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The fungal genetic system: a historical overview

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1. The early years

The genetics of filamentous fungi was initiated through the efforts of rather few people, whose work led to the explosive development of the genetics and biochemistry of *Neurospora crassa* and *Aspergillus nidulans* in the 1940s and 1950s. Among the major contributors is David Perkins, whom this issue of *Journal of Genetics* honours, and who continues to this day to be an international resource of new knowledge about *N. crassa*. This article is biased towards *Neurospora*, in keeping with its intent to honour David and with the focus of many of the articles to follow. I have chosen a historical theme, leaving to others the task of illuminating the present.

Neurospora became part of a continuous line of organisms underlying the twentieth-century revolution in biology. Many of the interests and traditions of geneticists working with *Drosophila*, mouse and corn were carried over to *N. crassa*, together with a new ambition to understand the relationship between genes and enzymes. It is easy for today's student to forget that work on *Neurospora* genetics and biochemistry preceded the modern development of these areas in *Escherichia coli* and yeast. In fact, *E. coli* genetics originated in the laboratory of E. L. Tatum, already a pioneer in *Neurospora*.

The clarification of the sexual life histories of *N. crassa*, *N. sitophila* and *N. tetrasperma* by B. O. Dodge (Shear and Dodge 1927) and his advocacy of the organism to others sparked the interest of T. H. Morgan. Morgan accepted the idea that *Neurospora* might be a useful experimental organism for genetic work. Morgan urged *Neurospora* upon Lindegren, who did the first detailed genetic studies on *N. crassa*, confirmed the observations by Dodge on second-division segregation, and demonstrated linkage (Perkins 1992). He thus began to realize the potential of this organism for other studies in which genetics might play a role. In a brief letter to Dodge in 1941, Beadle asked for *N. crassa* cultures, and with astonishing speed, he and Tatum published their first paper on the biochemical genetics of *N. crassa* later that year (Beadle and Tatum 1941). Work on the genetics, biology and biochemistry of *N. crassa* was soon extended to *A. nidulans*, with its parasexual mode of recombination. This mechanism was then quite novel, and it broadened the definition of sexuality to a point that it could include *E. coli* and bacteriophage as well. However, before and during the time of Dodge's studies with *Neurospora*, another tradition was developing elsewhere. Early studies on basidiomycetes by Kniep, Buller and others had revealed a multifactorial system of mating types, some of the properties of which were analysed correctly through tetrad analysis (Raper 1966). The two ascomycetes and several basidiomycetes dominated development of the field of fungal genetics.

By 1970 *N. crassa* had provided geneticists with the clearest model for Mendelian inheritance and recombination, and, with *E. coli*, the richest source of information about biosynthetic reactions. *A. nidulans* had provided the most evidence on the mutability of fungi, parasexuality and certain important problems, notably the enzymology and regulation of nitrogen metabolism. Early work on the genetics of filamentous fungi was dominated by an awareness of the simplicity and experimental benefits of haploid organisms. The earliest studies of Beadle and Tatum showed how complex processes such as biochemical pathways could be analysed in a straightforward manner in fungi by mutation, an approach wholly impractical in mammals, *Drosophila* and corn. With the characteristic clarity with which fundamental questions were posed by the new molecular biologists, researchers on filamentous fungi found themselves at the forefront of work that stressed universality rather than diversity. The diversity that now characterizes work on fungi developed only slowly. It would flourish after work on a few fungal species had provided suitable paradigms, and after workers on yeast and *E. coli* had developed the study of the universal themes such as replication, recombination and gene action in those organisms.

2. Great days for genetics

The development of fungal genetics in the years 1940–1975 gave us a fundamental appreciation of meiosis and intrachromosomal recombination. The ability to see meiotic phenomena such as segregation and reciprocal recombination in completely deterministic, rather than statistical, terms was compelling to all biologists. Only in such a milieu could gene conversion be dependably detected and studied, and pursuit of this phenomenon matured into our present theories of molecular recombination. Two early contributions to genetic analysis should be noted here. One was a summary of genetic analysis in *N. crassa*, 'Map construction in *Neurospora crassa*', by Barratt *et al.* (1954). It combined theoretical and experimental work with the first major compendium of *N. crassa* mutants, and became a handbook for the field. It contributed to the standardization of strains, genetic methods and nomenclature that still characterize the field. The second was 'The genetics of *Aspergillus nidulans*', by Pontecorvo *et al.* (1953), which reported the use of this homothallic organism in genetic experiments, and which embodied important intellectual and technical advances in the description of parasexuality and diploidy.

The genetics of *N. crassa*, *A. nidulans* and basidiomycetes was brought powerfully to bear on the research of the years 1940–1975. Genetic investigations of fungi included (i) tetrad analysis, chromosome mechanics, mapping and fine-structure analysis; (ii) heterokaryosis, parasexuality, and sexual and vegetative incompatibility; (iii) mutation and DNA repair; (iv) intragenic complementation; and (v) extranuclear inheritance. The articles in this issue demonstrate the continuing vitality of many of these lines of investigation.

2.1 *Genetics*

From the outset, tetrad analysis has provided enormous insight into genetic recombination. The reliable detection of gene conversion by Mary Mitchell led to an explosion of hypotheses on the nature of interaction of homologous DNAs at meiosis

(Stadler 1973). Integration of the concepts of negative interference and meiotic gene conversion led Holliday (1964) to propose what we know now as the 'Holliday structure'. Theories that embraced gene conversion and crossing over laid the foundation for study of both phenomena in the more experimentally accessible *Saccharomyces cerevisiae*. We now have a dominant theory of recombination by the double-strand break model in yeast (Orr-Weaver and Szostak 1985), but no adequate confirmation of its universality in the very fungi that gave rise to the field. This will probably come soon through molecular analyses, rather than strictly genetic techniques. In addition, the unusual regional variation of recombination rates, seen in *N. crassa* strains differing at *rec* and *cog* sites, is also yielding to molecular analysis (Yeadon and Catcheside 1995).

The extensive isolation and analysis of *N. crassa* chromosome aberrations, first summarized in a 1977 article (Perkins and Barry 1977), have had unusual effects in the field, some technical, others fundamental. The development of the *alcoy* strain of *N. crassa* and its later derivatives greatly facilitated genetic mapping from an early stage of biochemical genetics (Perkins *et al.* 1969). The study of the behaviour of duplications and deficiencies emerging from meiosis in crosses of aberrant and normal strains, the later use of chromosomal aberrations in construction of partial diploids, and mapping by duplication coverage have contributed to many investigations. Studies of the nucleolar organizer, duplication breakdown and vegetative incompatibility have been served by use of aberrations, and they were essential in relating linkage groups to chromosomes, and more recently in correlating cytologically defined chromosomes with whole-chromosome DNAs resolved on CHEF gels. The latter study yielded our best estimate yet of genome size in *N. crassa* (Orbach *et al.* 1988).

Fine-structure analysis of genes by recombinational methods was quite popular at one time, owing to the lack of other methods for resolving intragenic mutations, and to the hope that it would yield maps corresponding to amino acid order in the corresponding polypeptide. The low and variable recombination rates and the prevalence of negative interference impelled many geneticists to the use of *E. coli* or yeast as a more suitable organism, and, finally and productively, to molecular methods for molecular research. By 1970, the primacy of genetic analysis of biochemical and molecular phenomena had diminished considerably.

2.2 *Heterokaryosis and parasexuality*

Heterokaryosis, the coexistence of genetically different nuclei in coenocytic cells, was recognized very early in this century by Burgeff, in work with *Phycomyces nitens*. Later observations in a variety of fungi yielded a straightforward view of this phenomenon, perhaps the most distinctive genetic aspect of filamentous forms (Davis 1966). Beadle and Coonradt (1944), working with auxotrophic mutants, demonstrated the use of forced heterokaryons to judge nonallelic complementation. This was later appreciated as the clearest form of the *cis-trans* test, unconfused as it was by the possibility of nuclear fusion and recombination. From this work emerged the possibility of controlling nuclear ratios and putting dominance on a quantitative basis (Davis 1966).

Notably in *A. nidulans*, but also in many other fungi, heterokaryosis underlies parasexuality. With *A. nidulans* mutants differing in colour, morphology and nutritional requirement, forced heterokaryons are easily formed and recognized visually

(Roper 1966; Bos and Swart 1995). Upon subculture, such mycelia generate reasonably stable diploid nuclei. Mitotic crossing over in the diploid phase became an effective mapping method in this species. The breakdown of diploids to yield recombinant haploids facilitated assignment of new mutations to chromosomes and construction of desired genotypes without use of sexual crosses.

In the 1950s the genetics of tetrapolar sexuality in *Schizophyllum* and *Coprinus* were clarified (Raper 1966). The prior work on *N. crassa* and *A. nidulans* was a model for the isolation and genetics of biochemical and morphological mutants of *S. commune* and *C. cinereus* (formerly *C. lagopus*), and the latter organisms quickly became genetically tractable (Casselton 1995). An acute appreciation of heterokaryosis, a central feature of basidiomycete sexuality, developed in this period. The genetic resolution of multilocus *A* and *B* mating-type factors was achieved initially by Papazian and Raper in *S. commune* (reviewed in Raper 1966), and by Day in *C. cinereus* (Day 1960). We know now that the mating factors control two developmental cascades by way of interactions of heteromultimeric transcription factors and of pheromone signalling systems, and the analysis is now in its molecular phase (Kothe 1996). The basidiomycetes helped focus interest on the variety of sexual systems in fungi, an interest that has returned to *N. crassa* itself via yeast (Metzenberg and Glass 1990).

Early workers recognized that heterokaryosis was not an invariant outcome of pairing mycelia, even if forcing markers were used. The mating-type alleles of *N. crassa* confined vegetative fusions to one or the other mating type, and additional vegetative-incompatibility loci, having no role in the sexual process, have been recognized in *N. crassa*, other euascomycetes, and many of the Fungi Imperfecti (Glass and Kuldau 1992; Leslie 1993). Vegetative incompatibility has enforced care in development of genetic stocks of most fungi. The study of incompatibility loci, laborious by genetic means, has also entered a molecular phase, which will yield important information about biochemical interaction of allelic gene products in ascomycetes, their roles in nature, and their relationship to the mating-type genes of basidiomycetes.

2.3 *Mutation*

Beadle and Tatum (1945) used X-rays to obtain their initial mutants of *N. crassa*, but ultraviolet radiation and chemical mutagens, shown to be gentler and in most cases more specific mutagenic agents, were used thereafter as standard fungal mutagens. Three aspects of the study of mutation were important in these years.

The first became an important controversy over the proportion of genes encoding 'indispensable functions'. The issue hung on the definition of 'indispensable'. Horowitz and Leupold (1951) claimed that temperature-sensitive mutants that could not grow on complete medium at the restrictive temperature (about 50% in their experiments) represented functions that were unsupplementable, and thus indispensable. Atwood and Mukai (1953) used heterokaryon analysis, by which spontaneous mutations unable to survive except in heterokaryotic association with a wild-type allele (about 90% in their experiments) were truly indispensable. The truth transcends this controversy, as our knowledge of the biochemistry and molecular biology of the cell has become more detailed. At the time, however, this controversy was a framework for testing the validity of the one gene–one enzyme hypothesis, and thus for dertermining just how simple or how complicated life really was.

The second aspect of the study of mutation was exemplified in fungi by detailed analyses by de Serres and his colleagues (Overton *et al.* 1989) of the relationship between mutagens and the recombination, complementation and reversion of the resulting mutants. This work was part of the widespread effort to infer the nature of DNA lesions by their induction and reversion by specific mutagens. In the process, the occurrence of suppressor mutations, within or outside the gene that was the target of reversion, led to many discoveries of amino acid interactions within proteins, informational suppressors, and gene interactions through indirect suppression. In the process of analysing induced mutation, spontaneous mutations received their due, and were shown to have a different spectrum than chemically induced mutations. More recent work has defined spontaneous mutations in molecular terms, and suggested mechanisms by which they arise (Dillon and Stadler 1994).

The third area of interest in mutation was initiated by isolation of strains sensitive to UV and other mutagens (Schroeder 1975). This has led to a definition of the action and induction of certain genes in repair, and the isolation of genes clearly homologous to repair genes in other organisms (Cheng *et al.* 1993). Their involvement in meiosis is less certain, but this difficult line of work is being pursued currently.

2.4 *Complementation*

Genetic complementation was at the outset a simple matter of two simultaneous dominance relationships between singly mutant nuclei, much as one sees it in double heterozygotes of diploids. Heterokaryons of *N. crassa* (Beadle and Coonradt 1944) became tools in defining alleles on the basis of their failure to complement.

The resolution of genes by fine-structure recombinational analysis of allelic mutations became common in *Drosophila* in the early 1950s. The prevailing question was why mutations apparently in the same gene could recombine, while failing to complement one another. Benzer (1957) clarified this conflict with phage experiments, giving separate operational definitions of genes, alleles and units of mutation, and by certifying the *cis-trans* test as a test of allelism. However, even with a clear vision of the relationship between genes and proteins, this did not prepare biologists for intragenic complementation. Revealed clearly in *N. crassa* by several workers (Fincham 1966), this phenomenon reflected the partial restoration of function in multimers of heteroallelic polypeptides. It therefore promised to be a valuable genetic tool by which to analyse protein substructure and interaction. Indeed, it was possible to draw complementation maps, which initially had resemblance to the genetic maps of the same genes. The maps and their topological correspondence, however, became more and more complicated as more information accumulated, and finally this approach died of its own Ptolemaic weight. The biochemical exploration of the phenomenon, however, gave much insight into protein–protein interaction, and into the behaviour of multimeric proteins.

2.5 *Extrachromosomal inheritance*

A persistent genetic curiosity since the early 1900s, extrachromosomal inheritance arrived early in fungal genetics. The 'barrage phenomenon' in *Podospora anserina*,

described by Rizet (1952), was a heritable phenotype that appeared to be infectious, and which in turn depended on the genotype. The maternally inherited *poky* mutation of *N. crassa* (Mitchell and Mitchell 1952) was shown ultimately to reside in mitochondrial DNA. The classic work on *petite* yeast by Ephrussi (1953) stimulated a great deal of work on the inheritance of mitochondrial characters in fungi and on mitochondrial biogenesis and function, even though answering the early genetic questions took a surprisingly long time. Besides these classic phenomena came reports from other fungi of non-Mendelian phenotypes such as senescence, slow growth and other abnormalities that developed over time with suitable selection. The definition of their nonchromosomal character came from the 'heterokaryon' test, by which the character in question could be associated with a second nuclear type through formation and resolution of a heterokaryon (Jinks 1964). In anisogamous species, the sexual test of nonsegregation also applied. Ultimately, the basis of most extrachromosomal elements had to await detailed biochemistry and molecular-biological techniques; many of these cases were revealed to be due to alterations in mitochondrial DNA or to mitochondrial plasmids (for example, Bertrand *et al.* 1986).

3. Fungal genetics today

Above, I have given my impressions of the days when genetics seemed to be sufficient to answer many questions. During that time genetics was at the core of many investigations, but, like biochemistry before it, it had to be joined by other rationales to assure continued progress. Many biochemical systems could be analysed, at least in a formal way, with a set of mutants and the associated complementation, genetic and nutritional analysis. This thinking came to be applied to more complex phenomena such as the morphology of conidial development in *A. nidulans*, the mycelial morphology of *N. crassa*, the sexual process in *S. commune*, the nuclear cycles of *A. nidulans* and *N. crassa*, biological clocks and light responses in *N. crassa*, and other developmental sequences. Gene interactions gave us much insight into cross-pathway relationships and regulatory sequences. But when all was said and done (and a great deal was said), the 'classical' genetic approach could be seen as the most efficient way to pose, rather than answer, questions, and to restrict hypotheses that, to be tested, required detailed biochemical and molecular analysis. Even pure biochemistry, redeemed and extended by genetic work on filamentous fungi, had met its limits as attention turned to the informational aspect of macromolecules.

Genetic work on filamentous fungi has now diverged in character from work on yeast and bacteria. Latent in the period reviewed above, and waiting for the paradigms to solidify, were many other fungi and many problems peculiar to the fungi already used so heavily. From the mid-1970s to the present, the study of filamentous fungi has exploded with diversity, and with it an enormous potential to explore evolution, natural populations, fungal plant pathology, genome structure and sexuality, together with continued studies of the more highly developed problems and systems with their huge background of information and mutants.

Hinnen *et al.* (1978) announced the successful transformation of yeast in a paper that dealt lucidly with both the molecular and the genetic aspects of the phenomenon.

Because it addressed ambitions already well developed among workers on filamentous fungi, they immediately embraced the paper and its promise. Much earlier, Mishra had shown that *N. crassa* could be transformed, but in the late 1970s recombinant DNA technology allowed a new approach to the problem (Mishra 1991). Quickly, *N. crassa* (Case *et al.* 1979) and a number of other fungi were shown to be transformable in practical terms, and a renaissance of old problems, particularly in gene structure, biochemistry and regulation, ensued. In the process, a common vocabulary and set of molecular resources began to unify the field of fungal genetics technically, even as the scientific questions and range of experimental organisms increased.

Among the genetic questions originating in the classical period, some have been mentioned above. We have begun to know the structure of centromeres, telomeres, repair genes, ribosomal sequences, promoters, cis-acting regulatory sites. Many attributes of the genome, including the mutational process, integration of foreign DNA, homologous recombination, transposable elements and premeiotic damage (RIPing) of duplicated sequences (Selker 1990), have come to light. I can only call attention to the enormous advances in our knowledge of biochemistry, regulation and development, since these matters can be studied easily now in filamentous fungi with molecular techniques (for review of *N. crassa* work, see Davis 1995).

Perhaps the largest area to flourish is fungal plant pathology, because previous limits imposed by fastidious culture requirements (often limited to hosts), difficult genetics owing to a refractory sexual phase, the inability to obtain mutants, and long life cycles have been bypassed with direct molecular study, including genomic analysis and intraspecific comparisons by RFLP and RAPD techniques (Valent and Chumley 1991; Kistler and Miao 1992).

Another development is the comparative study of sexuality and sexual compatibility, because mating-type genes can now be compared directly with one another, and even interchanged as a test of function in a heterologous context. In basidiomycetes, studies of mating-type function have greatly illuminated the molecular basis of specificity and action in multiallelic systems, and the coordinated control of developmental events (Kothe 1996).

A third emerging area is the evolution of the genus *Neurospora* (Perkins 1991), facilitated by Perkins' collection of wild-type *Neurospora*, allowing him to describe the distribution and correlated biological attributes among heterothallic and homothallic species. This collection has become one of the finest assemblages of natural genetic variation available for study for its own sake, as well as for use in some unique studies of the genome (e.g. mitochondrial plasmids, spore-killer genes, transposons, chromosomal polymorphisms and mating-type evolution).

I have celebrated here a field of biology that developed in a classical way. An organism was found with manifest usefulness for the solution of a biological problem, in this case the gene–enzyme question. A huge effort driven by technical necessity followed, and led to fundamental genetic and mycological understanding. This brought into being the increasingly prominent and well-defined field of filamentous fungal biology in its varied manifestations. At the centre of these developments stands David Perkins, dedicated to one organism that has illuminated many others, persistent in theoretical and innovative technical contributions to the field, master of the evolution and present structure of the genus *Neurospora*, and a tireless advocate of free, sharing and harmonious enquiry.

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