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Sir John Gurdon and the rise of molecular developmental biology

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ABSTRACT

John B. Gurdon was one of the most beloved developmental biologists of our times, who enjoyed a long life completely immersed in science. Blessed with a very important discovery at age 25, he used his distinguished position for the common good of other biologists. John's life epitomizes the Golden Rule of Western Civilization – love your neighbor as yourself – to the great benefit of his field. As a graduate student, he demonstrated that somatic cells retained the complete gene repertoire to differentiate into all cell types. He developed the *Xenopus* oocyte as a living test tube for molecular biology. His microinjection studies provided the first vertebrate system to translate mRNA, transcribe DNA, and express cloned genes. He investigated the reprogramming of somatic nuclei to the gene expression pattern of oocytes for many decades. His discoveries were foundational to the use of stem cells for tissue therapies and were recognized with the 2012 Nobel prize for Medicine. He was responsible, more than any other person, for introducing *Xenopus* as a research organism for molecular biology. He was a wonderful mentor who taught by example and built new research institutes. His tireless support for scientific societies organized by scientists independently of governments led him to deliver incomparable lectures throughout the world, inspiring generations of developmental biologists. His secret weapon was to never stop working at the bench with his beloved oocytes and embryos. Above all, he was a good man. Sir John passed away peacefully at home, surrounded by his family at age 92.

1. Introduction

John B. Gurdon turned the good fortune of an early important discovery as a graduate student into one of the most influential lives in contemporary biology. An unquenchable curiosity was the driving force behind this remarkable man of science. Through a deep sense of duty to the institutions that keep the machinery of science running, his beneficial influence spread throughout Developmental Biology. A passion for science led him to tirelessly experiment with frog eggs and oocytes throughout a long and very interesting life.

John Bertrand Gurdon came from an ancient and distinguished English family of Norman origin. A village named Gurdon is still found in Normandy. In his genealogical tree, the names John and Bertrand appear repeatedly. A Bertrand de Gurdon was recorded circa 1200, and a John (Jean) de Gurdon circa 1400. The noble “de” was, rather unfortunately in my view, dropped in later centuries. Many Gurdons were knights, but John's branch of the family did not inherit the title. Even today, one of his second cousins, also of the surname Gurdon, is a hereditary member of the House of Lords. Receiving a Bachelor Knighthood in his own right in 1995 gave Sir John well-deserved satisfaction.

John's parents lived in India, where his banker father made his fortune and later returned to the U.K., where John was born in 1933. Together with his sister Catherine, he was sent to the safety of the countryside during WW II and was always reluctant to discuss any penuries during this period. The most he would say was that eggs were first cracked open in a teacup to make sure they were in good condition,

as they were so valuable.

Gurdon's early education is described in a beautiful autobiographical review (Gurdon, 2006). It is a highly recommended read because it is written just as he spoke every day in the laboratory. His education at Eton specialized in Latin, Greek, and becoming captain of the Squash team. He was considered unsuitable for science. John knew how to hold a grudge and, famously, kept above his desk a framed copy of his biology master's report: “I believe Gurdon has ideas about becoming a scientist. On present showing, this is quite ridiculous. If he can't learn simple biological facts, he would have no chance of doing the work of a specialist, and it would be a sheer waste of time both on his part and of those who would have to teach him.” He was admitted to Oxford University on condition that he did not study Latin or Greek. In this way, in a most fortunate event for developmental biology, he met a great doctoral mentor in Russian émigré Michail Fishberg.

Gurdon's contributions can be divided into three parts.

First, an early start with a very important discovery at a young age.

Second, providing a living developing system for analyzing the emerging molecular technologies in *Xenopus* oocytes and embryos.

Third, a lifetime dedication to the service of scientific institutions for the common good.

His secret weapons were an unquenchable curiosity and continuing hands-on experimentation at the bench with his beautiful frog embryos and oocytes (Fig. 1).

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Fig. 1. Sir John Gurdon on the occasion of his 80th birthday. Original portrait by Prof. Nadia Rosenthal of The Jackson Laboratories, pencil on Arches paper. Courtesy of the artist.

2. Genetic information is not lost during cell differentiation

Michaël Fishberg in Oxford, together with Pieter Nieuwkoop in Holland, introduced *Xenopus* as an experimental organism for embryology (Gurdon and Hopwood, 2000). This South African frog species had the advantage of laying eggs throughout the year after stimulation with Human Chorionic Gonadotropin, providing a convenient pregnancy test. Fishberg had trained with Ernst Hadorn in Zürich, who had studied with Fritz Baltzer in Bern, who had studied with Theodor Boveri (together with Hans Spemann) in Würzburg. Through John Gurdon, a multitude of current *Xenopus* researchers can trace their lineage to Boveri, the founder of European Cell Biology (De Robertis and Gurdon, 2021).

Three months into his PhD, John was tasked with reproducing the nuclear transplantation experiments that Robert Briggs and Thomas King had recently made in *Rana*. The question addressed was a classical one in embryology: Is genetic potential lost during cell differentiation? This question can be traced to August Weismann, who in the 1890s,

inspired by the phenomenon of chromatin diminution in the nematode worm *Ascaris*, had proposed that genetic material was lost from the soma (body) but was kept intact in the germ line. Spemann had used ligature of fertilized amphibian eggs with baby hair to show that nuclei from 16-cell embryos kept the ability to form tadpoles, and Briggs and King showed that transplanted nuclei from blastula stages kept their totipotency and could form clones of tadpoles. However, when they took nuclei from tailbud tadpoles, the frequency went down to almost nothing (Briggs and King, 1957). They concluded that totipotency was lost in later development.

2.1. Differentiated nuclei can be reprogrammed to develop into adult fertile frogs

Using *Xenopus* embryos and an improved enucleation method with ultraviolet light, Gurdon could show that transplanted single nuclei could give rise to mature frogs even from neural plate and tailbud

tadpole stages (Gurdon et al., 1958). These experiments were made possible by the foresight of Fishberg, who had kept breeding a spontaneous mutant observed in the lab that had a single nucleolus rather than the usual two. This lineage tracer was essential to show that the genetic material came from the transplanted nucleus and not from the host egg.

Gurdon published this landmark discovery at age 25 and did not rest on his laurels. Pressing on, he proceeded to show that nuclei of differentiated cells had a full developmental potential (Gurdon, 1962). He chose endodermal cells from feeding tadpoles that could be recognized as differentiated because of their cylindrical shape and brush border of microvilli for nutrient absorption. The frequency of normal development was very low, so he devised the technique of serial nuclear transplantation. Most embryos failed to divide, and John reasoned this was due to nuclei not having enough time to complete their DNA replication during the 90 min available before the first cleavage. Many embryos did not cleave at all, but others had partial cleavages. When he transplanted nuclei from partially cleaved embryos a second time, the frequency of normal development increased to 24 %. Serial nuclear transplantation was challenging and took several days of continuous work. His technician of those times told me that she had never seen someone work so hard, although I think it is likely he was just enjoying himself. Upon completion of his DPhil, John left for a postdoc at Caltech. Fishberg accepted a professorship in Switzerland and, fortunately, took John's tadpoles with him to Geneva, where they were raised by his technician V. Uehlinger and shown to be fertile (Gurdon and Uehlinger, 1966). Michail Fishberg generously declined authorship. These experiments established that genetic information is not lost during cell differentiation. Differentiated somatic cells could be reprogrammed and maintain the complete set of genes required for development.

2.2. Why did it take 50 years for John Gurdon to receive the Nobel prize?

Like most important discoveries in science, the nuclear transplantation results were initially met with scepticism. Many decades later, I was directly asked by the Chair of Biology at Caltech whether I really believed Gurdon's results. Some thought that there he might have picked up germ cells instead of differentiated cells. Others argued that advanced feeding tadpoles are not really adults. John forged ahead and kept doing similar experiments in different ways for the next decade. The most famous was with his ex-graduate student and longtime close colleague Ronald Laskey, in which they reprogrammed keratin-positive differentiated skin nuclei (Gurdon et al., 1975). All objections dissipated when Dolly the sheep was cloned in Scotland (Wilmut et al., 1997). Named in honor of country singer Dolly Parton, this sheep was obtained by fusion of the nucleus of a cell from an adult mammary gland. The path was open for nuclear reprogramming in mammals.

Shinya Yamanaka was able to reprogram fibroblasts into induced Pluripotent Stem Cells (iPSC), dispensing with oocyte cytoplasm altogether, by simply transfecting a cocktail of four transcription factors into mouse and later human fibroblasts (Takahashi and Yamanaka, 2006). Previously, Harold Weintraub had found that the transfection of a single cDNA clone into a fibroblast cell line was sufficient to trigger myoblast differentiation (Davis et al., 1987). The discovery of iPSCs opened the stem cell field to patient-derived iPSC cell lines to devise therapies and potentially tissue replacement. The revolutionary Yamanaka reprogramming factors and the pioneering and continuing studies of Gurdon in *Xenopus* were a perfect match, recognized by the 2012 Nobel prize for Medicine for “the discovery that mature cells can be reprogrammed to become pluripotent”.

3. Living oocytes and embryos as a biochemical test tube to study gene expression

3.1. A brief postdoctoral stay at Caltech

In 1962, Gurdon undertook a one-year postdoctoral stay at Caltech.



Fig. 2. Sir John Gurdon returning to the famed Caltech Athenaeum 50 years after his postdoctoral studies. Photo by Eddy De Robertis.

In New York, he purchased a used Chevrolet and drove to Los Angeles along Route 66, visiting many labs along the way. At Caltech, he worked on phage genetics with Bob Edgar. Although no publications resulted from this period, John met many interesting scientists at the famed Athenaeum Faculty Club, which he remembered fondly (Fig. 2). Among these was James Ebert, director of the Carnegie Institute of Embryology at Baltimore, who introduced John to a beginning staff member working with *Rana* by the name of Donald Brown.

3.2. Donald Brown and the nucleolus as the site of ribosomal RNA synthesis

Gurdon and Brown struck an enduring friendship, cemented by a mutual love for tennis. John sent him the 1-nucleolus *Xenopus* mutant, and it was found that 0-nucleolus tadpoles completely lacked synthesis of large ribosomal RNAs labelled with C¹⁴ bicarbonate (Brown and Gurdon, 1964). This was a momentous discovery that established the nucleolus as the site of ribosome biosynthesis. At Carnegie, Don Brown introduced his postdoc, Igor Dawid, to *Xenopus* eggs, which he later used to discover mitochondrial DNA. In this way, investigators working on *Xenopus* in the United States can be traced back to a young John Gurdon.

3.3. Nuclear activity in oocytes and eggs

While Gurdon was at Caltech, Fishberg was appointed Professor in Geneva, Switzerland. This opened the way for a return to Oxford, although to a more junior position than Fishberg's. There, John started investigations into nucleic acid synthesis, showing that multiple brain nuclei introduced into fertilized eggs synthesized DNA, that oocytes matured with progesterone did not synthesize DNA but instead condensed the chromosomes, and that oocytes dissected from the ovary (where they are in meiotic prophase) promoted RNA synthesis (Gurdon, 1968). To culture oocytes, he modified a saline solution, previously used by Lester Barth to study neural differentiation in embryos, in which ovarian oocytes could be kept alive for many days and weeks. The cell cycle differences in nuclear activity between oocytes, maturing oocytes and eggs provided the basis for the discovery of Maturation Promoting Factor and Cytostatic Factor by Yoshio Masui in Canada and for a Nobel prize for Tim Hunt.

During these studies on nucleocytoplasmic interactions, Gurdon first identified the power of introducing purified molecules into living oocytes. He iodinated histone proteins and found that when injected into oocyte cytoplasm, they shuttled into the large oocyte nucleus (called the



Fig. 3. Gurdon working at the bench in his office at the Cambridge Laboratory of Molecular Biology circa 1974.

Note the small desk in the background where John did all his administration (exclusively on Fridays) and took microphotographs in a Wild microscope. He would zip back and forth to his desk on this chair with rollers to write detailed experimental protocols. Photo courtesy of MRC LMB Cambridge.



Fig. 4. The Gurdon and Laskey groups at the Laboratory of Molecular Biology, Cambridge, circa 1980.

Top row: Doug Melton, Marvin Wickens, William Earnshaw, Eddy De Robertis, Ruth Longthorne, Richard Harland, Kazuko Nishikura, Laurence Korn, Stewart Weisbrod, John Gurdon (at age 46) and Julian Wells (sabbatical visitor from Australia). Lower row: Sue Whytock (John's technician), two young ladies, Barbara Rodbard (John's wonderful secretary) and Jeff Partington. Ron Laskey is missing from this photo. John worked together with only 2 or at most 3 colleagues at a time. Photo by Sue Whytock.

germinal vesicle). This meant that the signal sequence for nuclear transport resided in a mature nuclear protein, opening an entire field of research. An anecdote John liked to retell was that he performed the radioactive iodinations by the Chloramine-T method on his desk which, unbeknownst to him, turns iodine gaseous. Days later, someone came by and tested him with a Geiger counter and found his thyroid to be screaming hot. This work, introducing the first purified molecules into an oocyte, went mostly unrecognized because it was published within a review paper (Gurdon, 1970).

3.4. The translation of mRNA in *Xenopus* oocytes

It was John Gurdon who singlehandedly introduced the oocyte as a test tube for molecular biology. This discovery would have deserved a Nobel prize in its own right. Previously, amphibian embryos had been used by embryologists to analyze the cascade of events occurring during development. However, oocytes taken from the abdomen of female frogs could be cultured for weeks without dividing and were biochemically active. In 1971 a truly daring experiment was performed. The group of Jean Brachet in Belgium had purified a sedimentation peak of 9S from rabbit reticulocytes that was suspected to consist of globin mRNA. However, no system to translate mRNA into protein existed at the time, as the wheat germ and reticulocyte translation systems had not been invented yet. Working with graduate student Charles Lane, the son of his friend Dame Miriam Rothschild, they showed that microinjected purified mRNA was able to direct the abundant synthesis of rabbit globin in *Xenopus* oocytes (Gurdon et al., 1971). This was a revolutionary assay system that has since been used in a myriad of experiments studying not only the synthesis of proteins, but also their cell biology, secretion, and function as neurotransmitter receptors in living oocytes. Following the introduction into embryology of synthetic mRNA from cloned genes by Douglas Melton, *Xenopus* became the indispensable organism (Krieg and Melton, 1984). The work on mRNA translation led to an invitation to join the Laboratory of Molecular Biology (LMB).

3.5. Move to the famed LMB Cambridge

This was an excellent move, for the Medical Research Council (MRC) laboratory was at the very center of the rise of molecular biology. In the 1970s the Chair was Max Perutz, and one could not walk a corridor without seeing legendary luminaries such as Francis Crick, Fred Sanger, Aaron Klug, Sydney Brenner, Cesar Milstein and many more who went on to earn Nobel prizes (Finch, 2013). As Gurdon wrote of the MRC-LMB in 2006: "With a current tally of 15 Nobel laureates who largely earned their recognition there, and an annual budget (in 1980) of less than 1% of that of the National Institutes of Health in Bethesda, it doesn't seem to me to have much competition." John was able to carry on his tireless work in this most stimulating environment (Fig. 3).

It was a very exciting period when Sanger was inventing DNA sequencing and Cesar Milstein monoclonal antibodies. Discussions at lunches in the canteen looked after by Mrs. Gisela Perutz were memorable, as were the coffee and tea breaks. There were few formal group meetings, but John would come by your bench in the morning and ask if you were free for lunch. This meant that your work was to be discussed that day, and we dropped whatever we were doing. Every experiment was discussed endlessly. The philosophy at the LMB was that no one was to be co-author in a paper to which he/she had not made a meaningful contribution, by which it was meant at least one figure. This stimulated the free exchange of ideas in the English tradition of "measure twice, cut once". The groups of Gurdon and close colleague Ron Laskey became magnets for postdoctoral fellows, even though John would collaborate directly with only 2 or at most 3 at any one time (Fig. 4).

3.6. The *Xenopus* oocyte as a living transcription-translation system

Building on the line of microinjection of mRNA, the next step was to

study the transcription of DNA. During his experiments, microinjecting multiple somatic nuclei into oocytes, John noticed that sometimes nuclei were deposited inside the germinal vesicle. By injecting into the animal (top) oocyte pole it was possible to introduce SV40 DNA with high frequency into the oocyte nucleus, where it was transcribed by RNA polymerase II (Mertz and Gurdon, 1977). In a parallel transatlantic collaboration with his friend Don Brown, John showed that *Xenopus* 5S rDNA purified by density gradient centrifugation was also transcribed, this time by RNA Polymerase III (Brown and Gurdon, 1977). In a follow-up study, in which John also did microinjections, it was shown that cloned recombinant histone genes from *Drosophila* were transcribed into mRNA and translated into protein (De Robertis and Mertz, 1977).

At that time, recombinant DNA cloning was revolutionizing biology. However, there were no efficient means to express these genes, with the oocyte system representing a shining exception. John received many more invitations to speak at molecular biology conferences than he could possibly attend, and with typical generosity, he sent Ron Laskey, myself, Doug Melton and others as his substitutes. We became far better known than we deserved during those exciting days at the forefront of the scientific world. A rising tide lifted all boats.

3.7. The community effect

In 1983 Gurdon and Laskey started a new Cancer Research Campaign (CRC) Institute as part of the Department of Zoology at the University of Cambridge. Max Perutz had retired as Chair of the LMB and the move to CRC brought in new opportunities and funding. John became interested in how cells perceive small variations in a gradient of Activin, a mesoderm inducing factor discovered by James C. Smith, who years later became the institute director. Naïve embryonic cells and molecular markers such as muscle actin were used to measure the ratchet-like effects of concentration and duration of the activin signal during cell differentiation. To obtain muscle differentiation, a few hundred induced cells interacting close to each other were required, rather than cells separated from each other. These studies led to the proposal of a community effect during development that explained the formation of blocks of tissues in the embryo (Gurdon, 1988; Gurdon et al., 1994). His group also identified extremely important novel genes in embryonic development such as the key homeobox gene *siamois* and the T-box gene *eomesodermin* (Lemaire et al., 1995; Ryan et al., 1996); John did not pursue these in depth because his main interest was in biological processes rather than individual genes.

3.8. The battle for supremacy between nucleus and cytoplasm

The leitmotif of Gurdon's research was his continuing pursuit of how nuclear reprogramming of somatic cells is achieved. Beginning with his experiments with multiple brain nuclei introduced into oocytes that synthesized RNA (Gurdon, 1968), he continued to pursue this line of research throughout his career. He devised methods to gently isolate nuclei from cultured mammalian cells and investigated the molecular changes after reprogramming of a few hundred injected nuclei into the oocyte germinal vesicle (Gurdon et al., 1976). Injection of nuclei from a *Xenopus* kidney cell line into oocytes of the newt *Pleurodeles waltlii* caused the reprogrammed nuclei to reactivate specifically the expression of oocyte-type proteins and, remarkably, this reprogramming took place in the complete absence of DNA replication (De Robertis and Gurdon, 1977). This is unlike the case of iPSCs, which require extensive cell division. Later, nuclei for adult mouse tissues reactivated the expression of stem cell factors such as Oct-4 (Byrne et al., 2003). There is a battle for supremacy between the oocyte cytoplasm and somatic nuclei. Differentiated cells resist reprogramming through epigenetic chemical modifications in DNA and histones that try to keep stem cell pluripotency genes turned off but are overwhelmed by the vast supply of oocyte cytoplasm (Gurdon, 2013). Once a transcription complex is assembled in the oocyte, it is stable for hours and days in the absence of DNA



Fig. 5. The Gurdon party for the Nobel banquet, December 2012.

From left to right: Ann Laskey, Ron Laskey, Laurence Korn, Aurea Connolly (John's daughter), Lady Jean Gurdon, Sir John Gurdon, Catherine Thompson (John's sister), Alan Colman, Ann Clarke, Marvin Wickens, Valerie Moar, Douglas Melton, Eddy De Robertis, Serena Connolly, Oliver Connolly and Edward Connolly. John is wearing his knighthood insignia. Photo courtesy of Aurea Gurdon Connolly.

replication, as demonstrated by DNA competition experiments (Javed et al., 2022).

John was an extreme reductionist and used to say that if one understood how a globin gene is turned on or off, one would understand development. Although many of us would disagree with this simplified view, it was enormously productive. Even at age 90 he was reactivating pluripotency genes in mouse embryonic fibroblasts by treating them with extracts of manually isolated oocyte germinal vesicles after transient permeabilization of the plasma membrane (Wen et al., 2024).

4. Building institutions that serve the scientific enterprise

Despite his incessant work at the bench, Gurdon found time to generously serve the field of developmental biology. For example, he was president of the International Society of Developmental Biologists. The initial discussions to form the extremely successful British Society of Developmental Biology took place in his rooms at Christ Church College, Oxford. He was an indefatigable supporter of scientific societies because, as he liked to say, they are built by scientists to serve other scientists. He travelled throughout the world, giving lectures that were a model of clarity in his inimitable style. At meetings, he dutifully visited as many

posters as humanly possible in the time allowed, bringing joy to many young students. At least two scientists told me that they went into science because they heard John Gurdon speak. I once wrote tips for talks on how to try to give a Gurdonian-type seminar, but the UCLA Information Technology department, in their wisdom, decided to remove all PDF files from faculty websites. John enjoyed travelling, especially to exotic locations in Asia and Latin America, where he could indulge his hobby of chasing butterflies. John was the keynote speaker at the 2003 Valle Nevado conference in Chile, at which Roberto Mayor founded the now thriving Latin American Society of Developmental Biologists. His after-dinner or closing thank-you speeches reading from a folded sheet of paper were legendary. For decades he was the *éminence grise* behind the Company of Biologists that publishes Development and the Journal of Experimental Biology. The Company invests all its profits in subsidizing scientific meetings and courses throughout the world. Together with Igor Dawid in 1984 he started the biennial *Xenopus* conferences that alternate between the USA and Europe to this day.

In the United Kingdom, Gurdon served for many years as Master of Magdalen College in Cambridge and as Governor of the Wellcome Trust. He was remarkably disciplined in his use of time: microinjection experiments on Tuesdays and all correspondence answered on Friday. He would ride to work by bicycle or more rarely in a red Lotus (which he called Leo Sachs' gift), purchased with the Wolf Prize. He would travel to London by train with his bicycle, cycle to the Royal Society, and hand over his bicycle to the doorman who, in previous ages, was placed there to receive horses. He founded, together with Laskey, the Cancer Research Campaign (CRC) Institute of Cancer and Developmental Biology, and in 1988 the Wellcome Trust joined in this effort and provided a new building. His knighthood and Nobel prize (Fig. 5) were thoroughly deserved, for he was a builder of institutions.

John had a witty and understated English sense of humor. This is how he related in an interview the renaming of his institution as The Gurdon Institute in 2004: "Then the same combination of sponsors started up other institutes around the country also called Wellcome/CRC Institutes. It was very difficult to identify one from another. The view was that it would be better if we had a particular name to differentiate us. The director at the time was Jim Smith, a very fine director, but there were so many Smiths in the world that it didn't seem a very helpful name. So, they looked down the list, and they saw a rare name, and thought, 'Well, let's take that one, that'll do'. It was a bit of luck. There is no doubt about that. But if you are wise, you gratefully accept."



Fig. 6. John Gurdon and Alfred Nobel, 2012. Composite by The Nobel Foundation.

5. On being a good man

John was a gentleman of great kindness who mentored many generations of scientists through example. Always well mannered, he was a model of courtesy in the lab. His wonderful wife Jean took the families of arriving postdocs under her wing. Cambridge was a scientific heaven. Yet not all was empathy and gentleness, for John could be stern when needed. Allow me a personal anecdote. In his laboratory, my first project was to find out whether HeLa nuclei would direct protein synthesis in oocytes. After a couple of months, I thought I was not getting anywhere with the resolution of my gel electrophoreses and told John so. He turned red and in a strong voice (almost verbatim), said: “Eddy! I could give you easier projects but in that way you will never get anywhere.” I learned an enduring lesson. A few weeks later, John placed on my bench a preprint by Patrick O’Farrell describing two-dimensional electrophoresis consisting of isoelectric focusing followed by SDS Laemmli gels. Within a short time, we identified HeLa proteins made in oocytes (Gurdon et al., 1976). The most prominent protein was named the Eddy spot by Tim Hunt and yet another career was launched.

John’s example and joyful smile will be greatly missed (Fig. 6). In sum, John Gurdon was a good man.

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