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Narratives of Genetic Selfhood**

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Summary: This essay considers the mid-twentieth century adoption of genetic explanations for three biological phenomena: nutritional adaptation, antibiotic resistance, and antibody production. This occurred at the same time as the hardening of the neo-Darwinian Synthesis in evolutionary theory. I argue that these concurrent changes reflect an ascendant narrative of genetic selfhood, which prioritized random hereditary variation and selection through competition, and marginalized physiological or environmental adaptation. This narrative was further reinforced by the Central Dogma of molecular biology and fit well with liberal political thought, with its focus on the autonomous individual. However, bringing biological findings into line with this narrative required modifying the notion of the gene to account for various kinds of non-Mendelian inheritance. Hans-Jörg Rheinberger's reflections on narrative and experiment are valuable in thinking about the friction between the postwar ideal of genetic selfhood and actual observations of how organisms adapt in response to the environment.

Keywords: adaptation, antibody, antibiotic resistance, genetic selfhood, immunology, microbiology, narrative, selection, Synthesis, Hans-Jörg Rheinberger

Between the 1930s and the 1960s, genes—or their mutations—emerged as the explanation for many biological phenomena, including nutritional adaptation, antibody formation, and the origins of antibiotic resistance. In each of these

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examples, genetic selection or induction vanquished an alternative "instructive" or adaptationist explanation, one that emphasized the ability of living organisms to change in direct response to their environment, sometimes in a lasting way.[1] This was also the period when the so-called neo-Darwinian Synthesis was consolidated.[2] As Stephen Jay Gould has argued, the emerging Synthesis of the 1930s still had room for neo-Lamarckian heredity as well as evolutionary change through genetic drift. By the 1950s, the Synthesis hardened to exclude any form of non-Mendelian inheritance and any evolutionary mechanism besides natural selection. Genetic variation always emerged randomly, and that provided the only basis for natural selection of the most fit organisms.[3]

The identification of DNA as the hereditary material—as well as the elucidation of the relationship of RNA to protein synthesis—reinforced this hardened evolutionary view at a molecular level. Nucleic acid was genotype; protein was phenotype. As David Depew and Bruce Weber nicely put it, "The picket-fence of Weismann's barrier, on which the genetic theory of natural selection was based, was suddenly transformed into the Berlin wall of the central dogma of molecular biology: *Information in biological systems flows unidirectionally from nucleic acid to protein.*"[4] This metaphor of information has been a fruitful way to understand the historical consequences of molecular genetics for biology more broadly, in conjunction with a view of DNA as the master molecule.[5]

Without contesting the informational turn of biology in the 1950s and 1960s, I am interested in drawing out how shifts in microbiology, immunology, and evolutionary thinking reconfigured understanding of the organism's essential self and its relation to its environment. (Notably, work on DNA was not the driver of the shifts I discuss in these fields.) The very definition of "adaptation" became restricted (especially for microbes), so that physiological acclimatization was excluded in favor of genetic change via natural selection.[6] The genome was viewed as the essential and impermeable core of even the single-celled organism. Often the rise of genetic determinism and the hardening Darwinian synthesis are understood in terms of what was explicitly rejected, namely Lamarckianism (and, implicitly, Lysenkoism).[7] But one could cast the trend as producing a narrative about biological selfhood, rather than simply avoiding disreputable explanations.[8] This account presupposed (1) the biological individual as inherently competitive, (2) heredity as impervious and

[1] Creager 2007. My historical account of research on nutritional adaptation and antibiotic resistance offered in this essay draws on material presented in much more detail in this 2007 article.

[2] I will use the term "Synthesis" despite Joe Cain's well-reasoned objections developed in Cain 2009.

[3] Gould 1983.

[4] Depew and Weber 1995, on 354.

[5] Kay 2000.

[6] Creager 2007.

[7] Monod 1997; Jacob 1973; Sapp 1987.

[8] Selfhood has been a prominent theme in the history of immunology: Tauber 1991; Tauber 1994.

deterministic, and (3) selection as the only motor of lasting change to organisms. Insofar as microbes provided key model systems for understanding genotype and phenotype in molecular terms, single-celled prokaryotes were seen as valuable proxies for complex eukaryotes, as made clear by Monod's reference to the "well-known axiom that anything found to be true of *E. coli* must also be true of Elephants."[9] For biological fields that dealt specifically with embryological development, host-pathogen interactions, physiology, and learning, the resulting genetic self was both orthodox and insufficient to explain many phenomena.[10]

In *Spalt und Fuge*, Hans-Jörg Rheinberger explores several ways in which phenomenology can illuminate the connections between experimental knowledge and broader historical trends. He examines the role of narrative in experimentation, the relationship of macrohistory to "microhistory," and what is lacking in both Jean-François Lyotard's notion of master narratives and Georges Canguilhem's "scientific ideology."[11] As Rheinberger explains about ideology,

> [T]his is a level that is not particularly illuminating from the perspective of scientific research—at least as long as one remains convinced that scientific exploration, together with a few other activities such as the arts, ultimately possesses an irresistibly subversive power. In the end, being subversive means nothing other than to possess the capability of resisting such totalizations.[12]

He goes on to suggest that narratives are necessarily concrete and indeterminate, like the process of experimentation itself.

Here I offer a somewhat different way of considering narrative as a unit of scientific explanation.[13] In the cases I examine, the commitment to genetic explanation, especially notable in the US, guided research into alignment with Cold War values extolling the autonomous individual.[14] I return to Canguilhem, who defines "scientific ideology" in this way:

> By it I mean a discourse that parallels the development of a science and that, under the pressure of pragmatic needs, makes statements that go beyond what has actually been proved by research. In relation to science itself it is both presumptuous and misplaced. Presumptuous because it believes that the end has been reached when research in fact stands at the beginning. Misplaced because when the achievements of science actually do

[9] Monod and Jacob 1961, on 396.

[10] There is a strong literature on developmental biology: Gilbert 1991; Keller 1996; Keller 2002.

[11] Rheinberger 2021. Elsewhere Rheinberger (2013) has considered how Canguilhem's "scientific ideology" might be used to describe Mendelian genetics and molecular biology; see Löwy, this issue.

[12] Ibid., on 219. The translation is from the English version of the book in production at University of Chicago Press.

[13] On narratives in science I am inspired by Mary Morgan and Norton Wise: Morgan 2008; Morgan and Wise 2017.

[14] In this essay I will use "individual" and "self" as synonymous, favoring the latter due to its significance in immunology. For a more nuanced understanding of biological individuality, see Lidgard and Nyhart 2017.

> come, they are not in the areas where the ideology thought they would be, nor are they achieved in the manner predicted by ideology.[15]

Genetic selfhood would seem to fit well with his notion of scientific ideology, being both grounded in material observation and consonant with the ideology, here that of liberalism and anti-Communism, and more specifically anti-Lysenkoism. Yet Canguilhem also opens up a space for mismatch between cultural expectation and biological research. The cases I explore reveal interesting countercurrents in the attempts to reconcile experimental results with a genetic narrative. The picture of the self as defined by its genes included, at the level of biological detail, striking exceptions and concessions, even as the DNA double helix became its icon.[16]

1. Enzyme Adaptation and Antibiotic Resistance

As Michel Morange has shown, what came to be termed enzyme adaptation was first observed by Émile Duclaux in a section of the second volume of his massive *Traité de microbiologie.*[17] In two different fungal species, *Aspergillus glaucus* and *Penicillium glaucum*, certain digestive enzymes were only produced (and, in these microbes, secreted) when the nutritional substances they broke down were present. He referred to this phenomenon as "accoutumance."[18] Duclaux's student Frédéric Diénert further studied this nutritional responsiveness in a PhD dissertation on galactose fermentation in yeast (*S. cerevisiae*).[19] He found that yeast grown in glucose could not immediately ferment galactose, but if cells were transferred to a galactose-containing medium that also had a nitrogen source, they could acquire the ability to grown on galactose. Diénert attributed this to an enzyme, galactozymase, which was either activated by the presence of galactose or synthesized de novo. In addition, he showed that cell's fermentation of different sugars was coordinated. Media containing other disaccharides such as melibiose and lactose, which contain galactose, also exhibited galactozymase activity, whereas the availability of glucose would slow fermentation of galactose. Most importantly, such acclimatization could occur without the multiplication of cells. In the context of French neo-Lamarckianism, this physiological change was not in contrast to selection, but could be a mechanism for evolutionary adaptation.[20]

As Soňa Strbáňová has observed, during the first third of the twentieth century biochemists and microbiologists in several European countries worked on this phenomenon of nutritional adaptation via enzyme formation, some

[15] Canguilhem 1988, on 57–58.
[16] Nelkin and Lindee 1995. De Chadarevian (this issue) makes a similar argument.
[17] Morange 2010.
[18] Duclaux 1900, chapter 27.
[19] Loison 2013, on 170.
[20] Loison 2013.

providing additional examples, others questioning the observations.[21] The issue of how the cell responded physiologically was entangled with that of variation between cells in a culture, even as the meaning of variation for bacteria, which might not possess Mendelian genes, was also unclear.[22] Moreover, the identification of various enzymes, starting with Buchner's zymase, led to questions about whether each enzyme was produced independently, or whether adaptation involved the adjustment of a preexisting enzyme to a new substrate. Lastly, the language around this kind of change in response to (often nutritional) environment was not uniform, although adaptation became the most common term in English. Henning Karström's widely cited review, "Enzymatische Adaptation bei Mikroorganismen," not only introduced the phrase "enzyme adaptation," but also distinguished "constitutive enzymes," which are formed irrespective of conditions, from "adaptive enzymes," which are formed in response to specific nutrients or other environmental cues.[23] Yet the term "training" was also commonly used to describe such a physiological response, in ways that blurred the line between enzyme adaptation and (genetic) variation, because the stability of new trait often correlated with amount of the time under these conditions, sometimes becoming a permanent feature of a bacterial culture.[24]

In 1932, John Yudkin (who was working with Marjory Stephenson at Cambridge, England) drew a distinction between "training" and "adaptation": training, in his view, involved "obtaining a bacterial strain which carries out a reaction which it was previously incapable of doing, by growing it for a large number of sub-cultures in a medium containing the new substrate."[25] This becomes a new property of that strain, a heritable variation. Adaptive enzymes, by contrast, are formed in response to the chemical environment, and "with the removal of the stimulus, the character is lost by the descendants of the organism."[26] Thus an adaptation is an "uninheritable acquired character."[27] Training involved natural selection; adaptation (in his sense) did not.[28] At the same time, Yudkin's view of training allowed for exposure to a substrate to *induce* a mutation. In this respect, the generation of genetic variation was not blind to the environment, i. e., not necessarily random.[29]

Salvador Luria and Max Delbrück's "fluctuation test," published in 1943, was aimed at testing whether "training" could generate mutations or whether they represented truly random variation.[30] Luria realized (by way of analogy to

[21] Strbáňová 1997, on 263.

[22] See Beadle 1945.

[23] Karström 1937.

[24] Burnet and Fenner 1949, on 93.

[25] Yudkin 1932, on 1860.

[26] Ibid.

[27] Ibid., on 1870.

[28] Yudkin 1938, on 94.

[29] On the enduring idea of induced mutation among biologists (most notably John Cairns), see Keller 1992.

[30] Luria and Delbrück 1943.

a slot machine, according to his autobiography) that a *fluctuation* in the number of bacteria with phage resistance would indicate that the change was due to a random mutation.[31] They presented two hypotheses which their experiment would differentiate: (1) "mutation": exposure to phage selects for bacteria which possess a random variation of resistance; (2) "acquired hereditary immunity": exposure to phage elicits immunity in bacteria, which is then inherited in their descendants. While they did not use the term induced mutation, hypothesis 2 accords to some degree with Yudkin's training. Hypothesis 1, as they made clear, had already been proposed by Frank Macfarlane Burnet.[32]

As it turned out, their experiment showed that fluctuations in the number of variants resistant to bacteriophage among otherwise identical cultures were significantly greater than would be expected from the acquired immunity hypothesis. (According to Luria's analogy, this was a "jackpot" effect; the origin of immunity was a matter of chance.) Luria and Delbrück's finding was seen as providing an empirical basis for bacterial genetics, showing that microbes display the same kind of random variation that characterizes Mendelian organisms, and demonstrating that inheritance in bacteria was not Lamarckian.[33]

At Cold Spring Harbor Laboratory, while doing war-related work on penicillin, Milislav Demerec extended Luria and Delbrück's fluctuation experiment to study the emergence of antibiotic resistance. Drawing an analogy between resistance to phage and resistance to drugs, Demerec exposed cultures of *Staphylococcus aureus* to penicillin and analyzed the statistical frequency of appearance of resistance. Echoing Luria and Delbrück, Demerec asserted,

> Two alternate mechanisms can be visualized as responsible for the origin of bacteria resistant to certain concentrations of penicillin: (1) Resistance is an acquired characteristic, which develops through interaction between bacteria and penicillin when the two are in contact with each other. (2) Resistance is an inherited characteristic, which originates through mutation and whose origin is independent of penicillin treatment; resistant mutations occur at random, in a small fraction of a population, and, since a certain concentration of penicillin eliminates all non-resistant individuals, the resistant ones are selected out from the population by the treatment.[34]

The observed distribution of resistant colonies supported the second interpretation, of mutation and selection. Additionally, Demerec showed that resistance was transmitted as a permanent inherited trait through twenty transfers of culture in non-penicillin-containing broth. At the same time, he did see evidence for resistance developing in a gradual, step-wise fashion, which advocates of training saw as evidence for acquired immunity. Opposing this view, Demerec suggested that resistance was a complex genetic character that might involve multiple mutations.[35] After the war, the fluctuation test was

[31] Luria 1984, on 75–77.

[32] Burnet 1925; Burnet 1929; Sankaran 2021.

[33] Summers 1991; Keller 1992.

[34] Demerec 1945b, on 19.

[35] Demerec 1945a.

extended to other bacterial strains and their antibiotics, providing further evidence for the genetic origin of antibiotic resistance.[36]

These findings were not lost on evolutionary biologists. Theodosius Dobzhansky included a section on "Mutation and Selection in Micro-organisms" to his 1951 edition of *Genetics and the Origin of Species.* He argued that the interpretation of "changes in bacterial strains" had long had "a Lamarckian flavor, as implied by the words 'dissociation,' 'adaptation,' 'training,' etc., used in this connection."[37] This distasteful association had, however, been disposed of by the "brilliant analysis by Luria and Delbrück" and by Demerec's demonstration that resistance could involve multiple mutations.[38] As Dobzhansky concluded, "[t]his accounts for the gradual adaptation of bacterial strains to unusual environments, which was known in bacteriology for a rather long time but was misinterpreted in a Lamarckian fashion."[39]

As is well known, enzyme "adaptation" was reconceptualized and formally renamed enzyme "induction" by a group of microbiologists associated with the Pasteur Institute.[40] Over the 1950s and early 1960s, Jacques Monod and François Jacob drew analogies between induction of β-galactosidase and the phenomenon of lysogeny to develop their operon model of gene expression.[41] This model gave a place for environmental cues while attributing the organism's capacity to respond to changing conditions strictly to its genes.[42]

2. Acquired Immunity in Vertebrates

Adaptive immunity in higher organisms threw up similar problems as that in microbes: how was the acquisition of immunity, a response to the organism's conditions, related to heredity and evolution? It had long been recognized that exposure of a vertebrate to a pathogen or toxin could confer subsequent protection. This is one of the most striking examples of how multicellular organisms acquire a persistent biological trait in response to their environment. In 1890, Emil von Behring and Shibasaburo Kitasatō showed that a guinea pig injected with a sublethal dose of diphtheria toxin produced antitoxic serum that could be transferred to another guinea pig and bestow protection from that toxin.[43] In 1891 Paul Ehrlich introduced the term *Antikörper* to refer to certain antitoxins; this word, or its English equivalent antibody, soon came to

[36] Oakberg and Luria 1947; Demerec 1948.

[37] Dobzhansky 1951, on 87.

[38] Ibid., on 87 and 89.

[39] Ibid., on 89–90.

[40] Cohn et al. 1953.

[41] Jacob and Monod 1961; Loison and Morange 2017.

[42] The physiological nature of the operon model, and of work with microbes at the Pasteur Institute, has been connected by some historians to the legacy of Claude Bernard: Burian and Gayon 1991.

[43] Behring and Kitasato 1890; Silverstein 1989, on 49.

denote these blood-born (humoral) agents of protection.[44] How were they produced, and why did they continue to be produced, even after the initiating antigen was no longer present?

Ehrlich demonstrated that these protective factors possessed chemical properties and that their affinity for an antigen was highly specific and quantifiable.[45] His view of antibody-antigen interactions rested on a notion of chemical specificity, the diagrams in his 1900 Croonian Lecture depicting antibodies as latching tightly onto structurally complementary protrusions from a cell (which could also be released and bound to antibodies in the milieu).[46] In the hands of other chemists such as Karl Landsteiner and Felix Haurowitz, immunology was among the earliest of biomedicine's experimental cultures to shift from in vivo to in vitro work, using Rheinberger's apt terms.[47] Agglutination tests and titration series were key tools for identifying the presence of antibodies. Michael Heidelberger and Forrest E. Kendall provided evidence that antibodies were globulins (i. e., proteins), soon confirmed by Felix Haurowitz and Friedrich Breinl.[48] In the early 1930s, several researchers —including Haurowitz and Breinl—proposed that an antigenic determinant was carried in the body to the site of protein synthesis, where it provided a template for the antibody formation.[49]

Chemists were favorably inclined toward this template theory, but it also had some biological support. Landsteiner had shown that animals could produce antibodies against thousands of different substances, including synthetic chemicals. If the immune system "learned" to produce an antibody by encountering it, this would explain how the body could produce an antibody to an entirely foreign (even xenobiotic) substance. In addition, advances in protein chemistry were bringing antibodies into better view. When Arne Tiselius developed his electrophoresis apparatus in the 1930s, his demonstration of the power of the technique was the separation of horse blood serum into several discrete protein constituents: albumin, and α, β, γ, and δ globulins.[50] Subsequently, Tiselius and Elvin Kabat showed that the γ (gamma) globulin in rabbit serum contained antibodies.[51]

In 1936 Linus Pauling gave a seminar at the Rockefeller Institute for Medical Research and visited Landsteiner's laboratory there. Landsteiner drew Pauling's attention to the specificity of antibodies, asking how serological reactions could be explained by chemical bonds. Interested in the problem, Pauling read Landsteiner's book, *The Specificity of Serological Reactions*, as well

[44] Lindenmann 1984.

[45] Ehrlich 1897.

[46] This was indebted to the lock-and-key metaphor for enzyme-substrate binding. See Mertens 2019.

[47] Rheinberger 2021, chapter 7.

[48] Heidelberger and Kendall 1929; Breinl and Haurowitz 1930.

[49] Silverstein 1989, on 68–69; Breinl and Haurowitz 1930; Topley 1930; Mudd 1932; Alexander 1932.

[50] Tiselius 1937; Tiselius 1940, on 49.

[51] Tiselius and Kabat 1938.

as other publications on immunochemistry.[52] He began working on how new ideas of protein structure and hydrogen bonding might be used to revise the template theory of antibody formation. He attributed the high degree of specificity of an antibody to the folding of its polypeptide chain, which he argued was preformed, but not folded, before its direct contact with antigen.[53] Pauling's own published evidence for this theory could never be replicated.[54] However, over the 1940s and 1950s, different (gamma) antibodies were shown to have very similar compositions of amino acids, which supported Pauling's view that the antigen did not change the polypeptide sequence but rather its three-dimensional structure.[55]

However, as Frank Macfarlane Burnet observed, some biological observations did not square with the template theory.[56] First, specific antibodies were produced long after the instigating antigen was present. Second was the booster effect, or the fact that the secondary response to an antigen involved a greater antibody response than the first encounter. Neither of these could be explained through the chemical model, though Burnet agreed with proponents of the template model that the presence of an antigen (and, more specifically, its hapten portion) was essential for antibody to be formed. He and Frank Fenner offered a more biologically-oriented version of the template model, drawing on the behavior of so-called adaptive enzymes to explain antibody formation.[57] Burnet suggested that adaptive enzymes, unable to break down completely foreign substances, might generate antigens that, in turn, stimulate production of an antibody by the enzyme—a similar kind of adaptation to this new environmental cue. Immunity, on this view, was not due to changes in nuclear genes, but to enzyme reactions in the cytoplasm, which could be sustained because adaptive enzymes were regarded as entities that could replicate themselves outside the nucleus (plasmagenes) (Figure 1).[58] Strikingly, Burnet had used the term "training" to describe immunological reactions in the 1941 edition of this same book.[59]

It was in response to Burnet's adaptive template model that Nils Jerne proposed in 1955 a "natural-selection theory of antibody formation." Jerne proposed that the antigen, once introduced into the organism, was neither a template nor an "enzyme modifier," but rather "a selective carrier of spontaneously circulating antibody to a system of cells which can reproduce this antibody."[60] Key here was that some of the antibody with a particular specificity is already present in the body, but binding to the complementary antigen triggers formation of more of the same antibody, through assimilation

[52] Pauling 1970.
[53] Pauling 1940.
[54] Deichmann 2021.
[55] Haurowitz 1957.
[56] Burnet and Fenner 1949, on 83.
[57] Ibid., on 93.
[58] Ibid., on 95.
[59] Burnet 1941, on 46 and 63; Löwy 1991, on 61.
[60] Jerne 1955, on 849.

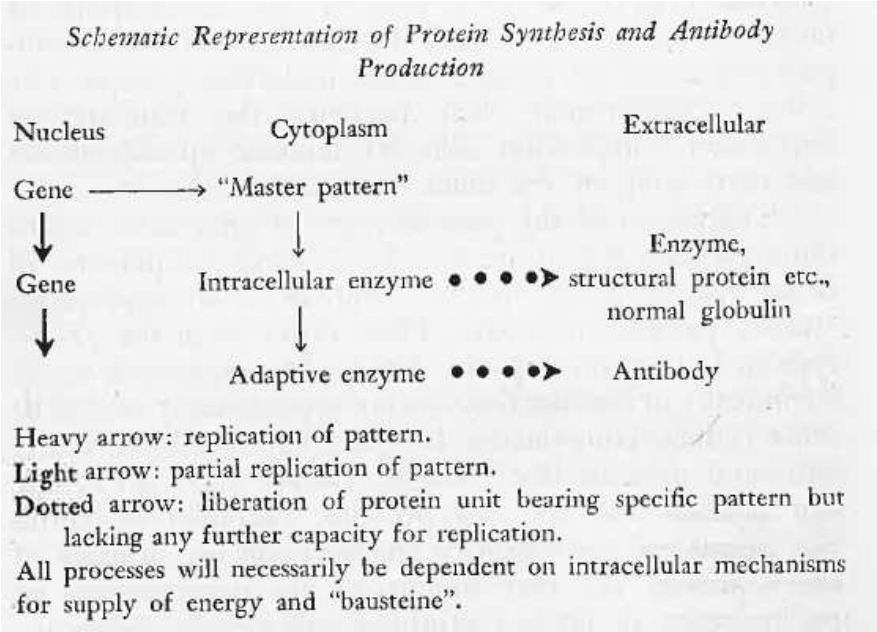

Figure 1. Burnet and Fenner 1949, on 94.

into phagocytes and transfer to other immune cells. As for the increase in antibody formed after exposure, Jerne said this could be due to "autocatalytic replication of the specific globulin molecules and to a multiplication of the cells."[61] Jerne's model relied on "a spontaneous production of random specificities [in antibodies]" either early in development or continuously.[62] David Talmage and (independently) Burnet subsequently modified Jerne's model so that selection operated not at the level of the antibody, but at the level of the antibody-producing cell. It was Burnet who christened this sort of somatic cellular change "clonal," resulting in the term clonal selection theory.[63]

As Michel Morange has observed, Jerne's selective model did not rely on DNA or genetic information though it suggested possible involvement of RNA (already known to be involved in protein synthesis from the work of Jean Brachet).[64] There had been contributions from geneticists in the 1940s that argued for interactions between genes and antibodies, quite distinct from Jerne's ideas. In separate papers published back-to-back in *PNAS*, Alfred Sturtevant and Sterling Emerson suggested that antibodies might cause specific mutations in genes structurally resembling their antigens. Sturtevant picked up on Landsteiner's earlier observations that antigens both (1) induced the

[61] Ibid., on 850.
[62] Ibid.
[63] Talmage 1957; Burnet 1957.
[64] Morange 2014b.

formation of antibodies and (2) bound specifically to antibodies. If genes were structurally similar to antigens, he reasoned, these could be related via mutation. The "natural selection" models of Jerne, Burnet and Talmage went in a different direction, thinking of the antibody-antigen reaction not in terms of mutation, but rather selective protein synthesis. Talmage specifically cited Cohn et al.'s renaming of adaptive enzymes to "inducible enzymes" in proposing his cellular selection theory.[65] This put gene expression at the heart of the antibody formation. Burnet's modification emphasized the key role of natural selection in the proliferation of some antibodies over others: "Each such clone will have some individual characteristic and in a special sense will be subject to an evolutionary process of selective survival within the internal environment of the body."[66] Joshua Lederberg then rendered the clonal selection model in terms of DNA.[67]

3. Ironies of (Molecular) Genetic Selfhood

Evelyn Fox Keller has analyzed elegantly how the role of genes, especially in development, changed from one of "action" to "activation."[68] When Monod and Jacob introduced their 1961 operon model to explain protein synthesis in *E. coli*, they immediately suggested that selective regulation of genes could also explain cellular differentiation in higher organisms.[69] While their general framework remained fundamental to molecular genetics, the mechanisms involved in gene expression were found to be more and more complex, involving a wide a variety of enhancers and transcriptional factors. In the genomic and post-genomic era, the turn to investigating phenotypes in terms of regulatory networks has further complicated what it means to attribute a trait to genes. Biologists have discovered that mutations in genes involved in differentiation often have a dramatic impact on embryological phenotype, calling into question the assumption that evolution works by "small" adaptive variations.[70]

In immunology, the acceptance of clonal selection theory created a new problem for biologists. If every specific antibody was produced by one gene, how could the genome containing all of them be so small? The "Generation of Diversity"—or "GOD"—problem became a major arena in which molecular biologists were able to demonstrate the power of their techniques to answer immunological questions. As Scott Podolsky and Alfred Tauber have shown in magnificent detail, over the course of the 1960s and 1970s, biologists including David Talmage, Philip Leder, Leroy Hood, Susumu Tonegawa and many others uncovered the complex recombinatorial diversification through which

[65] Cohn et al. 1953; Talmage 1957, on 244.
[66] Burnet 1957, on 67.
[67] Lederberg 1959; Morange 2014b.
[68] Keller 1994; Keller 1995.
[69] Jacob and Monod 1961; Monod and Jacob 1961; Morange 1996.
[70] Morange 2014a.

three hundred or so germline genes can produce somatic cell lines that synthesize billions of different antibodies. Individuals do not inherit the specific antibody-producing genes from their parents, but rather generate them during embryological development.[71] This provides a radically different picture of what heredity means compared to Mendelian transmission of germline genes. The solution of the GOD problem was a triumph for molecular biology, and yet the further attempt to pin down selfhood to a genetic signature (the major histocompatibility complex) proved elusive. Rather, as network theorists in immunology have argued, the immune "self" is produced dynamically in response to events within the organism and through ongoing encounters with its environment.[72] As immunological "memory" suggests, the system is a product of the organism's history, not only its genes.

The success of the mutational explanation of antibiotic resistance resulted in a similar irony. Consider the discovery of "multiple resistance," or the simultaneous emergence of resistance in a single bacterial species (as observed in an infected patient) against several antibiotics.[73] How could a mutation in one bacterial gene confer resistance to many antibiotics, each having different mechanism of action? Tsutomu Watanabe and his collaborators solved this puzzle by determining that resistance was not arising via a mutation on the bacterial chromosome but acquired via cytoplasmic plasmids called R factors.[74] These R factors could carry genes for resistance to many antibiotics and seemed able to promote their own dissemination in bacterial populations. The vindication of a genetic view of drug resistance necessitated recasting the gene to include extrachromosomal hereditary units carried on viruses and plasmids. In fact, the transmission of such plasmids between bacteria leads to inheritance of acquired characteristics, in this case bits of cytoplasmic DNA.

In contemporary research, such as on epigenetics and the microbiome, most biologists continue to qualify genetic selfhood without calling that edifice into question.[75] Meanwhile, the fuzzy interface between self and environment remains comparatively underexplored. In representing DNA damage and repair, for instance, free radicals generated by normal metabolism and polymerase errors in DNA replication are depicted alongside industrial chemicals and natural carcinogens (such as sunlight) as equally part of the gene's destructive environment (Figure 2). A historian of biology might note that Claude Bernard's differentiation of *milieu intérieur* from *milieu extérieur* is sorely missed.[76]

[71] Podolsky and Tauber 1997, on 92. A recent study offers estimates the number of antibodies that humans can produce to be as high as one quintillion. Briney et al. 2019.

[72] Varela et al. 1988; Podolsky and Tauber 1997, chapter 9.

[73] Akiba et al. 1960.

[74] Watanabe 1963.

[75] Some do question the assumptions of genetic individuality, proposing instead that living organisms are inherently symbiotic, i.e., holobionts: Gilbert et al. 2012. On epigenetics, see Morange 2020, chapter 26.

[76] Bernard 1878; Holmes 1986.

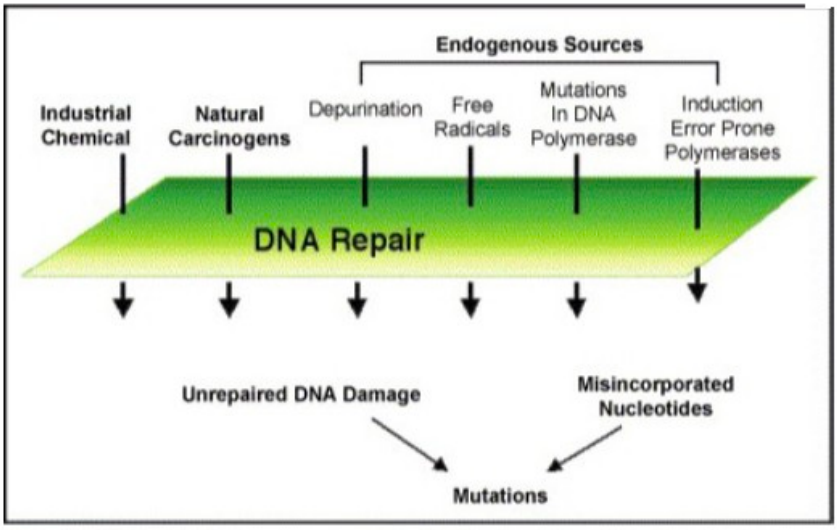

Figure 2. "Equilibrium between DNA damage and DNA repair. Above the screen are listed exogenous and endogenous sources of DNA damage. Below the screen are the small number of DNA alterations that escape DNA repair and result in mutagenesis." Diagram and caption reproduced from Wogan et al. 2004.

Commentators have pointed to problems with the scientific conception of the self, above all in immunology, where it is so central.[77] Richard Lewontin has observed that the notion of the biological individual is moored in a broader ideological framework, one that is now deeply embedded in the assumptions of life scientists.

> The historical development of a modern mechanistic biology had depended critically on a successful separation of the internal from the external. […] Environments set the problems. Organisms whose inner nature allow them to solve the problems successfully survive and leave offspring. The others fail. The nature of the organism itself is a consequence of internal forces that are independent of the external world, that is, at random with respect to the problems created by the environment. The individual organism is then the locus of connection between the internal and external. It is called into being by the internal and disposed of by the external. It has, in this way, no separate existence, but is simply the nexus of autonomous internal and external forces. We then have the curious irony that although Darwinism is a theory of individual survival and reproduction, of individual adaptation, the organism as organism plays no role at all. […] So, the critical role of the individual is threatened and contradicted by its placement at the boundary between autonomous internal and external forces. The contradiction is a very deep one, for if there is no boundary between the internal and the external, if they flow continuously into each other as the premodern natural philosophers thought, then how do we locate the

[77] Burnet 1969; Anderson and Mackay 2014; Cohen 2017.

> individual at all? "Self," by its own nature, demands the definition of its dialectical partner, "other."[78]

The notion of genetic selfhood would seem especially susceptible to Lewontin's critique: what is the genetic individual's other? In the experimental examples I have presented, attention to the dynamic interaction of the organism with its environment, which was initially the object of study, was sidelined by explanations that highlight the variation, expression, and selection of genes. The picture of genetic selfhood that emerged was one in which an organism's ability to respond to the environment had to arise randomly in its hereditary material, even though for higher organisms, components such as the immune system and nervous system are clearly generated not directly by genes but also through encounters with the environment—as well as within the self.

The postwar explanations for enzyme adaptation, antibiotic resistance, and antibody production were ultimately vindications of both molecular biology and the Synthesis. The atomistic and competitive view of the genetic individual that emerged fit well with Cold War political liberalism and (as others have noted) gave no evolutionary standing to symbiosis, cooperation, and other forms of biological collectivism.[79] And, to be sure, the technologies of genetics have proven exceedingly useful in research, medicine, and the production of biocapital.[80] As Rheinberger observes, the usual notion of ideology—which would seem to be operative here, both conceptually and economically—gives so much causality to politics that it barely leaves any room for the subversive effects of scientific exploration (or the arts).[81] Yet the cases discussed here also show how experimentation at times interfered with the dominant narrative. Researchers in immunology and antibiotic resistance had to revise the notion of the gene to fit with their findings, loosening the grip of Mendelian inheritance. The "genetic self" resides in this space between expectation and experiment, an ideological script qualified and sometimes undermined by the complexities of organismal life, even as it is treated as settled.

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[78] Lewontin 1991, on xv.

[79] Mitman 1992; Sapp 1994; Amadae 2003; Nyhart and Lidgard 2021.

[80] Sunder Rajan 2006.

[81] Rheinberger 2021, on 219.

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