV, the experimental model presented here could be used advantageously to study the regulation of HBV gene expression. This model may also be suitable for HBsAg production which, in the absence of virion synthesis, may have potential practical applications." See Dubois et al., "Excretion of Hepatitis B Surface Antigen Particles from Mouse Cells Transformed with Cloned Viral DNA," 4553. In the U.S., Vettel identified an important shift from philanthropic to federal research

A definition of genetic engineering as the manipulation, transfer, replication and expression of specific genes had been given in a 1980 review of the state of the science. Writing specifically on the application of genetic engineering to industrial microbiology, author Kenneth Murray noted that his was the particular use of "a term subject to various interpretations."[190] Outside the reward structure for U.S. biomedical innovation, eukaryotic models were expected to reference human molecules but not necessarily to make them to scale.[191] When Japanese scientists developed their own yeast promoter at this time, they saw in it the opportunity to study eukaryotic gene expression, produce a vaccine, and develop other mammalian and plant gene products with the understanding that yeast would scale.[192] The University of Washington and Chiron collaborators outpaced this rival group by just a few months to achieve yeast-expression of HBsAg. They reported synthesis and assembly in the yeast cell factory in a *Nature* paper in July 1982.[193]

That August, Rutter resigned as the chair of biochemistry and began directing the University of California, San Francisco Hormone Research Institute while he continued to lead Chiron. The company went public the following year with an offering of twelve dollars per share.[194] At that time, Chiron was still the size of a big university laboratory with a staff of fifty-

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funding in the postwar period which resulted in demand for return on basic research in the form of practical applications. In Vettel, *Biotech: The Countercultural Origins of an Industry*, xi.

[190] K. Murray, "Genetic Engineering: Possibilities and Prospects for Its Application in Industrial Microbiology," *Philos Trans R Soc Lond B Biol Sci* 290, no. 1040 (1980): 91.

[191] On the biomedical reward structure, see Vettel, *Biotech: The Countercultural Origins of an Industry*, xi.

[192] A. Miyanohara et al., "Expression of Hepatitis B Surface Antigen Gene in Yeast," *Proceedings of the National Academy of Sciences* 80, no. 1 (1983): 5.

[193] P. Valenzuela et al., "Synthesis and Assembly of Hepatitis B Virus Surface Antigen Particles in Yeast," *Nature* 298, no. 5872 (1982): 347-350.

[194] Chiron Corp., Corporate Prospectus, Securities and Exchange Commission (Filed Aug. 5, 1983), (August 2, 1983), Chiron Corp. Collection, Life Sciences Foundation Archives, San Francisco, CA. Following on the heels of Amgen's successful IPO, the Chiron share price ended

five full-time research personnel. It had positioned itself as an innovator of genetically-engineered substances in yeast, with a specific focus on vaccines and related diagnostic tests, hormones, and therapeutic enzymes. Rutter explained, "We are also vigorously expanding our activities in manufacturing based upon what we feel is the technological leadership in the use of yeast as a commercial organism and the development of several processes involving this organism."[195] Chiron would leverage a system of single-celled factories for rapid reproduction and commercial scalability of its products.

Chiron's prospectus outlined the company's expected progress under two categories. In the research phase, Chiron's researchers would aim for expression of desirable proteins in microbial cells. In the development phase, they would work to improve yields and purities, sell the products for research purposes, or deliver them to contracting sponsors for testing. The company would act as a virtual corporation and form partnerships with large pharmaceutical companies for later-stage marketing, sales, and distribution.[196] In the case of HBV, this meant that Merck would test the biological activity of yeast-produced HBsAg, first in mice, grivet

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up lower than initial filing expectations. See Chiron Corp. Files Offering of 2 Million Common Share, (June 14, 1983), Chiron Corp. Collection, Life Sciences Foundation, San Francisco, CA. Some saw this signal the end of runaway investor speculation in biotech. In Rasmussen, *Gene Jockeys: Life Science and the Rise of Biotech Enterprise*, 122. Rutter found the SEC filing process frustrating, but said that the money they did raise from going public was very helpful. Chiron had an annual budget of $7 million. William J. Rutter, Correspondence F 1971-1990, (January 24, 1984), Box 1 of 13, Subgroup I, Series I, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[195] Rutter, Correspondence F 1971-1990, (January 24, 1984), Box 1 of 13, Subgroup I, Series I, William Rutter Papers MSS 94-54.

[196] Penhoet explained that the company relied on industry partners to handle the promotional aspects of the work. "We don't turn out a hepatitis B vaccine," Penhoet said. "We turn out the enabling technology." In Lawrence M. Fisher, "Biotechnology Spotlight Now Shines on Chiron," *The New York Times*, October 13, 1986. "Over the years we've more often than not been criticized for the extent to which we work with other companies rather than doing it ourselves," he was quoted as saying. In Lawrence M. Fisher, "A New Model for Biotechnology," *The New York Times*, April 4, 1993.

monkeys and chimpanzees, and then in human clinical trials.[197] Merck had the upper hand in these initial dealings with Chiron, and Rutter was discouraged from pursing testing with other collaborators.[198] Within three months of testing the experimental vaccine on thirty-seven Merck employee-volunteers, eighty to one hundred percent of participants had produced antibodies specific to HBsAg with no serious reactions.[199] Immunogenicity of the product appeared to be equivalent to mammalian-derived antigen.[200] Chiron was forced into a lower royalty rate agreement with Merck when it looked like the vaccine might actually be successful.[201] In June 1984, the researchers announced that the candidate vaccine had a protective effect against HBV. They anticipated that the first experimental vaccine made by gene-splicing methods would be available in two or three years at a yet-undetermined price.[202]

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[197] *Biotechnology News: A Biweekly Newsletter*, vol. 1 (Summit, NJ: CTB International Publishing Co., 1981).

[198] Rutter, Research, Merck, Correspondence (5), 1981-1987, (February 2, 1982), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54.

[199] Galambos and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*, 203.

[200] Illman, "Pathbreakers: 1981 - a Triumph of Biotechnology." The blood-derived HBsAg particle had been 1,000-fold more immunogenic than unassembled HBsAg protein produced by bacteria, but the immunogenicities of the yeast-derived and mammalian-derived HBsAg were comparable, and presented “no a priori reason for choosing one system over the other.” In Y. Chiu, *Drug Biotechnology Regulation: Scientific Basis and Practices* (Taylor & Francis, 1991), 361.

[201] Merck gave Chiron an ultimatum: “you can either participate with us at this lower royalty rate or fight us. But if you fight us, you have a much smaller set of resources; you are much more vulnerable to externalities”, such as the desire to seek public market financing. Chiron accepted the lower rate. In William G. Green, interview by Sally Smith Hughes, 2005, "General Counsel Chiron Corporation," Berkeley, CA, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

[202] In E. M. Scolnick et al., "Clinical Evaluation in Healthy Adults of a Hepatitis B Vaccine Made by Recombinant DNA," *JAMA* 251, no. 21 (1984). See also Harold M. Schmeck, "Hepatitis Vaccine Produced by Gene-Splicing," *The New York Times*, June 1, 1984. Some hoped for a price as low as $1 per dose to enable access in developing nations. In Michael Waldholz, "Vaccine Produced by Genetic Process Is Tested on Humans," *The Wall Street Journal*, June 1, 1984.

To prepare for mass market production, Merck needed to begin a scale up of Chiron's experiments. As a representative from Novo Nordisk who had overseen early production of the company's yeast expression of insulin explained, "Accurate scaleup… is of paramount importance for the final economy." Over a two-year period, Novo Nordisk had scaled up accurately and incrementally from 1-liter batches of insulin to 80m^3 in the final production, and did so while simultaneously constructing its primary fermentation facility.[203] Accurate scale up was important if Merck was going to keep the recombinant vaccine cost low. While the company initially lacked the facilities for large-scale production of recombinant yeast, Merck discovered ways to preserve the cultures, diversify the strains used in production, and develop the process for large-batch fermentation.[204] Chiron, too, developed its capacity to test large batches of insulin-like growth factor. By the mid-1980s, the company had acquired 10-liter, 200-liter, and 4,000-liter fermenters.[205]

Large-scale yeast production with mass fermentation tanks was challenging, but there was the extensive experience of others to draw upon.[206] "Many of the techniques which are now recognized as essential to the modern subject of biotechnology such as the development and

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[203] Chiu, *Drug Biotechnology Regulation: Scientific Basis and Practices*.

[204] Galambos and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*, 203. The strains are described in Rutter et al. Synthesis of Human Virus Antigens by Yeast. See also William J McAleer et al., "Human Hepatitis B Vaccine from Recombinant Yeast," (1984).

[205] The largest fermenter had been an ethanol production facility. "The fermenters were not even designed for sterile operation. We had a hell of a time getting those to go… For that kind of fermentation capacity you'd pay many millions of dollars. We couldn't afford it at the time. We made do with what we had." In Carl J. Scandella, interview by Mark Jones, August 28, 2013, "Oral History with Carl Scandella," San Francisco, CA, Life Sciences Foundation.

[206] For example, "One of the major problems in scale up of a fermentation process is that when the fermenter increases in size, the oxygen transfer, the mixing capability, and the removal of heat, all become more and more limited. One the other hand, in large-scale production the measurement and the control of flow and other parameters becomes easier." In Chiu, *Drug Biotechnology Regulation: Scientific Basis and Practices*, 172.

storage of industrial strains of micro-organisms, the use of fed-batch cultures, the use of continuous culture and tower fermenters, have found an early application in yeast industries," wrote one observer in the early 1980s.[207] Existing equipment could be adapted to new purposes. In April 1983, for example, Interferon Science signed a three-year, six million dollar contract with Anheuser-Busch Companies to make available a modern fermentation pilot plant for yeast-based interferon production out of the company's beer brewing facilities.[208]

Efforts to scale up also meant achieving compliance with industrial containment rules for recombinant microorganisms. Asilomar had raised concerns about the uncontrolled release of genetically modified organisms and the spread of dangerous molecules.[209] The NIH guidelines, which had prohibited experiments using greater than ten liters of culture, also assumed that large-scale processes were inherently riskier and required more stringent containment unless the rDNA was rigorously characterized to establish the absence of harmful sequences.[210] While the guidelines were later revised to allow appeals for exceeding this limit, it was not until 1987 that recombinant organisms could be used under the same conditions as those required for unmodified organisms.[211]

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[207] Berry, *Biology of Yeast*, 57.
[208] "Interferon Pact with Anheuser," *The New York Times*, April 29, 1983.
[209] Rose, *The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century*, 15.
[210] M. K. Turner, "Categories of Large-Scale Containment for Manufacturing Processes with Recombinant Organisms," *Biotechnology and Genetic Engineering Reviews* 7, no. 1 (1989): 7.
[211] The NIH advisory committee had been taking applications from industry for large-scale production since September 1979, although the committee had no familiarity with large-scale fermentation until a technology expert was appointed in January 1981. In *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*, 212. As late as 2012, Valenzuela argued that there could be no guarantee about the safety of transgenic organisms. "Anything can happen. This is the basis of science. And doubt everything." In *La Belleza De Pensar*, Pablo Valenzuela, destacado científico Chileno premio nacional de ciencias aplicadas, April 15, 2012, Canal 13C, 50:15.

For most of the decade, the NIH offered three categories of containment for large-scale genetic research. By this later period, yeast expression systems could be used under the lowest physical containment level, P1, which required "good laboratory procedures, trained personnel, [and the decontamination of] wastes." The biological containment level, HV1, also required use of "weakened strains of micro-organisms that are less able to live outside the laboratory."[212] Internationally, the Organization for Economic Cooperation and Development (OECD) had similar requirements for the use of recombinant yeast. OECD emphasized Good Industrial Large Scale Practice (GILSP), which drew heavily on the rules of Good Manufacturing Practice for containment as a means to ensure safe processing and quality control of the product.[213] The lowest OECD category for yeast proposed a closed system of primary containment and the inactivation of cultures before their planned release as wastes and in airborne emissions.[214]

Accurate scale up also required consistency of the product since the start of fermentation in large-scale facilities typically used the inoculation of cells from a master seed stock of culture. The FDA approval process required proof of genetic stability in this single-transformant colony.[215] Recombinant yeast culture was grown in stirred tank fermenters until it could be

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[212] *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*, 213.

[213] In the UK, the Advisory Committee on Genetic Manipulation (ACGM) issued rules for Good Large Scale Practice (GLSP), "the adjective 'Industrial' being dropped to emphasize the need for its application wherever large-scale processes are carried out", which included laboratory-scale reaction vessels, pilot plant work and commercial manufacture. In Turner, "Categories of Large-Scale Containment for Manufacturing Processes with Recombinant Organisms."

[214] Accidental release was also addressed by the commission, and continued to raise concern at the end of the decade. "It is almost as if, having raised the concept of biological containment, we are not prepared to believe in it as a practical method of control," wrote one analyst. As for physical containment, materials and personnel needed to cross the containment barrier making the closed system "a figment of our imagination." In ibid.

[215] Manufactures did not necessarily maintain their own master seed stock. Tiger beer, for example, used a special strain of yeast shipped on ice to Singapore from Heineken's Dutch laboratories in a vacuum-sealed stainless-steel cylinder. In Patricia Wells, "The Favorite Brew of Singapore," *The New York Times*, June 12, 1983.

harvested, washed, and ruptured using high pressure. Unlike liver cells which secreted HBsAg, yeast accumulated the antigen intracellularly until it was later engineered to discharge the product.[216] To make the vaccine, antigen had to be collected, purified and preserved.[217] Each lot was then quality controlled for consistency, and tested for safety in mice and guinea pigs. Finally, there was the FDA approval process, but yeast's long history as a food product suggested that it might "be free from government health-related constraints which govern many such new products."[218]

Safety was a primary concern in these efforts to manufacture recombinant molecules on a commercial scale. Scientists of the early 1980s believed that the yeast *S. cerevisiae* had no pathogenic relationship to man, unlike the bacteria *E. coli*, or mammalian cells which could have the problems of retroviruses or potential tumorigenicity.[219] Because yeast had been genetically modified for centuries in traditional agricultural practices without any special concern about variation, some analysts assumed there was no reason to expect greater problems from the genetic engineering of well-characterized and specific modifications.[220] When later asked by Merck to comment about the potential danger of working with genetically-engineered yeast to produce the HBsAg particles, Rutter wrote that not only did specific use of the surface antigen sequence eliminate the risk of viral infection, but, with respect to dealing with the host organism, "People have been known to eat baker's yeast in quantity over the years. As far as one can tell it

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[216] Chiu, *Drug Biotechnology Regulation: Scientific Basis and Practices*, 363-364.
[217] Galambos and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*, 203.
[218] S.K. Harlander et al., *Biotechnology in Food Processing* (Noyes Publications, 1986), 97.
[219] In J. Mellor et al., "Efficient Synthesis of Enzymatically Active Calf Chymosin in Saccharomyces Cerevisiae," *Gene* 24, no. 1 (1983): 1.
[220] W. J. Brill, "Safety Concerns and Genetic Engineering in Agriculture," *Science* 227, no. 4685 (1985): 384. As a common constituent of many diets, yeast was seen as especially compatible with food processing. See C. G. Goff et al., "Expression of Calf Prochymosin in Saccharomyces Cerevisiae," *Gene* 27, no. 1 (1984): 45.

is completely innocuous."[221] Prior mass consumption was a good indicator of future safe consumption of yeast products.

This same period witnessed a surge of interest in the possibility that certain yeast species caused certain human diseases. These questions echo the tensions characterizing the study of yeast models and yeast cell factories in terms of the molecular relationship between species, and whether yeast and humans were merely related or definitely intra-active.[222] In the early 1980s, a handful of medical reports that *Saccharomyces cerevisiae* had caused human diseases and contributed to death by other causes led scientists of the Veterans Administration to claim by 1984 that "*S. cerevisiae*, when found in culture material, can no longer be confidently dismissed as a nonpathogen, especially in debilitated patients."[223] Many early AIDS cases were being identified by the opportunistic cryptococcosis infection caused by a pathogenic strain of yeast. In September 1981, *Freeman Reports* aired an interview on health problems related to another pathogenic strain - the infectious *Candida albicans*. Following the cable broadcast, conferences on the "yeast-human interaction" were held in Dallas and Birmingham, and books describing a yeast syndrome, such as "The Missing Diagnosis" and "The Yeast Connection," found their way into the popular press.[224] In addition to vaginal and oral thrush, a number of common health problems, including chronic fatigue, anxiety, acne, allergies, heartburn, migraine, and muscle

[221] William J. Rutter, Research, Merck, Correspondence (5), 1981-1987, (November 24, 1981), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.
[222] On "intra-activity" see Karen Barad in Juelskjær and Schwennesen, "Intra-Active Entanglements–an Interview with Karen Barad," 20.
[223] R. H. Eng et al., "Saccharomyces Cerevisiae Infections in Man," *Sabouraudia* 22, no. 5 (1984): 407.
[224] The latter noted that, "even today… summer, 1983… only scant additional medical references are available to help physicians seeking further information. Yet, during the years, 1981-1983, interest in the relationship of Candida albicans to human illness skyrocketed." In William G. Crook, *The Yeast Connection: A Medical Breakthrough*, 2nd ed. (Jackson, Tenn.: Professional Books, 1984), 271; C.O. Truss, *The Missing Diagnosis* (Missing Diagnosis, Incorporated, 1983).

ache, were attributed to overgrowth of the organism in the human body. These global symptoms were said to be alleviated by dietary choices in the controversial new "*Candidiasis* hypersensitivity syndrome" (later rejected by mainstream physicians).[225] The onset of a public "*Candida* consciousness" raised an important question in this period about the reciprocal and sometimes troubling relationship of humans and yeast, which was often not differentiated by strain in the public consciousness: who consumed whom?[226]

While proponents of the unsupported *Candida* diagnosis held that the untempered bloom of intestinal flora was a problem of modernity associated with stress, birth control pills, sugary diets and overuse of broad-spectrum antibiotics, recombinant microbes of the 1980s hit upon a further "problem" of late-stage capitalism – that of overconsumption.[227] "Growth in microbes can make scarce substances plentiful, but that very abundance can cause other problems," reported the *New York Times* in 1984. "Bacteria can make human growth hormone on such a mammoth scale that doctors are worried there may actually be too much - so much it might be used indiscriminately at the insistence of parents who want their perfectly normal children to be

[225] In 1986, the American Academy of Allergy and Immunology issued a statement that the proposed candidiasis hypersensitivity syndrome was a concept that was "speculative and unproven." See John A. Anderson et al., "Candidiasis Hypersensitivity Syndrome: Approved by the Executive Committee of the American Academy of Allergy and Immunology," *Journal of Allergy and Clinical Immunology* 78, no. 2 (1986).
[226] See Homei and Worboys, *Fungal Disease in Britain and the United States 1850-2000: Mycoses and Modernity*, 88.
[227] On politics of birth control consumption in the 1980s, Elizabeth Watkins has related American attitudes on abortion and the need for barrier methods of protection against HIV and AIDS to the lack of pharmaceutical innovation for oral contraceptives during this period. In Elizabeth Siegel Watkins, "How the Pill Became a Lifestyle Drug: The Pharmaceutical Industry and Birth Control in the United States since 1960," *American Journal of Public Health* 102, no. 8 (2012): 1466.

a little, or even a lot, taller than nature would have them."[228] Following initial transformation of the cell, yeast was expected to produce exponential amounts of HBsAg as the cells divided.[229]

The Yeast-Made Human

Merck received a U.S. commercial license for Recombivax HB in July 1986 and the HBV vaccine joined other FDA-approved recombinant products already on the market.[230] Human insulin, human growth hormone, and alpha interferon had each applied the "theoretical knowledge" of genetic engineering for intended therapeutic use.[231] Recombivax HB was publicized widely as the world's first genetically-engineered vaccine against a human disease, the first vaccine against a sexually transmitted disease, and the first vaccine against a virus that leads to human cancer.[232] It was also the first vaccine made in yeast. Other companies had already produced the first recombinant vaccines for animal health using *E. coli*. Genentech had developed a vaccine against a livestock strain of foot-and-mouth disease in June of 1981, and the Norden Laboratories unit of SmithKline Beckman Corp. had licensed their technology to Cetus Corp. for a vaccine to prevent a fatal diarrheal disease of newborn pigs.[233]

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[228] Harold M. Schmeck, "Strange Alliance: Legions of Bacteria Created to Serve Man," *The New York Times*, January 3, 1984. On the politics of human growth hormone production for the treatment of short stature see Aimee Medeiros, *Heightened Expectations: The Rise of the Human Growth Hormone Industry in America* (Tuscloosa: University of Alabama Press, 2016).
[229] Galambos and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*, 197-198.
[230] It was licensed by the West German government in May of 1986. Ibid.
[231] "The New Age of Vaccines," *The New York Times*, August 16, 1986.
[232] Illman, "Pathbreakers: 1981 - a Triumph of Biotechnology."
[233] Genentech collaborated with U.S. Department of Agriculture (USDA) biochemist Howard Bachrach, who had demonstrated animal immunity with the viral surface protein in 1975 at the Plum Island Animal Disease Center, a high-security federal facility off the Long Island coast. Genentech handled the recombinant aspects of the project in California, and in exchange received patent and manufacture licensing rights. USDA Secretary John Block declared that the breakthrough would amount to "annual savings of billions of dollars and an increase in the

Following market entry of Merck's Recombivax HB, multiple other recombinant vaccines for HBV entered animal and human testing. Analysts forecasted "a limited number of big winners in this race to market." There would only be room for three or four players once high-risk populations had been vaccinated, a *Nature Biotechnology* article predicted.[234] Biogen together with University of Edinburgh scientists, the Wellcome Foundation and Green Cross Corp. had promised yeast-made HBV vaccine as a cheaper and "less dangerous" alternative to blood.[235] Amgen was collaborating with Johnson & Johnson, and toward the end of the decade the Salk Institute, working with Phillips Petroleum, used an alternative yeast species, *Pichia pastoris,* to achieve higher yields of the antigen.[236] Another yeast-made recombinant HBV vaccine, SmithKline Beechman's Engerix-B, emerged as a serious global competitor to Merck's Recombivax HB.[237] Three additional yeast-derived HBV vaccines received FDA marketing

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world's supply of meat." For his efforts, Bachrach was awarded the National Medal of Science in 1983. See Jeremy Pearce, "Howard L. Bachrach, 88, Early Polio Researcher, Is Dead," *The New York Times*, July 25, 2008; "Gene Splicing Produces Safe Foot and Mouth Vaccine," *The San Bernardino County Sun*, June 19, 1981; "Hoof and Mouth Vaccine Developed," *Del Rio News Herald*, June 21, 1981; Harold M. Schmeck, "Vaccine Developed by Genetic Splicing," *The New York Times*, June 19, 1981; Waldholz, "Vaccine Produced by Genetic Process Is Tested on Humans."

[234] Arthur Klausner, "Who Will Win the Race to Market Hepatitis B Vaccine?," *Nature Biotechnology*, no. 2 (1984): 40.

[235] See Robert Cooke, "New Gene Vaccine for Hepatitis," *Boston Globe*, July 20, 1983; Robert Cooke, "New Hepatitis B Vaccine Ready for Test on Humans," *Boston Globe* 1983.

[236] Jennifer Van Brunt, "Hepatitis B Vaccine Makers Multiply," *Nature Biotechnology* 5 (1987); Waldholz, "Vaccine Produced by Genetic Process Is Tested on Humans." See also the description of *Pichia pastoris* in Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 60.

[237] Galambos and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*, 205. Smith, Kline and French had launched their vaccine in Singapore in 1986, and was planning that year "to transfer the technology to the Third World, rather than the product." In Gail Vines, "Drug Firms Vie over Hepatitis Vaccine," *New Scientist*, September 4, 1986.

approval in the form of combination products against multiple viruses and were recommended for use first recommended in high-risk adult groups, and later for newborns and children.[238]

Merck had initially assessed three doses of Recombivax HB at the same price as Heptavax-B, and promised a price reduction as "prolific yeast" made it easier to mass-produce the recombinant version and to recover the costs of development.[239] The price dropped marginally, but yeast economies of scale did not significantly factor into price reductions for consumers.[240] By the early 1990s, sales of recombinant vaccines demonstrated commercial profitability on par with pharmaceuticals and far outpaced the typically low margins of the classical vaccine industry.[241]

Scientists looked to other expression systems in pursuit of alternative HBV vaccines. Both the Pasteur Institute and Genentech (the latter with Mitsubishi Chemical and the Merieux Institute) used Chinese hamster ovary (CHO) cells with the expectation of higher immunogenicity since the cells were from complex eukaryotes. Mammalian cell cultures were more expensive, however, and difficult to keep alive.[242] Integrated Genetics used mouse cells

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[238] Annually, nearly two million Chinese children were infected with HBV in the early 1990s. In one $7 million technology transfer deal, Merck worked with the Chinese government to develop two state-of-the-art recombinant plants that would produce enough vaccine for all of China's newborns. In Vagelos and Galambos, *Medicine, Science and Merck*. See also D. Barboza, "China Investigates Vaccine Maker after Deaths of Infants," *The New York Times*, December 25, 2013. These combination vaccines are GlaxoSmithKline's Hepatitis A/B vaccine Twinrix, Diphtheria/Tetanus/Pertussis/Hepatitis B/Poliovirus vaccine Pediarix; and Merck's Haemophilus influenzae type b/Hepatitis B vaccine Comvax.

[239] Janice Castro, "A Breakthrough for Biotech," *TIME*, August 4, 1986.

[240] Galambos and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*, 206.

[241] Chiron's royalty payments for HBV vaccine remained a modest 8-10 percent of revenues. In Green, "General Counsel Chiron Corporation." See also Fisher, "Biotechnology Spotlight Now Shines on Chiron."; "New Vaccine Star Is Born," *Industry Week*, August 4, 1986.

[242] Genentech offered this CHO expression system to Merck while the company was collaborating with Chiron and University of Washington scientists. When Ammerer was able to raise the level of yeast expression, Merck lost interest. In Hall, "Oral History with Ben Hall."

and a bovine viral vector.[243] Even the New York State Health Department had entered the race with the development of a canary pox vector by its for-profit subsidiary Virogenetics Corp.[244]

Continuous with the development of other systems, therapeutic claims for yeast biotechnology were wide ranging and extended to a number of clinical areas. They included such molecular possibilities as the use of yeast dental implants to grow cloned enamel in cavities for the "end of most tooth decay."[245] Over the course of the 1980s and into the 1990s, other therapeutic claims for yeast biotechnology included the successful manufacture of several interferons, α*1*-antitrypsin for treatment of the hereditary protein deficiency, human epidermal and human *platelet-derived growth factors* for soft-tissue repair, Epstein-Barr envelope protein as a vaccine candidate against the virus, human superoxide dismutase for prevention of tissue damage, human serum albumin to restore blood volume after blood loss, human insulin for treatment of diabetes, Malaria vivax CS protein for a viral vaccine, and hirudin as an anticoagulant.[246] Chiron used yeast to develop screening tests for Hepatitis C and HIV.[247] In

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Ammerer had developed a new promoter to give high expression levels when the cells grew in high densities. The resulting production level gave several hundred doses of HBsAg vaccine from one liter of yeast cells. In Wilson, "Engineering Tomorrow's Vaccines," 31.

[243] N. Hsiung et al., "Efficient Production of Hepatitis B Surface Antigen Using a Bovine Papilloma Virus-Metallothionein Vector," *J Mol Appl Genet* 2, no. 5 (1984).

[244] See a description in B. Brotman and A.M. Prince. Nucleic Acid Based Immunotherapy of Chronic Hepatitis B Infection. 2004.

[245] Richard D. Lyons, "End of Most Tooth Decay Predicted for near Future," *The New York Times*, December 20, 1983.

[246] See Hitzeman et al., "Expression of a Human Gene for Interferon in Yeast."; MF Tuite et al., "Regulated High Efficiency Expression of Human Interferon-Alpha in Saccharomyces Cerevisiae," *The EMBO journal* 1, no. 5 (1982); R. Derynck, A. Singh, and D. V. Goeddel, "Expression of the Human Interferon-Gamma Cdna in Yeast," *Nucleic Acids Res* 11, no. 6 (1983); R. Kramer. Novel Vectors for Interferon Expression. 1984; T Cabezón et al., "Expression of Human Alpha 1-Antitrypsin Cdna in the Yeast Saccharomyces Cerevisiae," *Proceedings of the National Academy of Sciences* 81, no. 21 (1984); A. J. Brake et al., "Alpha-Factor-Directed Synthesis and Secretion of Mature Foreign Proteins in Saccharomyces Cerevisiae," *Proc Natl Acad Sci U S A* 81, no. 15 (1984); L. D. Schultz et al., "Expression and Secretion in Yeast of a 400-Kda Envelope Glycoprotein Derived from Epstein-Barr Virus," *Gene*

2006, the yeast-based expression of human papillomavirus resulted in market approval of one of the best-selling vaccines of all time, Merck's Gardasil, which had licensed Hall's expression technology.[248] In 2013, *S. cerevisiae* biotechnology continued to make up twenty percent of the biopharmaceutical marketplace, but was by then outpaced by *E. coli* at thirty percent and mammalian cell cultures (primarily CHO cells) at forty.[249]

Apart from therapeutic development, yeast cloning was done routinely to diagnose the function of human and other genes. When more than six hundred scientists applied to attend the 1983 Cold Spring Harbor Meeting on the Molecular Biology of Yeast, for example, it was said to represent "both the proliferation of the laboratories and the rapid progress in application of molecular approaches to a variety of biological problems in yeast" using routine engineering approaches.[250] Applications of yeast biotechnology also extended outside of biological research. Yeast was used to produce glucoamylase as a biocatalyst in the food industry, for example, as

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54, no. 1 (1987); Robert A Hallewell et al., "Amino Terminal Acetylation of Authentic Human Cu, Zn Superoxide Dismutase Produced in Yeast," *Nature Biotechnology* 5, no. 4 (1987); S. M. Kingsman et al., "High-Efficiency Yeast Expression Vectors Based on the Promoter of the Phosphoglycerate Kinase Gene," *Methods Enzymol* 185 (1990); A. Smith, *Gene Expression in Recombinant Microorganisms* (Taylor & Francis, 1994).

[247] Chiu, *Drug Biotechnology Regulation: Scientific Basis and Practices*. Early on, Chiron also hoped that yeast would be capable of manufacturing a vaccine against HIV/AIDS, the link between which had not yet been definitely established. See Richard Levine, "Genetic Progress in Aids Research," *The New York Times*, September 16, 1984.

[248] Merck cloned and expressed the human papillomavirus 6a (HPV6a) genome in yeast in 1995. See Kathryn J Hofmann et al., "Sequence Determination of Human Papillomavirus Type 6a and Assembly of Virus-Like Particles in Saccharomyces Cerevisiae," *Virology* 209, no. 2 (1995). The vaccine which resulted was approved for use in select clinical populations as a measure for cervical cancer prevention. In Timmerman, "Uw's Gardasil Connection Generates Windfall for Research, Tech Transfer." In 2013, worldwide sales of Gardasil were more than $2.1 billion. See Merck & Co. Inc., "Annual Report: Form 10-K for the Period Ending December 31, 2013 (Filed Feb. 27, 2014)," accessed May 27, 2014, www.merck.com.

[249] Jens Nielsen, "Production of Biopharmaceutical Proteins by Yeast: Advances through Metabolic Engineering," *Bioengineered* 4, no. 4 (2013): 207.

[250] *Annual Report*, (New York: Cold Spring Harbor Laboratory, 1983), 119.

well as a rennin for cheese making.[251] Recombinant techniques for strain improvements were incorporated into the yeast-based industries in the early 1980s.[252] In August 1983, for example, Guinness & Co. was reportedly constructing yeast-based solution to a common contamination problem in their Dublin stout-brewing process. A recombinant yeast strain was hoped to save the company tens of thousands of pounds, but would have to show that it could ferment the company's beer acceptably. Guinness was also concerned with the FDA approval process to import a beer containing leftover recombinant yeast as part of the final product.[253] It was hoped that recombinant methods might be used to explore variation among the strains of *Saccharomyces cerevisiae* for possible agricultural or other commercializable utility since this gene pool was "wide, deep, and almost unplumbed."[254] By the end of the decade, the launch of

[251] The FDA approved *E. coli*-derived chymosin as the first enzyme for food use in March of 1990. By 2006, the recombinant product was estimated to have up to 80 percent of the global market share. In M. E. Johnson and J. A. Lucey, "Major Technological Advances and Trends in Cheese," *J Dairy Sci* 89, no. 4 (2006): 1167; Mellor et al., "Efficient Synthesis of Enzymatically Active Calf Chymosin in Saccharomyces Cerevisiae," 13. For recombinant yeast-based production of chymosin, see Edward Yoxen, *The Impact of Biotechnology on Living and Working Conditions - Consolidated Report* (Luxembourg: Office for Official Publications of the European Communities, 1987), 56; Goff et al., "Expression of Calf Prochymosin in Saccharomyces Cerevisiae," 35-36. On glucoamylase, see M. A. Innis et al., "Expression, Glycosylation, and Secretion of an Aspergillus Glucoamylase by Saccharomyces Cerevisiae," *Science* 228, no. 4695 (1985).

[252] In Timberlake, *Molecular Genetics of Filamentous Fungi: Proceedings of a UCLA Symposium Held in Keystone, Colorado, April 13-19, 1985*, 345. See also J. F. Spencer and D. M. Spencer, "Genetic Improvement of Industrial Yeasts," *Annu Rev Microbiol* 37 (1983): 123.

[253] The contamination problem was related to glucan formation. "Guinness, which is reluctant to add anything extraneous to its dark beer, ordinarily relies on the β-glucanase activity of its malted barleys to degrade the glucans. If an engineered yeast could be used to control glucan formation, then Guinness could use more of the cheaper unmalted barley." In John Henahan and Arthur Klausner, "Guinness Brewing New Yeast," *Nat Biotechnol* (1983): 463.

[254] Spencer and Spencer, "Genetic Improvement of Industrial Yeasts," 139. See also Chiu, *Drug Biotechnology Regulation: Scientific Basis and Practices*, 17; G. Gellissen and C. P. Hollenberg, "Application of Yeasts in Gene Expression Studies: A Comparison of Saccharomyces Cerevisiae, Hansenula Polymorpha and Kluyveromyces Lactis -- a Review," *Gene* 190, no. 1 (1997).

genome sequencing projects on multiple species would include the full-scale diagnosis of the *Saccharomyces cerevisiae* genome of wild-type strain S288C.

Although Merck's HBV vaccine continues to be produced in yeast, several problems were identified with yeast recombinant therapeutics over the course of the 1980s. Yeast did not always make enough of a desired product to make extraction feasible and some yeast protein secretion could trigger undesirable human immune response.[255] Already by the mid-1980s, genetic engineers began to relax their claims of the exceptionalism of yeast-made molecules. Yeast had "not lived up to its promise," according to a senior scientist at Hall's Seattle-based startup, Zymos (then Zymogenetics Inc.), and the company which had started out as specializing in yeast was forced to diversify its pipeline. Biotech leaders at Genentech and Cetus Corporation said publically, as Chiron's vaccine technology was being shepherded to market in 1985, that they preferred to let the product dictate the choice of host production system. "I'd hate to be a company dedicated to yeast qua yeast," Cetus chairman Ronald Cape said. "'That's the tail wagging the dog."[256]

Yeast was not the first, the best, nor the only scalable organism for genetic engineering projects of the 1980s. However, as a well-defined model eukaryotic cell, it had helped to advance a process of molecularization in the 1970s which could conceive of molecules made by other organisms as homologically human.[257] At the start of the 1970s, genetic engineering technologies

[255] Immunogenic yeast secretion is described in David Botstein and Gerald R Fink, "Yeast: An Experimental Organism for 21st Century Biology," *Genetics* 189, no. 3 (2011): 702.
[256] Andrew Pollack, "Cell Cultures as 'Factories'," *The New York Times*, July 18, 1985.
[257] Pablo Valenzuela recently defended yeast's likeness to higher organisms, explaining, "One of the easiest organisms to study how the cell functions, in a cell very similar to human cells, at a complex level, is yeast. Yeast isn't a bacteria. It has a series of characteristics which make it more like man than bacteria, in spite of the fact that they are pure cell - a single-celled organism… In a plural organism there are a series of [developmental] changes but as a cell, yeast

physically liberated eukaryotic molecules and raised fears about potentially hazardous molecular exposures for humans. Yeast offered particular advantages for this science in the latter half of the 1970s as a culturally-familiar industrial and experimental organism generally recognized as safe.

Mimicry was one basis for the safety claims of recombinant experiments. In November 1977, Rutter wrote a high school student correspondent:

> It is frequently asked whether there are ethical problems involved in this research. The issues center about whether it is "ethical" to tamper with the genes of biological systems including our own. For me, this connotes a strange use of the word ethics. Genetic recombination among organisms occurs in nature. We mimic this process and remove the usual species barrier. These experiments should provide new knowledge, some of this knowledge may be of extraordinary value to humankind.[258]

Rutter's understanding of genetic engineering had undergone a shift by this time from a method to produce theoretical knowledge to a method to pursue applied value. He had long been interested in the applied benefits of eukaryotic molecular biology and had set up his department in San Francisco for this purpose. In May 1977, he had been surprised by the commercial attention his team received following their successful bacterial cloning of the rat insulin gene. "In the end, I learned there was intense interest in the technology as a process which could be scaled to any demand," he recalled.[259] He recognized the opportunity to scale up and worked to establish a nonprofit technology transfer group at the University of California, San Francisco, and later entered the "mad scramble for equity."[260] Hall had recognized the political benefits of

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is like man." In *La Belleza De Pensar*, Pablo Valenzuela, destacado científico Chileno premio nacional de ciencias aplicadas, April 15, 2012, 13C, 50:15.

[258] William J. Rutter, Correspondence: High School Students Information Requests, (November 8, 1977), Box 1 of 13, Subgroup I, Series I, William Rutter Papers MSS 94-54 University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[259] Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco."

[260] Biological research had enormous commercial potential, Rutter later said, and even "the poorer educational institutions have been enticed into considering the possibility of joining the mad scramble for equity." In William J. Rutter, Correspondence K 1970-1991, (c. 1984,

applied science for public benefit and worked to convince his colleagues of the acceptability of biotechnical commercialization at the start of the 1980s as he took over leadership of Herschel Roman's department. He saw equal benefit in applied and theoretical knowledge of the eukaryotic cell, and began the biotech startup Zymos. But Hall did not work for there long. As he remembered it, "Happily for me, this adventure lasted only one year. I was just not cut out for work in industry."[261]

When genetic researchers envisioned yeast as a new and precise molecular means of recombinant protein production, it entailed a type of molecular work that one historian has described as "the 'intracellular' representation of an extracellular project."[262] Gene products, rather than mechanisms, were studied to further an understanding of the molecular functions of the eukaryotic cell. Seattle scientists developed a promoter of applied eukaryotic molecular biology with commercial potential not immediately apparent in other practices of genetic engineering, for example, like the mouse cell expression of HBsAg in France. U.S. biomedical research rewarded entrepreneurship and enabled new kinds of academic-industry partnerships as a result.

Process knowledge from the yeast-based industries enabled genetic engineers to move quickly into therapeutic production. Between the sixth (1971) and seventh (1983) editions of *Dictionary of the Fungi*, a new entry was made for "biotechnology," which included the application of fungi to manufacturing processes.[263] By this definition, the entry had been delayed

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Undated), Box 1 of 13, Subgroup I, Series I, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[261] Hall, "A Conversation with Industry Pioneer Dr. Benjamin Hall."

[262] Rheinberger, "Recent Science and Its Exploration: The Case of Molecular Biology," 7.

[263] G. C. Ainsworth and Guy Richard Bisby, *Ainsworth & Bisby's Dictionary of the Fungi*, 6th ed. (Farnham Royal: Commonwealth Agricultural Bureaux for the Commonwealth Mycological

since at least the nineteenth century, when fermentation was understood to be the work of the yeast organism.[264] Because industrial microbiology had long been concerned with high volume production of yeast cells and their products, engineers had many tools at their disposal to maximize the efficiency of recombinant cell factories. In 1979, for example, food technologist Emil Mrak of the University of California, Davis was invited to speak at the Cuban meeting of the United National Industrial Development Organization (UNIDO) on utilizing microorganisms of fermentation for pharmaceutical fermentation and economy of scale.[265]

With the synthesis of "human" interferon as the first commercially useful yeast-made protein, Hall's expression system became a patentable technology. This commercialization made his yeast promoter the "right tool" for Merck and the University of California, San Francisco's HBV project at the same time the AIDS virus made problematic the use of other mammalian cell systems for vaccine production. Rutter, Valenzuela and Penhoet built their new company on yeast's promise, knowing before the antigen had even been synthesized that use of the organism would mean business.[266] Three years after the recombinant HBV vaccine entered the market,

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Institute, 1971), 69; G. C. Ainsworth et al., *Ainsworth & Bisby's Dictionary of the Fungi (Including the Lichens)*, 7th ed. (Kew, Surrey: Commonwealth Mycological Institute, 1983), 53.

[264] As a living technology, yeast performed the labor of fermentation and produced more labor with economies of scale. "The worker becomes an ever cheaper commodity the more commodities he creates... Labor produces not only commodities; it produces itself and the worker as a *commodity*..." In Karl Marx, *Economic and Philosophic Manuscripts of 1844* (Start Publishing LLC, 2013).

[265] Emil M. Mrak, Regional Seminar on Industrial Application of Microbiology in the Pharmaceutical Industry, (1979), Box 75, Folder 12, Emil Mrak Papers (D-096), University of California, Davis Special Collections, Davis, CA.

[266] This attribution of agency builds on that previously ascribed to nonhuman actors such as viruses and infectious diseases. See William Hardy McNeill, *Plagues and Peoples*, 1st ed. (Garden City, N.Y.: Anchor Press, 1976); H. Zinsser, *Rats, Lice and History. Being a Study in Biography, Which, after Twelve Preliminary Chapters Indispensable for the Preparation of the Lay Reader, Deals with the Life History of Typhus Fever, Etc* (Boston, 1935); Alfred W. Crosby, *Ecological Imperialism: The Biological Expansion of Europe, 900–1900* (Cambridge University Press).

Chiron's scientists were reflecting: "Is there a line between industrial or applied research and academic or basic research? If so, nowhere is the distinction more nebulous than in yeast genetic engineering."[267]

In an effort to characterize his work as innovative, Rutter claimed in the early 1980s that the HBV yeast work "was really unpredictable," but "it came out about as well as we could possibly hope."[268] The resulting production of a human-like, immunogenic particle "was unexpected, and a spectacular result!"[269] Later, Rutter, Valenzuela, Hall and Ammerer entered into a patent dispute with Genentech scientists which made this very point. Just a few weeks after the Seattle-San Francisco patent filing on yeast-based HBsAg expression in August of 1981, Genentech filed a second patent on yeast-based HBsAg expression.[270] This placed the burden of proof on Genentech to show knowledge that yeast would produce HBsAg particles virtually identical to those found in human blood in advance of Rutter, Valenzuela, Hall and Ammerer's claim. Genentech lost the argument that "yeast, once transformed… necessarily produce[d the] particles" since they had conceded that, "One skilled in the art at the time this application was filed would not have been able to reasonably predict that HBsAg could be expressed by yeast and, even if this was reasonably predictable, would not have expected yeast to process and assemble HBsAg particles from virally-infected sources." When the case went to appeal,

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[267] P.J. Barr, A.J. Brake, and P. Valenzuela, *Yeast Genetic Engineering* (Butterworths, 1989), xvii.

[268] William J. Rutter, Research Project – Hepatitis 1972—1981, (September, 1981), Box 2 of 13, Subgroup 11, Series IIIa, William Rutter Papers MSS 94-54, University of California, San Francisco Archives & Special Collections, San Francisco, CA.

[269] Rutter, Research, Merck, Correspondence (5), 1981-1987, (February 2, 1982), Box 3 of 13, Subgroup 11, Series IIa, William Rutter Papers MSS 94-54.

[270] After the interferon collaboration with Hall, Genentech had used the yeast promoter in additional projects without his permission. See Kleid, "Scientist and Patent Agent at Genentech." When Genentech filed a similar patent on yeast-derived HBsAg, the patent office did not recognize the overlapping claims until 1985. It was at that point that Hall discovered the unapproved use of his clones. In Hall, "Oral History with Ben Hall."

this contradiction was used to determine that Genentech had had only a "bare hope" of yeast's ability to produce human-like particles, but this was insufficient to establish earlier conception. In March of 2001, the U.S. Court of Appeals found in favor of Rutter, Valenzuela, Hall and Ammerer.[271] In legal terms, it could not have been known in advance that yeast would make human-like particles.

In later years, Rutter argued that he deserved more of the credit for the yeast-based HBsAg expression technology than did Hall since the promoter component was really "non-proprietary." Other investigators had other promoters, but they just wouldn't collaborate. Rutter argued that, "Yeast turned out to be a good biological system to produce more complicated structures. But it was not an absolutely necessary component of the strategy."[272] In 1982, the Seattle-San Francisco researchers had reported yeast synthesis of the HBsAg with the expectation that "such particles can be formed in many other heterologous cell systems, perhaps even in bacteria."[273] Because the HBsAg sequence itself was thought to contain the instructions for particle assembly, the commercial innovation was seen to have derived from gene sequences with biomedical significance. In fact, yeast molecular biology had already turned toward biomedical applications of the eukaryotic cell more than a decade earlier to help define human molecules. That other cell types could contribute now to the commercialization of eukaryotic molecules was only testament to its influence.

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[271] "Ronald A. Hitzeman, Arthur D. Levinson, and Daniel G. Yansura, Appellants, V. William J. Rutter, Pablo D. T. Valenzuela, Benjamin D. Hall, and Gustav Ammerer, Appellees.," in *99-1604 (Interference No. 102,416)*, ed. United States Court of Appeals for the Federal Circuit (2001).
[272] Rutter, "William J. Rutter: Co-Founder and Chairman, Chiron Corporation," 47.
[273] Valenzuela et al., "Synthesis and Assembly of Hepatitis B Virus Surface Antigen Particles in Yeast," 350.

Epilogue

The advent of recombinant DNA technology was said to have revolutionized yeast genetics to allow for direct manipulation of the genome in ways more sophisticated than other eukaryotes and on par with phage and *E. coli*. In the early 1980s, many appreciated that yeast had been "prokaryoticized" as a general tool for the molecular biologist. Excitement over the new technology, however, obscured the larger transition which had occurred in biology since the 1960s. This "prokaryoticized yeast" was a reflection of "eukaryoticized" biology.

As a graduate student at Stanford University, biochemist Kevin Struhl had been the first to transform *E. coli* bacteria with yeast DNA in 1976.[1] He recalled that his motivation had been to extend the utility of the *E. coli* system to the study eukaryotic gene regulation.[2] In 1983, then on the Biological Chemistry faculty at Harvard Medical School, Struhl claimed that, "It is important to stress that although yeast genetics has been 'prokaryoticized', the organism itself is a eukaryote... Thus, yeast is useful for studying many basic questions in eukaryotic biology."[3] By the early 1980s, the study and manufacture of eukaryotic molecules, whether in bacterial, yeast, or mammalian systems, were the result of a biomedical research project that had produced eukaryotic molecules as human. Basic research on the yeast organism oriented to the problem of human disease had helped the gradual "eukaryoticization" of many systems by generating eukaryotic molecules and eukaryotic questions as a central focus of biology.

Since the earliest chemical studies of fermentation, yeast has been analogized to humans with implications for understanding and intervening in disease processes. Statistical methods and

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[1] Struhl, Cameron, and Davis, "Functional Genetic Expression of Eukaryotic DNA in Escherichia Coli."
[2] Kevin Struhl, "Q&A: Kevin Struhl," *Current Biology* 18, no. 1 (2008): R8.
[3] Struhl, "The New Yeast Genetics," 391.

microbiological techniques extended these analogies from cell culture to human tissues with implications for development and from cell culture to human populations with implications for evolution. The study of yeast in genetic terms rooted those analogies in the specificity of genes believed to offer unity to biology. From the mid-1960s, the yeast analogy to humans was then gradually extended through the homology of the eukaryotic cell until a political opportunity to analogize *humans to yeast* produced the rise of yeast model organisms and cell factories. These tools had been engineered to molecularize humans in a broader effort to reap societal benefit from American public investment in science and to fuel the economic engine of research as an industry in its own right.[4]

Since the end of the 1960s, yeast molecular biology has held a central position in academic and industrial biomedical research on the world stage. In the 1970s, this manifested in the development of genetic engineering methods and the beginnings of the biotech industry. By the end of the 1980s, the initiation of a yeast genome sequencing project opened the door to a number of additional ways for yeast science to model and engineer human health and disease. The *Saccharomyces cerevisiae* S288C genome was again subjected to extensive negotiations as it came to serve as an experimental standard in the Human Genome Project.[5]

[4] In 1966, Stephen Toulmin characterized science as a “tertiary industry” of post-manufacturing society, the outcome of which was not any specific output, but rather employment and prosperity for entire communities of scientists and nonscientists. See Toulmin, "The Complexity of Scientific Choice II: Culture, Overheads or Tertiary Industry?."

[5] Belgian yeast physiologist André Goffeau “began to advocate for sequencing the yeast genome in the middle 1980s, when many people were skeptical of (indeed, even hostile to) the idea that an organized effort to sequence the yeast genome was advisable.” He eventually convinced European colleagues and secured European Commission funding the project. In Mark Johnston, "The 2002 George W. Beadle Medal: Robert Mortimer and André Goffeau," *Genetics* 164, no. 2 (2003): 422-423; P. Goujon, *From Biotechnology to Genomes: The Meaning of the Double Helix* (River Edge, NJ: World Scientific Publishing Company, 2001), 369-420.

Sequencing the S288C Yeast Genome

The wild-type yeast genome was proposed as one of several model organisms that would be sequenced alongside the human genome as part of the Human Genome Project. Yeast geneticists played a large role in establishing the value of comparative analyses and helped to organize the project from its earliest days by arguing that U.S. federal support should elevate all areas of biology equally. David Botstein, one of the project's organizers, later explained that the "only way we had of really understanding what most of human genes do is to compare them to the mouse genes or the worm genes or the fly genes or the yeast genes."[6] The functional experiments that could be performed in these organisms could not be done in humans, genetic knowledge of whom was confined to epidemiologic study, clinical observation, and bench work with DNA samples.[7] In contrast, a vast quantity of data already existed on yeast gene function and had from the mid-1980s been deposited into the first data libraries, the European Molecular Biology Laboratory Databank and GenBank.

Sequencing of the S288C genome began in 1989, as a continuation of the mapping efforts begun by University of California, Berkeley biophysicist Robert Mortimer in the 1950s. James Watson, the newly-appointed National Institutes of Health (NIH) Associate Director of Genome Research, saw the Human Genome Project as the "redemption of a longstanding bargain" between scientists and the taxpayer who had supported biomedical research.[8] Watson offered to build a building for the yeast geneticists' sequencing efforts, but Botstein together with fellow yeast geneticists Ira Herskowitz and Ron Davis preferred the idea of a quasi-industrial academic

[6] Botstein, "Oral History Interview."
[7] Botstein, "Why Yeast?," 157.
[8] Harold M. Schmeck, "DNA Pioneer to Tackle Biggest Gene Project Ever," *The New York Times*, October 4, 1988.

base for the project. They talked about the possibility of leasing space from Genentech, but eventually a facility was established at Stanford.[9]

When the yeast sequence was finished in 1996, S288C became the first eukaryotic organism to have its genome sequenced and was found to contain 6,000 genes.[10] Six hundred scientists from over one hundred laboratories in Europe, the U.S., Canada and Japan had worked together cooperatively on what was then the world's largest decentralized experiment. The "open and cooperative" culture of the yeast model organism community and the coordinated efforts of these collaborators were held up as models that could help make future sequencing endeavors successful.[11] Yeast became the example of how to coordinate sequencing efforts in terms of the compilation, ownership, and storage of large genomic datasets.

As a model of eukaryotic cell biology, yeast had also yielded a number of technical approaches for the study and manipulation of molecules that were later applied to large-scale mapping efforts in other organisms. In the early 1980s, the synthesis of Yeast Artificial Chromosomes (YAC) permitted study of the malfunction of nuclear division during eukaryotic mitosis, with possible implications for human development, birth defects, and disorders such as Down's syndrome.[12] Later, the YACs were developed as a cloning technology to help map the genome of yeast and other organisms.[13] They were used for a time in human genome sequencing,

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[9] Edwards, Letter to Ira Herskowitz, (July 12, 1989), Carton 10 Correspondence A-Fi, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25); Botstein, "Why Yeast?," 161.
[10] Goffeau et al., "Life with 6000 Genes."; HW Mewes et al., "Overview of the Yeast Genome," *Nature* 387, no. 6632 (1997).
[11] For the common "open and cooperative" claim see Botstein and Fink, "Yeast: An Experimental Organism for Modern Biology," 1442.
[12] A. W. Murray and J. W. Szostak, "Construction of Artificial Chromosomes in Yeast," *Nature* 305, no. 5931 (1983); Walter Sullivan, "First Synthetic Chromosome Reported Made," *The New York Times*, September 18, 1983.
[13] Patricia Tekamp-Olson and Pablo Valenzuela, "Gene Expression and Engineering in Yeast and Other Fungi," *Current Opinion in Biotechnology* 1, no. 1 (1990): 31.

as a way of cloning and maintaining large segments of human DNA along the chromosomes.[14] The yeast two-hybrid system (Y2H) was developed as an approach for functionally characterizing proteins by looking at their interactions in yeast, and this too was adapted for later protein linkage mapping.[15]

Following completion of the yeast genome sequence, Herskowitz sensed an end to "business as usual" for yeast geneticists. "Society (the funding agencies)," he wrote, "will not support unlimited, detailed albeit marvelous studies of the eukaryotic cell. We yeast people must deliver, that is, contribute to learning about disease."[16] Future students of yeast molecular biology would be expected to interface with clinical and public health inputs, Herskowitz believed.

Following publication of the yeast sequence, the National Human Genome Research Institute (NHGRI) put out a call for proposals for "Large-scale functional analysis of the yeast genome." Investigators were encouraged to use "new, global approaches to the study of biological phenomena important for human health and disease, including cancer."[17] This call for "functional genomics" was the second phase of the genome projects. Sequencing had been sold to the taxpayer on the promise that it would yield functional information about the genome. Thus

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[14] U. J. Kim et al., "Stable Propagation of Cosmid Sized Human DNA Inserts in an F Factor Based Vector," *Nucleic Acids Research* 20, no. 5 (1992): 1083-1085; H. Shizuya et al., "Cloning and Stable Maintenance of 300-Kilobase-Pair Fragments of Human DNA in Escherichia Coli Using an F-Factor-Based Vector," *Proceedings of the National Academy of Sciences of the United States of America* 89, no. 18 (1992): 8794-8797; J. C. Venter, H. O. Smith, and L. Hood, "A New Strategy for Genome Sequencing," *Nature* 381, no. 6581 (1996): 364-366.

[15] S. Fields and O. Song, "A Novel Genetic System to Detect Protein-Protein Interactions," *Nature* 340, no. 6230 (1989): 245-246; P. L. Bartel et al., "A Protein Linkage Map of Escherichia Coli Bacteriophage T7," *Nat Genet* 12, no. 1 (1996): 72-77.

[16] Herskowitz, (Undated), Carton 11 Correspondence Fo-La, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

[17] Herskowitz, (Undated), Carton 12 Correspondence La-Ot, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25).

far, however, the efforts had entailed only the development of infrastructure and the publication of genome sequences.[18] The NHGRI now wanted proposals for *in vivo* measurement and experimental manipulations of yeast phenotypes in order to give meaning to the large stores of genomic data that had been generated.[19] These were expected to have value for human health and disease. The Yeast Gene Deletion Project, for example, was one effort to conduct high-throughput phenotypic analyses of various yeast gene functions. This was a collaborative project launched out of Stanford to create a complete set of knockout mutants of all yeast genes and to grow these up into strains for experimental manipulations. Such efforts gave meaning not only to yeast data, but, with availability of the "first draft" of the human genome sequence in the year 2000, they were also used to characterize the function of human genes by the analogies of sequence homology.[20]

The *Saccharomyces* Genome Database (SGD) was built to facilitate open access to annotated and summarized complex yeast datasets. Unlike Mortimer's Yeast Genetics Stock Center before it, SGC maintains information on genes rather than a material collection of the mutants themselves. The SGC was one of the first and largest contributors to the Gene Ontology Consortium, which aims to develop a controlled "species-independent" vocabulary relating gene products to biological processes, cellular components, and molecular functions - all with intended utility in "translational" research.[21]

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[18] Kumar and Snyder, "Emerging Technologies in Yeast Genomics," 302.
[19] Botstein and Fink, "Yeast: An Experimental Organism for 21st Century Biology," 696. See also B. Lehner, "Genotype to Phenotype: Lessons from Model Organisms for Human Genetics," *Nature Reviews Genetics* 14, no. 3 (2013): 168-178.
[20] Botstein, "Oral History Interview." In 2004, yeast geneticist Fred Sherman estimated that the future of yeast would still be important, but mainly as a tool for looking at the function of human genes. See Sherman, "Oral History Interview."
[21] Leonelli and Ankeny, "Re-Thinking Organisms: The Impact of Databases on Model Organism Biology," 32.

Postgenomic Applications

In the postgenomic era, the term "biomedical translation" has often referred to use of basic science research findings to guide the development of drugs and devices so that they can be "brought to market." The prioritization of genomic research over other types of "basic" research in epidemiology, behavioral science, psychology, communication, cognition, social marketing, economics, and political science, for example, has made clear the federal emphasis on clinical and commercial outcomes over other types of health interventions.[22] The model organism sequencing projects helped to shape this biomedical vision in that they were launched for the purpose of "translatable" molecular analogies. In 2012, Botstein argued that there was no lack of interest in human health among basic scientists and that their curiosity-driven research was critical to the success of research translation.[23] In fact, it had helped define it.

Within the efforts for personalized and precision medicine, yeast has been used as a human surrogate to understand the genetic basis of variable drug responses in terms of therapeutic efficacy and toxicity.[24] Yeast was expected to reduce the use of animal models as a "first screening" tool of toxicogenomics, but animal testing rates have not declined.[25] Pharmacogenomic yeast screens have been used to identify new targets and study the modes of

[22] S. H. Woolf, "The Meaning of Translational Research and Why It Matters," *JAMA* 299, no. 2 (2008): 211-213.
[23] Botstein, "Why We Need More Basic Biology Research, Not Less," 4160.
[24] Hyun Seok Kim and Justin C. Fay, "A Combined-Cross Analysis Reveals Genes with Drug-Specific and Background-Dependent Effects on Drug Sensitivity in Saccharomyces Cerevisiae," *Genetics* 183, no. 3 (2009): 1141-1151.
[25] Roberts and Oliver, "The Yin and Yang of Yeast: Biodiversity Research and Systems Biology as Complementary Forces Driving Innovation in Biotechnology," 477-487.

action of different compounds, including anticancer drugs, antimalarials, and antimicrobials.[26] There have been efforts to tailor of chemotherapy drugs to tumor type using yeast cell cycle mutations.[27] Efforts are underway to perform the "humanization" of yeast to further develop its potential in disease models. Some envision the use of "personalized" yeast avatars to identify patients' best treatment options by expressing any given allele of a human gene, or combinations of genes.[28] The recent precision medicine initiative announced by U.S. President Obama is expected to speed drug development by further "melding basic science together with the practice of medicine," since, "Every disease is ultimately a disease of the cell."[29] Yeast will likely have a hand in this work.

Rather than determining if or how yeast models may be generalized given their differences with humans, these practices show how yeast models are seen as already relevant. The question now becomes how to most accurately engineer yeast to justify these extrapolations since yeast has become both a model technology and a technology of modeling. The value of yeast models today lies in their ability to generate new types of functional, comparative, and systems level data – for this is where much of the emphasis on biomedical innovation exists currently. Belgian yeast geneticist Françoise Foury argued as early as 1997, "Despite the difficulty of assessing functional conservation between yeast and human genes, yeast offers invaluable guidance for approaching human disease-associated gene functions" since yeast genes

[26] S. C. Dos Santos et al., "Yeast Toxicogenomics: Genome-Wide Responses to Chemical Stresses with Impact in Environmental Health, Pharmacology, and Biotechnology," *Front Genet* 3 (2012): 8.
[27] Pray, "LH Hartwell's Yeast: A Model Organism for Studying Somatic Mutations and Cancer," 183.
[28] J. M. Laurent et al., "Efforts to Make and Apply Humanized Yeast," *Brief Funct Genomics* 15, no. 2 (2016): 7.
[29] Stefano Bertuzzi and Don W. Cleveland, "The Curious Incident of the Translational Dog That Didn't Bark," *Trends in Cell Biology* 25, no. 4: 187-189.

can be "deleted, mutated and reintroduced into yeast cells, overexpressed, tagged and thoroughly studied" to yield a considerable amount of information.[30] Herskowitz provided a critique of this vision, which has continued to trouble researchers in recent years.[31] In 1991, he warned that the ease of new molecular technologies would make it "even more acutely important to define problems and to ask questions and not simply generate data: there are a lot of things that can be done; the issue is what should be done."[32]

One new direction for biology has been toward the development of integrative computational approaches to compile and analyze the large amount of data that have been generated. Systems biology has emerged as a new field for the integration of information across many levels of biological organization. Yeast has been used to pilot bioinformatics methods that are then applied to the data of other organisms. The synthesis of many "omics" datasets – including genomics, transcriptomics, proteomics, metabolomics, infectomics, pharmacogenomics, and immunoproteomics - is hoped to produce a better understanding of "the system at a higher level."[33]

These new biological standards are forming at the same time that older practices in biology have come under fire. In recent years, the genetic stability which made wild-type S288C genome useful as a model organism, for example, has made it phenotypically atypical for the

[30] Foury, "Human Genetic Diseases: A Cross-Talk between Man and Yeast," 1-10.
[31] See a description of hypothesis-driven versus inductive modes of reasoning in Douglas B Kell and Stephen G Oliver, "Here Is the Evidence, Now What Is the Hypothesis? The Complementary Roles of Inductive and Hypothesis-Driven Science in the Post-Genomic Era," *Bioessays* 26, no. 1 (2004): 99-105.
[32] Herskowitz, (Undated), Carton 11 Correspondence Fo-La, Papers of Ira Herskowitz, 1974-2003 (#MSS-2002-25), Emphasis in original.
[33] Kishore R. Sakharkar and Meena K. Sakharkar, "Yeast Genomics for Bread, Beer, Biology, Bucks and Breath," in *Yeast Biotechnology: Diversity and Applications*, ed. T. Satyanarayana and Gotthard Kunze (Springer Netherlands, 2009), 482. See also B. Muller and U. Grossniklaus, "Model Organisms--a Historical Perspective," *J Proteomics* 73, no. 11 (2010): 2059.

species, and the once-standard strain has been criticized as an artefact of the laboratory.[34] The question has been posed if any single yeast can indeed serve as a standard since when grown from a single colony under constant environmental conditions "noise in cellular transcription or translation processes" is shown to produce "phenotypic individuality."[35] The case has been made for a yeast "pan-genome" project that would contain genes found within all sequenced *Saccharomyces cerevisiae* strains and wild isolates since it is believed that a better knowledge of the natural history of this species can help with interpreting its biology.[36] Systems biology and engineering projects are also expected to benefit from the exploitation of a more diverse yeast "gene pool." Currently, fungal genomes represent the widest sampling of any eukaryotic kingdom in terms of sequencing coverage, and more than one hundred complete fungal genome sequences have been made publicly available.[37] There are calls for more.

The latest iteration of yeast as a model has come from synthetic biology, a young computationally-oriented discipline that views biological creatures as programmable manufacturing systems. Here, yeast has been transformed into a "chassis" organism with a "minimal genome" that is capable of supporting self-replication and any additional genetic code to be inserted into it. Stripped of any evolutionary excess of genes, novel yeast genomes are the

[34] Warringer et al., "Trait Variation in Yeast Is Defined by Population History," 10. See also Gaisne et al., "A 'Natural' Mutation in *Saccharomyces Cerevisiae* Strains Derived from S288c Affects the Complex Regulatory Gene Hap1 (Cyp1)," 195-200.
[35] Roberts and Oliver, "The Yin and Yang of Yeast: Biodiversity Research and Systems Biology as Complementary Forces Driving Innovation in Biotechnology," 481-482.
[36] Engel et al., "The Reference Genome Sequence of Saccharomyces Cerevisiae: Then and Now," 396. See also Gianni Liti, "The Fascinating and Secret Wild Life of the Budding Yeast S. Cerevisiae," *Elife* 4 (2015): 6.
[37] Krishna Kant Sharma, "Fungal Genome Sequencing: Basic Biology to Biotechnology," *Critical Reviews in Biotechnology* (2015): 1-17.

subject of "rationale design."[38] Companies including Pfizer, British Petroleum, and DuPont are today developing these technologies for the synthesis of novel biotherapeutics, biofuels, and other chemicals since "controlled diversity" is expected to result in more targeted evolutionary improvements.[39] The "cell's agenda" must be tamed in these "genome transplantation experiments" – for although the genetic "program" replicates identical copies of itself, the cell reproduces only similar copies of itself and carries its own kind of information "recruited from the environment."[40]

In 2011, the *Saccharomyces cerevisiae* genome project "Sc2.0" began to synthesize a fully synthetic "designer" yeast genome.[41] An international team of scientists led by Jef Boeke at New York University's Institute of Systems Genetics reported the production of the first functional synthetic yeast chromosome in 2014. The project is supported by "an army of undergraduates" in the course "Build A Genome" offered at Johns Hopkins and elsewhere.[42] Project participants see the work as "carry[ing] out *in vitro* evolution" for a stronger, leaner, and more agile genome that will accelerate development of practical uses.[43] They have added favorable properties to the genome, removed repetitive sections, and skipped over "junk DNA." The investigators have also "shuffled" the "genomic deck" using a "built-in inducible diversity

[38] T. Fujio, "Minimum Genome Factory: Innovation in Bioprocesses through Genome Science," *Biotechnol Appl Biochem* 46, no. Pt 3 (2007): 145-146.
[39] Roberts and Oliver, "The Yin and Yang of Yeast: Biodiversity Research and Systems Biology as Complementary Forces Driving Innovation in Biotechnology," 485.
[40] Antoine Danchin, "Scaling up Synthetic Biology: Do Not Forget the Chassis," *FEBS Letters* 586, no. 15 (2012): 2136.
[41] J. S. Dymond et al., "Synthetic Chromosome Arms Function in Yeast and Generate Phenotypic Diversity by Design," *Nature* 477, no. 7365 (2011): 471-476.
[42] "Boeke Lab: About the Lab," accessed November 1, 2014, www.bs.jhmi.edu.
[43] "Company News: The Synthetic Yeast Genome Project - Sc2.0," accessed November 1, 2014, www.genscript.com.

generator" to aid genome minimization.[44] This yeast model is an engineering ideal representing the potential of molecularized biology to predict and control evolution through human programming.

A Model Technology

A history of yeast modeling suggests the diverse commitments and disciplinary perspectives that biologists bring to molecular work in the life sciences. It remains to be seen how more recent computational methods and engineering culture will transform yeast biology, but it seems likely that work with the organism will continue to attract biomedical funding and infrastructure in the years to come. While in the past, basic research support was made available for study of the yeast organism, today most resources allocated to yeast research in the name of human health and disease are earmarked for its use as a model technology. This is a fulfillment of the biomedical "molecularization" of humans that could find applications for the "eukaryoticization" of biology.

Yeast in the twentieth century had been one of the most studied and best understood organisms on the planet, and in our own times it has received some of the most personalized medicine to date. In the late 1980s, the American molecular biologist and science administrator Maxine Singer, who had once helped to decipher the genetic code, described for a general audience the common descent and shared biology of yeast and humans. She explained that the introduction of foreign DNA "can actually be therapeutic for a yeast cell that's sick because of a bad gene," and that scientists performing gene therapy could now "cure the yeast cell's genetic

[44] Yang, "NYU Langone Medical Center Press Release."

disease with a human gene."[45] As these homologies between yeasts and humans continue to grow the biomedical enterprise, yeast research – this "bio-medicine" – has stayed focused on ways for the organism to evolve.

[45] Interview of Maxine Singer Om "World of Ideas", (January, 1988 or 1989), Box 52, Folder 11, Profiles in Science: The Maxine Singer Papers, National Library of Medicine, Bethesda, MD.

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