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THE FRENCH SCHOOL OF GENETICS: From Physiological and Population Genetics to Regulatory Molecular Genetics

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■ **Abstract** French genetics had unusual beginnings. There are clear indications that the French biological establishment resisted Mendelian genetics strenuously from about 1910 to 1940. From about 1930 to 1950 several unconventional research programs with a strongly physiological orientation paved the way for the full entrance of French biology into genetics after World War II. This review examines some salient features of this history to clarify the strengths, weaknesses, and distinctive features of French genetics until about 1965. We suggest that after that date French genetics slowly merged into the international mainstream as genetics has become a largely molecular discipline.

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INTRODUCTION

In this review we explore some aspects of French biology before World War II to highlight certain key features of the founding of regulatory genetics in France in the 1950s and 1960s. The history we cover is puzzling: For nearly half a century mainstream French biologists expressed extreme misgivings about Mendelian and chromosomal genetics and virtually ignored it in university curricula. Yet in the 15 years after World War II they did much groundbreaking work in cytoplasmic, physiological, and regulatory genetics, culminating in the work that won the Nobel Prize for Jacob, Lwoff, and Monod for their contributions to regulatory genetics in microorganisms. To understand these rapid and dramatic changes, we examine the period from 1900 (the rediscovery of Mendel's laws) to 1965 (the awarding of the Nobel Prize, which marks the return of French genetics to the international mainstream). In our interpretation, the emergence of a French school of molecular genetics in the 1950s was not simply a decisive victory of a camp of enlightened scientists over obscurantist and retrograde colleagues. Rather, it also represented the culminating success of little-appreciated, autonomous traditions of work on heredity developed in independence of the standard Mendelian-chromosomal genetics that became the international mainstream during the first half of the century.

In what follows, we describe the reception and rejection of Mendelian genetics in the first three decades of the century. From 1930 to 1950, there was some interest in genetics, but several unorthodox lines of research paved the way, unforeseeably, for the achievements of the 1950s. The last part of the paper deals with those achievements, focussing on physiological genetics, cytoplasmic heredity, and nucleo-cytoplasmic relations. We touch on institutional as well as conceptual aspects of the history and locate some developments in an international context.

FRENCH BIOLOGISTS AND GENETICS, 1900–1930

To understand the resistance of French biologists to Mendelian genetics, it is important to discuss three matters: the diffusion of the new discipline within the scientific community, the teaching of genetics, and research directed toward problems of heredity. Each of these aspects tells a different story (25).

Scholarly Diffusion

We have studied six widely read French biological journals from 1900 to 1930.[1] Mendelian genetics was thoroughly discussed from the very beginning. The very first publication of the rediscovery, published by De Vries in March 1900, in the *Comptes Rendus de l'Académie des Sciences* (49), presented the law of disjunction without mentioning Mendel. This paper was reviewed twice in *l'Année Biologique* for 1900: by Cuénot (36) and by the editor, Yves Delage, who devoted a full page to it in his introductory overview of the volume. Between 1901 and 1903, *l'Année Biologique* published abstracts of major papers on Mendelism by Bateson, Castle, Correns, Cuénot, Darbishire, De Vries, Doncaster, Haecker, Tschermak, and Wilson. The 1902 volume included an extensive review of Mendelian research by Cuénot (38). The journal continued in this vein through 1914. Again, Cuénot, the leading French contributor to the early development of the new discipline, published Mendelian papers in five of the six journals on our list and was awarded the Cuvier Prize of the *Académie des Sciences* in 1911, with special mention of his genetic experiments. Those experiments stopped, however, in 1914.

Anti-Mendelians also reported Mendelian research fully, although critically. Thus, the *Bulletin Scientifique de la France et de la Belgique*, a bastion of neo-Lamarckism, published (and criticized) numerous accounts of Mendelian work, including a translation of Mendel's 1865 memoir in 1907. We must also mention the Fourth International Conference of Genetics, held in Paris in 1911 (154a). The Conference was organized at the instigation of the Vilmorin family (81), proprietors of a major seed company, and was attended by an impressive number of French biologists, though some were critics of genetics. In short, even though Mendelism was not widely accepted, it was widely known and discussed before World War I.

Textbooks and Teaching

The failure of genetics to enter into the curricula of French universities in the first decades of this century is enormously important, for it shaped the methodological and conceptual matrix of the next generations of scientists. International comparisons are useful here. By the onset of World War I, there were chairs of genetics (sometimes with different names) in England (Punnett), Germany (E Baur), and the United States (EB Brown). In Moscow, A Serebrovsky accepted a chair of genetics in 1930. In France, the first chair of genetics was created for Félicien Boeuf in 1936 at the National Institute of Agronomy in Paris (153), but this was not a University chair and was not widely influential. The first university chair in genetics was created only in 1946 for Boris Ephrussi.

[1]They are *L'Année Biologique, Archives de Zoologie Expérimentale et Générale, Comptes Rendus de l'Académie des Sciences, Comptes Rendus de la Société de Biologie, Bulletin Scientifique* [after 1917, *Biologique*] *de la France et de la Belgique,* and *Revue Scientifique*.

Textbooks also provide striking evidence. At least 13 English or American treatises or textbooks were specifically devoted to genetics before 1920, many of them in multiple editions. Five comparable books were published in German [listed in (25)]. No synthetic book on genetics was published in France until the mid-1920s. To be sure, Cuénot included significant chapters on Mendelian heredity in the successive editions (1911, 1922, 1932) of his book on the *Genesis of Animal Species* (43). Still, the first systematic book on Mendelian genetics in French was a poorly distributed translation of Morgan, Sturtevant, Muller & Bridges' *Mechanism of Mendelian Inheritance*, published in Belgium in 1923. The first French textbook was published a year later by Emile Guyénot (81); this remarkable book greatly influenced the young biologists of the time. Its successive editions (1930, 1942, 1948) remained the major French-language source of information into the 1950s for anyone seeking serious initiation into genetics.

Finally, genetics was barely taught in colleges and universities until after 1945. The only exception before 1930 was Nancy; there, Cuénot included genetics in his zoology courses from before World War I. In Paris in the 1920s, Blaringhem, a neo-Lamarckian, introduced some genetics at the Ecole Normale Supérieure (10), as did Caullery in the Sorbonne, in the form of a 12-hour optional course (32). Also in the 1920s, a course entitled "Génétique, phytotechnie and botaniq-ue appliquée" was taught at the National Institute of Agronomy (153, p. 109). But there was nothing more in the first three decades of the century; it was only in 1948 that the first "Certificate of Genetics" was instituted in university curricula under Ephrussi's supervision. The contrast with other major scientific nations is dramatic.

Research

The story of genetic research during these decades is even stranger. Thanks to Lucien Cuénot (1866–1951), the French were well represented in the first wave of Mendelian research. But, after a brilliant start, Mendelian genetics was eliminated from mainstream biological research in France in the second and third decades of twentieth century. Cuénot, briefly a Darwinian selectionist (106), switched, shortly before 1900, to a more saltational view of evolution that he eventually elaborated under the name of "the theory of preadaptation" (76). From 1900–1910, Cuénot was one of the most productive geneticists. His contributions include (*a*) extension of the laws of disjunction and independent assortment to the animal kingdom, specifically mice (37); (*b*) the discovery of multiple alleles (40, 41); (*c*) recognition of interaction among different Mendelian factors (41); (*d*) recognition that a given Mendelian determinant can mask the effect of other Mendelian factors (epistasis in a more modern sense) (41); (*e*) recognition of lethal homozygotes (42); (*f*) the first statement of the hypothesis that gene function is related to production of enzymes (39); and (*g*) pioneering work on the genetics of cancer, especially the recognition that tissues with a given genotype can behave differently according to the genotype of surrounding tissues [(45) and seven later papers].

Although he completely abandoned experimental research in genetics after 1914, Cuénot's reputation in mammalian genetics remained strong: In 1928, he reviewed the genetics of mice for *Bibliographia Genetica* (44). His stocks of mice were destroyed in World War I. When he returned to Nancy in 1918, it was clear that the Morgan school had already made the big breakthrough. Cuénot, "who wanted to be the first" (JG interview with Andrée Tétry), gave up. He also dissuaded his students from writing PhD dissertations in genetics because he thought that they would not find positions in France.

This last point reflects the French resistance to genetics. France was proud of Cuénot, but in general there was strong intellectual reluctance to pursue Mendelism, as is illustrated by the treatment of Emile Guyénot. In 1909, he began a PhD dissertation under the direction of Maurice Caullery. The theoretical objective (strongly supported by a major neo-Lamarckian, Etienne Rabaud) was to show that Morgan's Mendelian results were artefacts caused by improper control of the experimental conditions. The idea was that some "mutations" were conditions caused by failure to control the nutrition of the flies or by infections stemming from failure to establish a rigorously aseptic experimental environment. By 1917, in spite of the war, Guyénot had counted 400,000 flies and examined a large number of mutants. But the mutants did not change in altered environments; they arose in constant environments, and Mendel's laws were verified whatever the environment. Guyénot's dissertation, published by Rabaud in the *Bulletin Biologique de la France et de la Belgique* (80a), led to a violent dispute between them solely because Guyénot had supported Mendelism. In the end, Guyénot did not find a position in France. He was recruited to Geneva, where he acquired considerable influence as a geneticist, especially through his 1924 textbook. But he had no students in France, and, by 1930, no one there was carrying out fundamental genetic research.

Explanation of the Delayed Development of Genetics in France: A General Scheme

The resistance of the French biological community to genetics stems from at least four causes. First, certain intellectual traditions contributed to the reluctance to accept Mendelian genetics. A number of these that were influential near the turn of the century are of particular concern here. Consider, first, the influence of resistance to Darwinian evolution, quite virulent in France. Around 1900, French paleontologists, among the few who had been sympathetic to some aspects of Darwinism and who had expended considerable effort in constructing phylogenetic trees in the nineteenth century, abandoned this practice on grounds that no demonstration of filiation between species was feasible. Instead, the standard paleontological view became that one could only record the relative prevalence of different forms of organisms in successive strata, yielding results that simply could not reveal the process or sequence by which a species was formed (77a). Meanwhile, under positivist influences, many biologists, including many who accepted

evolution, became increasingly skeptical about the possibility of identifying causes of transformation of organismal properties and transmission of particular traits across a series of generations. They argued that neither selection nor modes of transmission were accessible. Again, adherents to the Bernardian ideal for biological sciences rejected Mendelian and chromosomal genetics for its formal and "unphysiological" character. A related argument was that Mendelians gave the nucleus exorbitant powers and neglected its physiological interactions with the cytoplasm so that no sense could be made of how Mendelian factors act. More generally, many biologists influenced by French positivism denounced the "metaphysical" character of Mendelian "factors"—speculative hypothetical entities in the service of a discredited preformationist approach to biological problems (25). These distinct traditions linked up to reinforce a generalized skepticism about the ability of biologists to determine the causes of evolution or of inherited traits and their transmission; the most that could be scientifically ascertained was a description of the "before and after" for changes of interest.

A second source of resistance concerns the connection of genetics to eugenics. Like it or not, the countries where genetics, which favored "hard heredity" and denied the inheritance of acquired characters, flourished from 1900 to 1930 (England, USA, Germany, the Scandinavian countries), are precisely the ones that developed strong eugenic traditions and legislation. Although a French Society of Eugenics was created in 1912 (with Cuénot as one of its most active members), it never achieved influential prominence. Historians connect this to the French obsession with their demographic decline vis-à-vis Germany—French eugenics, such as it was, took the paradoxical form of providing the best conditions for producing a maximum of mothers and babies (31, 53, 74, 77, 142).

A third is the failure of French academic biology to establish solid interactions with agricultural research. The countries where Mendelism flourished all had forged close ties between agricultural engineering and experimental biology (again, the United States, England, Germany, the Scandinavian countries, and perhaps, ambiguously, Russia). In France, the Vilmorin Company tried hard to develop such connections—genetics was a crucial discipline for its survival as the foremost seed company in the world before 1914 (79). But, in practice, the worlds of university research and plant and animal breeding remained widely separated until the creation of the Institut National de Recherche Agronomique in 1921.

Finally, there is the sheer loss of a generation of young men in World War I. So few students returned from the war that many disciplines were very seriously underdeveloped. In the climate we have described, genetics did not rank high on the list of the returnees' priorities. The lack of career paths and the discouraging climate regarding genetic investigations kept those biologists who sought work within the French mainstream away from that discipline.

None of these causes was sufficient, by itself, to account for the delayed development of genetics. Their conjunction, however, provides a reasonable account of that delay.

THE ROUTES TO GENETICS, 1930–1950

There are signs of a significant change in some French biologists' attitude toward genetics in the1930s. Mention of the topic in a few modest and nonmandatory introductory courses in the 1920s had produced some effect on the new generation. Jean Rostand's popular book of 1930, *From Flies to Humans* (141), had a considerable impact, and Guyénot's textbook of 1924 (81) served as a major point of entry for those who wanted to get reliable information on genetics in French.

In the 1930s, a handful of young biologists embarked on innovative research programs that defined the specific routes that led French biology into the international genetics community. None of them were formally trained in genetics in their courses or in French laboratories (how could it be otherwise?). They all worked outside the university system and had few or no teaching obligations. Georges Teissier and Philippe L'Héritier, originally mathematicians working at the Ecole Normale Supérieure, were the only ones to have some teaching duties. Boris Ephrussi worked at the Institut de Biologie Physico-Chimique (or Rothschild Foundation), a research institute founded in 1926 to foster innovative experimental research in biology, while André Lwoff, Eugène Wollman, and later Jacques Monod worked at the Pasteur Institute. These people knew each other, often spent summers together at the marine biological station in Roscoff, and published together in all possible combinations. They were all involved in international networks of some sort or other. Four of them (Ephrussi, L'Héritier, Monod, and Lwoff) received Rockefeller Foundation support in the 1930s. The first three used this support to work in US laboratories, Lwoff in Germany and England. Finally, considered in terms of genetics, all their research programs were either marginal or unconventional, but all led sooner or later to major breakthroughs. Let us examine some key features of the pathways they took.

Experimental and Theoretical Population Genetics

In 1931, Philippe L'Héritier (1907–1994) was the first French biologist to benefit from a Rockefeller grant. He left France with the "the task of learning genetics and of finding a research project which he could continue in France after returning from the US"[2] (102, p. 335). He studied genetics at Iowa State under Lindstrom and attended the International Congress of Genetics in Ithaca in 1932, where he met Fisher, Wright, Muller, and Dobzhansky. On his return to France in 1932, he had the idea of breeding Drosophila in "demometers," i.e. population cages, where food was periodically renewed. This allowed study of the kinetics by which competing strains approached demographic equilibrium and of the parameters of a population in equilibrium, both of which were impossible when breeding

[2]Our translation. In general we have used English texts where convenient and translated French texts ourselves.

flies in bottles. L'Héritier built the population cages himself and used them in association with Teissier (1900–1970) to test the abstract models of Fisher and Wright. From 1933 to 1937, they published nine papers on the evolution of experimental populations of *D. melanogaster*. L'Héritier then moved to Strasbourg and Clermont-Ferrand; Teissier continued working with the population cages, yielding 11 additional papers between 1942 and 1954. Their experiments were designed to study competition between genes, a problem that Dobzhansky took up considerably later. The most remarkable result was the unexpected finding that various deleterious mutants (e.g. *bar* and *ebony*) were not eliminated in competition with normal alleles. Rather, an equilibrium was attained (103, 104). The problem of the maintenance of genetic polymorphism became Teissier's major concern. In later papers, he tried to establish the hypotheses that he and L'Héritier had proposed in 1937 on a firm experimental basis—that maintenance of polymorphisms could be accounted for by heterosis (*ebony* against wild), frequency-dependent selection (*bar* against wild), and fluctuations of selective values due to changes of genetic context (*sepia* against *ebony*) (150). Wright, who visited Paris in 1938, appreciated the population cages and brought them back to Dobzhansky, who took up the method a few years later. The population cages became the preferred technical tool in experimental studies of evolution by Russian and American workers for analyzing natural selection and its effect on changing gene frequencies (W Anderson, personal communication).

One special investigation deserves notice here, namely the discovery of CO_2 sensitivity. CO_2 was used to anesthetize the flies for counting. It killed all the flies of some strains. L'Héritier found that this trait is maternally inherited and cytoplasmically transmitted. He devoted over 20 years to studying it (101a, 105). This is but one of a large number of cases of cytoplasmically inherited phenomena with which French geneticists became fascinated. We discuss the importance of their attention to cytoplasmic inheritance and nucleo-cytoplasmic relations below.

In the 1940s, Teissier formed a genuine research school, focused on the maintenance of genetic polymorphism in experimental and natural conditions. An example of the importance of its work is an often-neglected paper from 1942 (149a) in which Teissier, apparently the first to do so in an explicit mathematical formulation, analyzed the contributions of viability and fecundity as components of fitness (W Anderson, personal communication).

Four of his students deserve particular mention. Maxime Lamotte sought to verify Wright's distribution models in the land snail *Cepea nemoralis* (97). Bocquet, in association with others, chose to test models of isolation by distance on *Sphaeroma serratum*, a marine crustacean living along the coasts (11). Boesiger and Petit worked on experimental populations: the role of sexual selection in heterozygote advantage (12), and frequency-dependant selection (136). Finally, there is the outstanding contribution of Gustave Malécot to theoretical population genetics. A mathematician trained at Ecole Normale Supérieure, Malécot defended a groundbreaking PhD in 1939 (120), a first version of the famous *Mathematics of Heredity* (121). Malécot's major contribution can be summarized succinctly: He

provided a genuinely probabilistic interpretation of population genetics, in contrast to the previously dominant statistical approach. This approach led him to "kinship coefficients" and to a new understanding of isolation through distance, both extremely important for the development of human population genetics in the second half of this century. Thus, a significant and fertile school of population genetics was formed out of the work begun in the mid-1930s (78).

Genetic Control of Eye Pigmentation in Drosophila (Ephrussi and Beadle)

The most distinctive contribution of French laboratories to genetics from 1910 to 1940 is Beadle and Ephrussi's work on eye pigmentation in Drosophila. Boris Ephrussi (1901–1979) was born in Russia, arrived in France in 1920, and studied biology at the Sorbonne. From 1923 to 1932, he worked on sea urchin embryology and tissue culture under Emmanuel Fauré-Frémiet (professor of embryology at the Collège de France). Fauré-Frémiet provided him a position at the Institut de Biologie Physico-Chimique. In the 1930s this laboratory became known as "Ephrussi's lab."

In 1934–1935 Ephrussi, already convinced that the key to improved understanding in embryology was genetic determination of potentialities, received a Rockefeller fellowship to work under Morgan at Caltech and with Sturtevant at Woods Hole. This enabled him to learn Mendelian techniques; he published his first paper in genetics promptly in 1934. Based on Sturtevant's observations on mosaics, it showed that some characters exhibit "nonautonomous development," e.g. that the effect of a particular lethal gene can be suppressed by nearby genetically wild-type tissue (56). At Caltech, Ephrussi became acquainted with George Beadle, then a postdoctoral student. He convinced Beadle to come to Paris and combine their embryological and genetical skills to study the question of "autonomous" versus "nonautonomous" development of genes with a daunting new method. The idea was to combine embryological techniques with the genetic specificity made feasible by Drosophila genetic technology, specifically, to implant imaginal disks from flies of a given genotype into the abdominal cavities of flies of a different genotype, and thus "lay a bridge between causal embryology and genetics" (67). In practice, they worked on 27 different strains of Drosophila (26 mutants for eye pigmentation and a wild strain), testing 729 different combinations. In most cases, the implanted eyes developed autonomously. Two mutations, however, exhibited nonautonomous development: *vermilion* and *cinnabar*. For instance *v* and *cn* eye disks implanted in a wild strain yielded wild-type eyes. Furthermore, reciprocal transplantation between the two mutants produced asymmetrical results: *v* develops into a normal eye in *cinnabar*, but not the reverse. They explained this by postulating the existence of two diffusible substances, one of which results from transformation of the other. They represented this hypothesis with the following figure:

$$\rightarrow \text{ substance } v^{+} \rightarrow \text{ substance } cn^{+}$$

Thus, in some way or other, the *v* and the *cn* genes control two successive steps in the metabolism of a diffusible substance (6). In one of their last joint papers (7), they remained cautious about the interpretation of this hypothesis. They stressed that the sequence of steps they had hypothesized was a "skeleton" that might involve a number of more elementary reactions. They made no commitment about the nature of the diffusible substances (metabolic precursors of the pigment, catalytic substances intervening in the transformation of the precursors, or something else).

The collaboration ended in 1937, with a total of 18 papers. [For more information, see (25, 26, 75), the last of which lists all of Ephrussi's publications on this topic.] In 1938, Ephrussi published six more papers on the subject, arguing that the diffusible substances were not enzymes, but inter-transformable hormones that interacted with the precursors of the pigment. Thus neither Ephrussi and Beadle, nor Ephrussi alone, proposed the "one gene–one enzyme" hypothesis. That proposal came in two steps: First, the German biochemist Butenandt discovered the biosynthetic pathway leading from tryptophan to the brown pigment (30). Second, Beadle, Tatum, and colleagues gradually elaborated the hypothesis in their work on Neurospora [see e.g. (4, 5, 8); see also (96)].

During World War II Ephrussi served in the army, then fled France; in difficult circumstances for the rest of the war, his hope of quickly accomplishing something like what Beadle had were frustrated. Still, his experimental work with Beadle played a prominent role in the French entry into genetics. The collaboration was immediately recognized internationally as a major breakthrough in physiological genetics. It also had an important impact in France. In 1937, Ephrussi's lab was rebaptized "laboratory of genetics" and he became responsible for a series of books on physiological genetics at Editions Hermann. After the war, in 1946, after considerable infighting to overcome the opposition of the biologists (20, 137, pp. 132 ff.), he was offered the first chair of genetics in a French university, in Paris. With major help from L'Héritier, Teissier, and others, the first French university degree track in genetics was soon under way.

The establishment of additional research laboratories in genetics is related to the work in population genetics. After World War II Teissier became director of the Centre National de la Recherche Scientifique (CNRS) and devoted considerable effort to the creation of three laboratories of genetics in the CNRS, a process that took 15 years (137, pp. 132 ff.). They were directed, respectively, by himself, L'Héritier, and Ephrussi (21, 23, 137, 168). Thus, the direct routes leading to official support of genetics in France were population genetics and physiological genetics. Retrospectively, this is not surprising: Mathematics and physiology had been major concerns in the history of French science for centuries.

The three "routes to genetics" described in the three following subsections stand on another level. They do not count as "genetical" even in a loose sense. But they paved the way for the major accomplishments in molecular regulatory genetics described in the next section.

Lwoff's Physiological Evolution and "Genetic Continuity"

André Lwoff (1902–1944) is one of the most remarkable biologists we discuss. He insisted, repeatedly and correctly, that he was not a geneticist. Indeed, in some sense, he was an amateur in each of three remarkably successful programs of research that he initiated—on nutritional biochemistry of microorganisms (especially growth factors and vitamins), control of lysogeny and the viral life cycle, and animal virology. The name he chose for the laboratory he directed at the Pasteur Institute from 1938 to 1968—"Service de Physiologie Microbienne"—indicates how he conceived his work. Lwoff trained with Félix Mesnil at the Pasteur Institute and the protozoologist Edouard Chatton, participating (often with his wife, Marguerite) in Chatton's research program on morphology and morphogenesis of ciliates. This work was intense; from 1921 to 1935, Lwoff authored or co-authored 100 papers, most of them concerned with protozoa. Two groups of these papers deserve special mention: a series of 25 concerning growth factors and nutritional needs of microorganisms and a series of 12 concerning "genetic continuity."

The work on vitamins and growth factors is perhaps better known nowadays. It was of major importance in helping establish the biochemical unity of all living beings, and thus a crucial step toward a molecular understanding of biological processes. Although he began this line of work in 1923 in preparation for his dissertation (107), it was influenced by a year in the laboratory of O Meyerhof, 1932–1933, and a semester in the Molteno Institute with D Keilin, both funded by the Rockefeller Foundation. It eventually covered not only protozoa, but also bacteria and humans; by 1949, nearly 100 of the 200 papers and books published by Lwoff concerned nutritional biochemistry. He established an enormous wealth of data about the universality of various nutritional needs, the specific roles of various vitamins, growth factors, and co-factors, and the effects of nutritional deficiencies. He also developed methods for raising bacteria and protozoa on minimal media and testing the effects of specific nutritional deficiencies and metabolites (including effects on growth rates). Beadle knew this work well from his stay in Paris; it probably influenced his program of Neurospora research during World War II, leading, inter alia, to the one gene–one enzyme hypothesis. During the war, Lwoff began a series of experiments to distinguish mutational from exogenous causes of deficiencies in bacteria. His first international paper after the war dealt with spontaneous biochemical mutations in bacteria (110).

One aspect of Lwoff's nutritional work concerned physiological evolution, the topic of a major book published during the war, but not widely read outside France (109). Viewed in nutritional terms, he argued, evolution is not progressive, but proceeds by loss of function—from autotrophy to heterotrophy. This position, which closely parallels views advocated by Claude Bernard 70 years earlier (9, leçons 5–6), was shocking at the time (24). Like Bernard, Lwoff holds that free-living organisms can afford the costs of evolving morphological complexity and complex life cycles only when they no longer need to produce certain

nutrients or metabolites. Thus, those organisms that can dispense with "unnecessary" biosynthetic pathways can evolve morphological and other sorts of complexity.

The work on protozoa also had a major morphological dimension, which formed the basis for Lwoff's interest in "genetic continuity," an expression first introduced in 1929. Chatton and Lwoff applied this term on morphological, not genetic, grounds to organelles formed by division from a preexisting structure. For example, they held that kinetosomes, which play a crucial role in protozoan morphogenesis, are genetically continuous, a view that Lwoff retained throughout his career. It was controversial, among other reasons, because it challenged the geneticists' notion that morphology is controlled solely by nuclear genes. Lwoff's view, supported by beautiful experimental and observational studies, emphasized a non-Mendelian, indeed, Lamarckian, mode of inheritance for key features of ciliates (118). The terminology produced considerable confusion, caused by conflicting uses of the term "genetic," nicely illustrated in the second paragraph of the following quotation from 1950:

> The careful study of hundreds of flagellates has revealed that the kinetosome is always formed by the division of a pre-existing kinetosome. It is endowed with genetic continuity, and its existence has been demonstrated even in non-motile stages of the life cycle. This kinetosome gives rise to the flagellum. It is able to multiply independently of the nucleus, thus giving rise to chains of kinetosomes. The careful study of numerous ciliates has shown that the kinetosomes of ciliates are also endowed with genetic continuity. . ..
>
> These cytoplasmic organelles, endowed with genetic continuity, live in a genetically constant system, thus providing a beautiful model of a self-reproducing particle whose activity is controlled by its environment [ref. to (111)] (112, p. 7).

Lwoff's notion of genetic continuity is convergent with some geneticists' accounts of "plasmagenes," first proposed by Darlington in 1939 [(46); see also (47)], though it is really only after World War II that plasmagenes became a major concern. The hypothesis of plasmagenes ultimately came to a dead end, but it played a major role in the history of molecular genetics from about 1945 to 1955 (61, 112, 143, 145–147, 155). A crucial meeting, held in 1948 and funded by the Rockefeller Foundation, was organized by Lwoff and Ephrussi to help establish genetics in France [(1); see also (168)]. The theme chosen for the meeting was "entities endowed with genetic continuity" and the papers helped set the tone for the work done in the next 15 years. The contributors[3] argued that many entities

[3]The list of contributors is, in its own right, impressive: A Lwoff, T Sonneborn and G Beale, MM Rhodes, HE Taylor, RD Hotchkiss, A Boivin, FC Bawden, M Delbrück, PM Rountree, P L'Héritier, CD Darlington, R Gautheret, G Camus, J Brachet, B Ephrussi, and J Monod.

may turn out to be genetically continuous. These included enzymes, plasmagenes, transforming factors in bacteria (Avery's pneumococcus and Boivin's *Escherichia coli*), the units causing lysogeny in bacteria, numerous organelles in ciliates, the particles that produce respiratory enzymes in yeast (later identified as mitochondria), plastids, plant viruses, the genoïde responsible for CO_2 sensitivity in Drosophila, and many more. Here was new ground to be staked out, not yet overpopulated by geneticists and susceptible to physiological investigations of the sorts in which the French excelled. Here was a pathway for the French to take to join the new world of postwar genetics.

Lysogeny

Another line of work pursued in the Pasteur Institutes of Paris and Brussels concerned lysogeny, a contentious topic that came to be at the center of renewed debate after World War II. Lwoff decisively resolved the debate in 1950, yielding one of the key tools of microbial genetics. The story is complicated; we provide a drastically simplified outline of its key features, based on a paper in progress. [The best general review is (19); see also (71–73, 154).]

The phenomena of bacteriophagy were discovered in 1915 (152). Shortly afterward, Félix d'Hérelle (1873–1949), a Canadian working in the Pasteur Institute in Paris, made a parallel discovery, apparently independently, and gave its cause the name "bacteriophage." D'Hérelle was dogmatically committed to the view that the phenomena were caused by an ultramicrobe, an obligate parasite of bacteria (52). Starting in 1920, Jules Bordet (1870–1961), Nobel laureate for work in immunology and director of the Pasteur Institute in Brussels, denied d'Hérelle's interpretation of the phenomena. Bordet's considered position was that some strains of bacteria, which he called "lysogenic," cause others to lyse spontaneously by producing an excess of a normal enzyme that dissolves the cell wall. In some circumstances, lysogenic strains acquire the tendency to overproduce the enzyme, thereby lysing themselves. Those not killed in the process were immune to the effects of the enzyme and transmitted the immunity and the power to lyse other bacteria to their offspring. Thus, what d'Hérelle considered bacteriophagy [literally, eating of bacteria (by a parasite)] was, instead, a "hereditary nutritive vitiation"—an acquired character, inherited across bacterial generations (13–17). An enormous dispute broke out, especially in the pages of the *Comptes Rendus de la Société de Biologie*, which published more than 490 articles on bacteriophage between 1920 and 1940. Of these, about 50 were on lysogeny.[4] In the course of this dispute, Eugène Wollman (1883–1944), of the Pasteur Institute in Paris, became one of the leading theorists and experimenters on lysogeny. The problem of bacteriophagy, of course, received international attention, with important work being done else-

[4]Lysogeny was so ill defined, the terminology so confused, and the reality of the phenomenon so disputed that it depends on definitional choices whether many articles are or are not about lysogeny.

where, e.g. (3, 28, 29, 80). Both Bordet and d'Hérelle considered bacteriophagy to exemplify inheritance of acquired characters—Bordet in lysogenic strains of bacteria, d'Hérelle in the adaptation of bacteriophage (of which he thought there was only one species) to new hosts and environmental conditions.

The dispute was made more complicated by lack of agreement on the phenomena. From 1920 on, Eugéne Wollman sought to reconcile the conflicting viewpoints and demonstrate all the phenomena crucial to understanding bacteriophagy as a form of infectious heredity. Lysogeny was the key to Wollman's work; as early as 1920, he considered it a hereditary trait acquired by infection and speculated that Darwin's pangenesis might serve as a model for the inheritance of this acquired character (157). Although he never completely defeated the view of skeptics that lysogeny was an artefact resulting from phage contamination of initially phage-free cultures, his experimental work defined the phenomena ever more sharply. In the process, he revealed difficulties with the many contending theories and provided support for his own view that the phenomena involve a form of "paraheredity," with both vertical and horizontal transmission. The vertical transmission, presumably based on transmission of some sort of Mendelian factor, took place, as he showed, even in bacteria with no phage protein, and hence must involve some gene-like entity.

From 1925 to 1940 Wollman published six major memoirs in the *Annales de l'Institut Pasteur* (two with his wife Elisabeth), in which he established new experimental evidence and refined his theoretical stance (158–161, 163, 165). These papers provided experimental evidence for the reality of lysogeny and of distinct species of d'Hérelle's autonomous infectious bacteriophage, and sought to provide a theoretical interpretation of the significance of the combination of hereditary and infectious phases in bacteriophagy. As early as 1925, he claimed that the only secure proof of lysogeny would be to produce phage infection from definitively phage-free bacterial cultures. He sought to do so from then on, critically rejecting many experiments (including some of his own) in which this had allegedly been accomplished. He was very clear about what was required (162). Two possible ways would be decisive: experimental induction of bacteriophagy (with 100% success), and observation of spontaneous production of phages in definitively noncontaminated cultures—precisely the two experimental demonstrations accomplished by Lwoff around 1950. By 1938, Wollman had strong evidence for the following conclusions. Phages are antigenically distinct from bacteria and from one another, yet in many cases, the antigenic factors of bacteriophage cannot be detected in lysogenic strains of bacteria. According to den Dooren de Jong's experiments (51), developed further by Wollman, *Bacillus megatherium* (supplied by the former to Wollman) is a serious candidate for demonstration of lysogeny. Its sporulate form is resistant to a phage that it apparently introduces into its sensitive, nonsporulate, form (163). For a while, Wollman thought he had experimental proof that all the phage had been killed in lysogenic strains of *B. megatherium*, but by 1936, he had to admit that the experimental tests were not adequate to prove that phage were not hidden in the bacterial spores (160). Still, all the bacteria in cultures of

sporulate *B. megatherium* could initiate bacteriophage infections when plated dilutely on sensitive strains, even though nearly all tested individuals in those cultures, opened with lysozyme, contained no phage or antigenically detectable phage protein (164). A confounding problem, though, was the presence of about one phage per bacterium in the supernatant of many cultures. In 1936, the Wollmans tightened up these findings: Five successive washings and centrifugations produced cultures in which only 1 in 10,000 *B. megatherium* contained phage when opened with lysozyme; nonetheless all the bacteria in the cultures could trigger phage infection (164). They later argued that the bacteriophage infecting the sensitive bacteria could not be the direct descendants by division of the phage in the putatively lysogenic strain of *B. megatherium*. Thus, they held, in lysogenic bacteria, there is always de novo production of bacteriophage, which must be produced from an inherited factor. The reproduction is "true to type." "And there you have the very signature of hereditary phenomena" (165, p. 51).

Their work was ended, tragically, when the Nazis removed them to Auschwitz at the very end of 1943, never to be seen again.

Lwoff was deeply familiar with the Wollmans' work. In his 1953 review on lysogeny (113), he praised their 1936 article (164) as the first reasonable proof that there are no mature phage in lysogenic bacteria. In 1936, after close discussion with Wollman, Lwoff wrote a speculative theoretical paper (108) as an appendix to Wollman's fourth mémoire (160). There he amplifies Wollman's speculations, suggesting that phage are not microbes but rather aberrant genes, as proposed by Muller and others, and that lysogeny is due to the behavior of phage at cell division. He speculates that phage are inducers, inactive during the rest of the cell cycle, reactivated at cell division. They induce formation of copies of themselves and/or formation of complexes of enzymes. He links these phenomena to those of enzymatic adaptation and, like Wollman himself, to the behavior of mosaic viruses in plants.

When he himself took up the problem of lysogeny in 1949, he clearly knew what he was after. He chose the remarkable strain of *B. megatherium* that Wollman had obtained from den Dooren de Jong to demonstrate the reality of lysogeny. His remarkably rapid success in this project and his elucidation of the nature of viruses were clearly facilitated by his intimate knowledge of Wollman's work and the tradition behind it.

Monod and Enzymatic Adaptation

Background To understand Jacques Monod's (1910–1976) contributions to regulatory genetics and his collaboration with François Jacob, one must understand some aspects of his background and peculiarities of his scientific style. Dissatisfied with his university training in biology, his real initiation into biological research came from summer work at the marine biological station in Roscoff, starting in 1931. Four biologists there greatly influenced the directions of his work. He owed "to Georges Teissier his taste for quantitative description, to André Lwoff his

initiation to the power of microbiology, to Boris Ephrussi the discovery of genetics, and to Louis Rapkine the idea that only chemical and molecular descriptions could provide a complete interpretation of the functioning of living beings" (70, p. 7). His first scientific publications, with Chatton and André and Marguerite Lwoff (33, 34), supported the genetic continuity of cortical features of ciliates. Thus, early on, he was interested in non-Mendelian transmission of features and competences from cell to cell. Although he spent 1936–1937 with Boris Ephrussi in TH Morgan's laboratory at Caltech, his attempts at standard Mendelian experiments there were failures, partly because color-blindness prevented him from assessing eye colors correctly, and partly because he was distracted by musical interests. The two papers he published from the work begun there belonged to Beadle and Ephrussi's program in physiological genetics of implanting imaginal disks and testing the concentrations and effects of diffusible substances (131, 132). In brief, although he learned some traditional Drosophila genetics and was committed to genetic determination of cellular and organismal competences, he was an outsider, not a geneticist.

Enzymatic Adaptation Monod's long-term program of research in bacterial physiology and regulation is of crucial interest here. Starting around 1940 (but severely interrupted during World War II, when Monod served heroically in the Resistance), he employed biochemical kinetics to study enzyme formation in bacteria. He emphasized that the ability to produce enzymes is genetically determined, but also that bacterial cells switch their enzymatic constitution drastically in response to environmental changes (123). This phenomenon, widely known among bacteriologists and called enzymatic adaptation, was not clearly distinguished from mutation until the mid-1940s (129). He described his first major studies of enzymatic adaptation in an extraordinary dissertation in 1942 (122). He focused on the kinetics of the growth of cultures supplied with specific, well-defined carbon sources.

In the second part of the dissertation, Monod studied a phenomenon he discovered and labeled "diauxie," only to learn from Lwoff (126) that it was a case of enzymatic adaptation (95). The specific findings concerned the inability of certain bacteria to produce the enzymes required to utilize certain carbon sources (e.g. lactose) while other specific carbon sources (e.g. glucose) are present. Thus, various strains of *E. coli* provided with both glucose and lactose grow (with the cells dividing at a constant rate) until they totally exhaust the glucose, then cease to grow, perhaps even decline a little, and in about an hour, having produced the necessary enzymes, begin a second period of growth at a new rate specific to consumption of lactose. Already at this point he suggested that the reason for the delay in digesting galactose was "*suppression d'enzyme*" (122, p. 2; see also pp. 169–70, 197), although this phrase meant something very different then than it would 15 years later. Monod's mature investigative style is already manifest. He defines the phenomena sharply, demonstrates them in numerous systems, provides very clean graphic representations of the phenomena before suggesting physiological

hypotheses to explain them, and devises sharp, often decisive, tests of those hypotheses within his finely tuned systems.

Monod, like others [e.g. (57, 58, 147–149)], hoped to use enzymatic adaptation as a model of the controlled switching of cell identity in differentiation (123). From the beginning, this program was supposed to provide a general account of regulation at the cellular level and an important avenue for understanding the development of eukaryotes.

The research programs described in this section provided key problems and important tools that helped to disentangle the problems of genetic regulation around 1958–1960. The close connections among the principals are important as well. Ephrussi, Lwoff, Monod, and Teissier collaborated in various combinations; in addition, the latter two were brothers-in-law. Lwoff emerged as the central figure in the period from 1938 to 1945, partly because Ephrussi had to flee the war. Lwoff introduced Monod to enzymatic adaptation and took him into his laboratory. After the war, he also took on Elie Wollman, the son of Eugène and Elisabeth, and, later, François Jacob, a neophyte with a medical degree. The three of them vindicated many of the senior Wollmans' claims about lysogeny, which they converted into a major tool for studying regulatory genetics of bacteria and bacteriophage. Workers in all of the research programs remained in close contact. They had, of course, substantive ties and overlapping roles in building the postwar institutions of genetics in France. But they also formed an informal "Club de Physiologie Cellulaire," active after the war. It helped maintain the bonds among the researchers and provide contact with the constant postwar stream of international visitors to the laboratories in Paris and Gif. Its title also reflects the common focus already prefigured by Lwoff's chosen name for his *Service*, namely microbial physiology.

NEW WAYS OF HANDLING HEREDITY

Introduction

Shortly after World War II, the massive job of restoring French science was begun. As already indicated, genetics finally reached the universities. The CNRS opened three laboratories at Gif-sur-Yvette, though the process took 15 years—one (Teissier's) devoted to population genetics, one (L'Héritier's) mainly to cytoplasmic inheritance of CO_2 sensitivity in Drosophila, and the third (Ephrussi's) to a new program on yeast (23, 137). Ephrussi intended to follow Beadle's lead in working with microorganisms. The laboratory very quickly detoured to pursue a nontraditional problem: cytoplasmic inheritance of respiratory incompetence in yeast. This turned into a project of fundamental importance and is described here. In the meantime, the workers in the Pasteur Institute played a crucial role in the development of bacterial and viral genetics. Four of the programs of research there are discussed below. Although the restriction to the work of Ephrussi's group and the four Pasteurian programs forces us to omit much else that is of interest,

these programs were at the forefront of genetic research in France. They reflect the special strengths of French genetics and the pathways by which French genetics entered into the mainstream of molecular genetics.

Ephrussi and Nucleo-Cytoplasmic Relations

Ephrussi's lifelong interest in development guided all of his research programs. He sought to understand the commitment of cells to cell fates, the process of determination, its relationship to the separate process of differentiation, and the integration of organisms, developing unorthodox genetically rooted programs for these purposes (26). He suggested to Monod that enzymatic adaptation might serve as a model for differentiation of eukaryotic cells, but, unlike Monod, he remained committed to the use of eukaryotes to explore "his" issues. In the postwar years, he developed two major programs of research focused strongly on nucleo-cytoplasmic relations and explored the possibility that cytoplasmic determinants might be crucial in determination or differentiation (60–64, 66, 144). The first of these began from the finding that all progeny in baker's yeast exposed to acriflavin mutated to produce only small ("petite") colonies. All progeny of the mutagenized yeast lost respiratory competence (nonlethal in yeast!), a trait that turned out to be cytoplasmically inherited. With Piotr Slonimski and others, he demonstrated that an entire suite of respiratory enzymes, normally bound to sedimentable particles, was lost at once in petites. Thus, a fundamental physiological property was controlled by mutable cytoplasmic particles endowed with genetic continuity, prone to unidirectional change (59). Here was a worthy model system for cellular determination and heredity! Ephrussi provided numerous speculative models of this and related phenomena, but always treated them with reserve and caution [see, for example, the General Discussion in (62)]. Ephrussi's group spent many years proving that the inheritance of respiratory (in)competence is genuinely cytoplasmic; they also showed that certain nuclear genes are required for the cytoplasmic particles to produce their respiratory enzymes and that some respiratory enzymes are produced from nuclear genes. They were very cautious in identifying the cytoplasmic particles; it was not until the late 1950s that their identification as mitochondria was finally accepted. Ephrussi finally moved fully into the laboratory in Gif in 1959. That laboratory played an important role in the founding of mitochondrial genetics, continuing to do fundamental work in that field under Slonimski well into the 1990s.

But Ephrussi moved to the United States in 1962, where he stayed for a decade. Shortly before moving, he began a new program of research in somatic cell genetics. Once again he pioneered new techniques and came up with findings that helped found a new discipline (117, 156, 169). Already in 1953 he had articulated the hope to achieve "direct genetic analysis of somatic cells, for the assumed functional equivalence of [nuclei of] irreversibly differentiated somatic cells, however plausible, is only an hypothesis" (62, p. 5). This hope was forlorn at the time because it was impossible to hybridize somatic cells reliably and with reliable

markers. That changed in 1960 when a difficult technique fell into his hands, to wit, interspecific hybridization of somatic cells, allowing use of karyotypic and a few enzymatic markers (68, 69). He did an enormous amount of work to make the new tool reliable, and immediately applied it to gene expression in development and differentiation (65). One central experimental topic was retention of the potentiality to express "luxury" functions, often unexpressed in cell hybrids. Phenotypically similar cells have different "epigenotypes" [a term from (2)] characteristic of their lineage. That is, each cell can be made to express only the luxury functions for which it had inherited competence. Such issues particularly interested Ephrussi in light of his long-standing efforts, begun in the 1930s (54, 55), to understand control of cell competences and regulation of the expression of those competences. Now somatic cell genetics could be built to attack just such problems (48, 66).

Like other programs of genetic research in France, these two programs, both emphasizing nucleo-cytoplasmic relations, were strongly influenced by interest in the physiological regulation of cellular states and the inheritance of those states. The pattern here is general: The roots of the postwar research are already found in nongenetic research carried out in the earlier part of the century. As we will now see, a similar characterization is appropriate to the postwar research in the Pasteur Institute.

Lwoff and Lysogeny

In the Cold Spring Harbor meetings of 1946 and 1949, Delbrück expressed very public doubts to the effect that lysogeny was nothing but sloppy experimentation and contaminated cultures (127).[5] Thanks in part to those expressions of doubt, in 1949 Lwoff set out to demonstrate once and for all the reality of lysogeny. He preferred manipulating his microorganisms to employing statistics, so he opted to employ a micromanipulator and start cultures from single individuals of putatively lysogenic *B. megatherium* (116). Together with colleagues and technicians, he demonstrated that most of the bacteria were entirely free of virions, that the free phage found in some cultures—approximately 1 phage per bacterium (the number found by Eugène Wollman)—came from 1 bacterium in 100 lysing and producing

[5]Lwoff's protégé Elie Wollman spent 1948–1950 at Caltech in Delbrück's lab. There he found a bibliography card referring to one of his father's experiments on lysogeny with "nonsense" scrawled on it. Lwoff and Wollman fils clearly had a personal stake in vindicating the parents' work on lysogeny. In 1950 Elie Wollman had the pleasure of writing the brief (positive) section on lysogeny in the syllabus by Benzer, Delbrück, Dulbecco, Hudson, Stent, Watson, Weigle, and Wollman on procedures, facts, and interpretations in phage, published by Delbrück as part of (49a). Five of the six principal empirical findings about lysogeny listed there (p. 140) were established by Eugène Wollman using *B. megatherium*. The remaining finding was Lwoff's demonstration (using the same strain) that all the bacteria of a culture started from a single bacterium, with no phage released into the medium after 19 cell divisions, and composed of bacteria which, when lysed, contained no phage—that these bacteria were, nonetheless, lysogenic.

about 100 phage, and that occasionally entire cultures lysed. Convinced that mass lysis was triggered by environmental factors, Lwoff et al tried exposure to mutagens and stresses of various sorts, finally proving that UV could induce an entire culture to switch to phage production (116, 119). This was rapidly accepted as the definitive proof that phage-free bacteria could produce phage, i.e. as proof of the reality of lysogeny.

Lwoff next developed his enormously influential elucidation of the life cycle of viruses. With coworkers he showed that temperate phage (and other viruses) can exist as "prophage"—without virions or phage protein. Eventually prophage was shown to be phage genetic material incorporated into the bacterial chromosome. In lysogenic bacteria, phage genes have to be activated in some way (induced), after which they control the cellular machinery and direct the making of phage proteins and DNA, plus the enzymes that lyse the cell (113–115). Although Lwoff's experimental work on phage only lasted until 1952, he continued for some years to elucidate the details of the viral life cycle and publish on the nature of virus. Elie Wollman and François Jacob in his laboratory undertook long-term studies of physiological and genetic control of induction as a means of understanding both bacterial and phage genetics. [Jacob landed his position in the laboratory the very week that UV induction of phage formation was achieved and was taken on to study the control of phage induction (85).] Lwoff himself, after he had developed a general doctrine of the nature of viruses, began a new experimental research program around 1955, seeking ways to combat the scourge of polio.

Jacob, E. L. Wollman, and Bacterial Genetics

The collaborative research of Elie Wollman and Jacob fused physiological work in the French tradition with postwar work on phage and bacterial genetics. Wollman completed a medical degree in 1943, with a thesis on the nature of antibodies; immediately after the war, he entered Lwoff's *Service* at the Pasteur Institute. His earliest papers concerned protein and enzyme synthesis in phage-infected and phage-resistant bacteria. Two of these, with Monod, were on the synthesis of adaptive enzymes, thus forging direct contact with Monod's program [(see (133)]. While in Delbrück's laboratory from 1948 to 1950, he learned American-style bacterial and phage genetics and worked with G Stent (167). Back at the Pasteur Institute, equipped with the genetic tools of the phage school, he began a close collaboration with Jacob [described in (85)]. Together, they dissected the various steps of the life cycle of phage and the bacterial and viral genetic controls of each step in that cycle. From 1953 on, most of this work was done with *E. coli* K-12 and the temperate phage λ, obtained from Esther and Joshua Lederberg. The switch to this system had momentous though unforeseen consequences (see below). Their papers on the interactions between phage and bacteria covered nutritional correlates of phage resistance, abortive and nonproductive infection by virulent phage, immunity of lysogenic bacteria to homologous phage, the nature of prophage, and controls affecting virulence versus lysogenization, formation of colicins, adsorption

of phage, etc [see reviews in (92, 93)]. Recombination studies with mutants of λ provided the first genetic map of a phage (89). Control of the rate of mutation by use of UV (90) allowed studies of recombination mechanisms and the construction of fine-grained maps.

Defective lysogenic phage, produced by mutagenesis, allowed dissection of the separate physiological steps in the phage life cycle and the timing and separation of closely related processes such as the formation of colicins, from the formation of vegetative phage. In studying genetic determination of lysogeny, Jacob and Wollman employed bacterial conjugation as a means of securing exchange of genetic material. With the discovery of Hfr (a factor for high frequency of combination) by W Hayes (82; see also 166), a number of important findings were made possible. Among these: (*a*) phage genetic material is incorporated into the bacterial chromosome (proved by exchange of distinct λ in crosses) near the *gal* (galactose) locus. (*b*) A cytoplasmic factor, produced by lysogenic phage, suppresses phage formation (proved by the discovery of zygotic induction, i.e. immediate triggering of phage formation by injection of phage genetic material into a non-lysogenic recipient, contrasted with blockage of phage formation in lysogenic recipients). (*c*) Genetic material can be incorporated in episomes [first described in (91)], or integrated into bacterial chromosomes, with corresponding differences in its effects on the bacterium [reviewed in chapter 16 of (93)].

Jacob and Wollman's elaborate studies of bacterial sexuality cannot be described here. Suffice it to say that they gained fine-grained control of crosses used to map the K-12 genome. Wollman devised the technique of "coitus interruptus"—halting a synchronized cross at a set time by use of a Waring blendor, which produces shear forces sufficient to break the cytoplasmic bridge required for conjugation. Since each Hfr strain initiates injection of its chromosomes from a fixed position, they were thus able to construct detailed chromosomal maps. Since these procedures enabled them to produce both temporary and lasting diploids, they allowed the application of Mendelian tools—e.g. testing for recessive versus dominant and *cis* versus *trans* effects—for the first time in bacterial genetics. And since *lac* is not far from *gal*, which is extremely near λ, the maps for λ, fortuitously, provided an excellent start toward maps suited to Monod's program.

In 1958, Wollman departed for another tour at Caltech. While he was gone, the collaboration between Jacob and Monod, already begun, displaced that between Jacob and Wollman. The tools that the latter pair had developed proved ideal for the new collaboration.

Monod and Lactose Digestion in *E. coli*

From 1948 until about 1957, Monod concentrated on characterizing "adaptive enzymes" [later "inducible enzymes" (130)] and the controls governing their formation (not, at first, synthesis!). The then-conventional theory of enzyme formation, to which Monod adhered well into the 1950s, was instructional. It held that bacteria re-form a precursor into the relevant enzyme(s) by using a template—perhaps

the substrate attacked by the enzyme, perhaps a gene exported to the cytoplasm reproducing as a plasmagene, perhaps (after around 1950) ribosomal RNA, thought to be gene-specific (84, see n. 18 for references). Competition for precursor led to equilibria that remained stable until a disturbance (such as absence of substrate) altered the balance among the reactions into which precursor entered. Since the enzymatic constitution of a bacterium was transmitted to daughter cells, many proponents of this theory thought that enzyme formation exemplified inheritance of acquired characters. Monod, recognizing that the genetic capacity for producing adaptive enzymes was genetically fixed, firmly opposed inheritance of acquired characters. Nonetheless, he held on to the instructional theory of enzyme formation until very late. In 1958, for example, he proposed a model according to which "induction consists in the conversion of a precursor resulting in liberation and activation of a *preexisting* enzyme-forming center[. This seems] to furnish a relatively simple and rational interpretation of the induction effect" (125, p. 585).

Because of the experimental advantages of the *E. coli lac* system, Monod's primary experimental focus came to be the galactosidases and related enzymes produced by *E. coli*. Monod published more than 20 experimental papers with colleagues, especially Melvin Cohn, on this system before 1957, when his and Jacob's joint genetic publications began to appear (128). The pre-Jacob papers generally did not study genetic questions beyond characterizing mutant forms of various enzymes and demonstrating, for example, that mutations in distinct enzymes connected with lactose metabolism are independent of one another [e.g. (139)]. We describe briefly some of Monod's salient findings about the enzyme β-galactosidase (hereafter β-gal) and related enzymes in order to indicate the sort of armamentarium available when he and Jacob began their collaboration on the genetics of the *lac* system. By 1955, Monod and colleagues already had the following results (124): Synthesis of β-gal in the absence of glucose or other inhibitors begins immediately upon addition of an inducer and is produced (when the inducer is present at a saturating concentration) as a constant fraction of the increase in bacterial mass. Under normal conditions, the inducer is a galactoside that serves as a substrate for the enzyme, but many inducers (e.g. methyl-β-D-thiogalactoside) are not substrates for the enzyme and some substrates (e.g. phenyl-β-D-galactoside) are not inducers. In the absence of inducer, or when its action is blocked, production of the enzyme ceases immediately. Contrary to prior interpretations by Monod and others, the enzyme is synthesized entirely de novo (83). Inducer is not consumed in the act of induction but functions as a catalyst. β-gal induction is blocked by some substances, notably glucose and phenyl-β-D-galactoside. Thus, in properly prepared cultures, one can produce the enzyme (including its mutant forms) at will by use of an inducer and arrest production at will in a variety of ways. A second inducible enzyme, first suggested by Georges Cohen in 1955 and quickly described as permease [(139); see also (35)], is required to import exogenous galactosides into the cell and thus to bring about induction of β-gal formation under typical conditions. Permease and β-gal are independent enzymes that exhibit independent mutations, but are located in

extreme proximity on the bacterial chromosome and are co-induced; "a single mutation determines the inducible vs constitutive character of both systems" (139, p. 855).

The problem of the co-control of the synthesis of bacterial enzymes in specific metabolic pathways was becoming widely recognized at about this time, as was the fact that the genes for the enzymes involved in a given pathway are often located in close proximity to each other (50). The system that offered the best opportunity to study the physiology and regulatory processes involved was, without doubt, Monod's. The *E. coli* K-12 *lac* system was the best-studied and most easily controlled inducible enzyme system, and mutants were available that switched it from inducible (i^+) to constitutive (i^-) and from capable of producing β-gal (z^+) to incapable of producing it (z^-), or to producing any of dozens of variants of the enzyme as well. i^- mutants were also constitutive for permease and one other β-gal-related gene, proving that the entire group of genes was regulated as a unit (126). Here was a clear opening for a genetically based study of the control of enzyme synthesis. It was thus natural, given Monod's extraordinary mastery of all of the relevant investigative tools and protocols and his firm belief in the underlying genetic control of the system, that he turn to François Jacob for a collaboration that would explore its genetics.

Regulatory Genetics and the Crowning Achievement of Jacob and Monod

E. coli K-12 is a marvelous beast. Monod began to use it around 1956.[6] The first strain he employed is lysogenic for λ (A Ullmann, personal communication). Without it, the collaboration with Jacob might well have been frustrated. With it, they were able to utilize two closely analogous inducible systems, one governing induction of the lac operon and one governing induction of λ, employing their different tools to a common object. With K-12, they could focus their tools and knowledge on a fairly small portion of a bacterial chromosome responsible for seemingly distinct, but structurally very similar regulatory processes governing quite distinct processes. The controls for both processes could be activated and deactivated at will. And in each system, there were "missing" mutants, described by analogy with mutants found for the other system. For example, there was a dominant mutant in K-12 that prevented phage from lysogenizing the bacteria. At one point, when only recessive mutations for converting bacteria from inducible to constitutive for β-gal production were known, Jacob recognized that if the systems were fully analogous there must also be a dominant constitutive mutant for Monod's system [(85); see also (88)]. Thus, analogies between the two systems were useful for identifying mutants that could be sought to evaluate hypotheses regarding

[6]The first acknowledgment that we have found from Monod's lab of the use of K-12, supplied by J Lederberg, is in (139). Most of the earlier work with *E. coli* was done with various strains of *E. coli* ML.

the genetically determined controls for the two systems. Given the years of exploration to which the two systems had been subjected, each of them offered a large battery of systematic variants (variant phage and enzymes) and tricks to control the interpretation of unexpected results. Thus Jacob and Monod had enormously powerful means for testing and interpreting the hypotheses they generated in intense debates over the detailed analogies between the control systems and over the location and behavior of the controls. This powerful confluence helped achieve not only the specific results, which are still widely appreciated, but a style of work that has become second nature to many investigators and is, therefore, not as easily recognized (84, 85).

We cannot examine the enormous experimental and interpretative complications of the collaboration, a task for another paper. [The complex story is well reviewed in (86, 87) and recounted in (19, 84, 85, 94, 126, 134).] We only mention certain high points here to provide an idea of how the protocols and findings built on the background described above. From this limited perspective, the so-called PaJaMo, [or pajama, "pyjama" in French] experiments [named by Monod for the authorial triumvirate, Pardee, Jacob, and Monod (135)] employed the tools of Jacob and Wollman's zygotic induction experiments to establish the kinetics of β-gal formation in various specifically prepared cytoplasms. The experimenters thus drew on the long tradition of studying nucleo-cytoplasmic interactions via kinetics, and they received a huge surprise. β-gal synthesis behaved, in key respects, just like λ induction. When a normal inducible *lac* locus (i^+z^+) entered the cytoplasm of a bacterium with i^- and z^- genes (i.e. a bacterium defective for inducibility of β-gal and incapable of producing the enzyme, hence a cytoplasm constitutive for formation of the enzyme in a bacterium unable to make it), it immediately utilized the injected z^+ gene to synthesize the enzyme. But, and this was the surprise, in about 60–80 minutes, inducibility became dominant. The constitutive character was lost, which (after some other possibilities were eliminated) meant that the injected i^+ gene produces a cytoplasmic factor that suppresses synthesis of β-gal just as bacteria lysogenic for λ produce a cytoplasmic factor that prevents incorporation or multiplication of λ (126). With further testing, it turned out (as was expected on grounds of Monod's prior work) that the i^+ gene co-regulated all the relevant co-produced gene products (e.g. permease as well as β-gal).

The tools for studying regulation of protein synthesis at the genetic level in *E. coli* were thus fully in hand as of 1958. And the full panoply of studies integrating the findings and features of the two parallel systems yielded, among much else, two of the most important findings of the era. These are, of course, mRNA and the operon. The interpretative and experimental struggle required to establish and understand both of these should not be underestimated—it is far too easy to see them, in retrospect, as inevitable consequences of work with an ideally suitable system. There was nothing inevitable here, no matter how much it looks so in hindsight. But it is clear that masterful use of the physiological and kinetic tools developed in the work on *E. coli* K-12 was of enormous help in devising and testing an extraordinary range of then-unexpected hypotheses.

Messenger RNA The rapid production of β-gal (with no more than a two-minute lag) when the z^+ gene entered the appropriate cytoplasm meant that there was no time for production of putatively specific ribosomes. This implied that either the DNA itself or some immediate product carried the information to the ribosomes, where the protein was synthesized. It was implausible that DNA could do this job because protein encoding DNA in eukaryotes was confined to the nucleus while protein synthesis occurred in the cytoplasm. Neither rRNA nor tRNA fit the bill. tRNA did not vary significantly from organism to organism and was too short to carry the necessary information. rRNA did not vary in composition either, as it would have to do to make different proteins. Furthermore, ribosomes were too stable to yield the extraordinarily rapid kinetics demonstrated in the PaJaMo experiments. Yet further, in a very difficult follow-up experiment (140), when the z^+ gene was destroyed but the ribosomes left intact, synthesis of β-gal ceased immediately. Ribosomes simply were not protein-specific. In consequence of these considerations, the hypothesis of a short-lived intermediate, a transcript of the DNA (originally called tape and then messenger RNA) was put forward even though there was no direct chemical evidence for it. And in a classic experiment Brenner, Jacob & Meselson (18) demonstrated the existence of exactly such an RNA associated, as expected, with ribosomes [see also (87)]. Thus the collaboration provided the conceptual basis for the first clear articulation of the distinction between transcription and translation and experimental support for its soundness (87).

The Operon Having proposed the distinction between structural genes, which specify the sequence of amino acids in a protein product, and regulatory genes, which determine whether or not genes are activated, a key feature of the λ and β-gal systems was that in the absence of inducer the gene was, in the new terminology, repressed. Furthermore, a cytoplasmic substance, repressor, was responsible for this condition, so that initiation of transcription required a step, later called derepression, accomplished by a substance interacting with the gene or with the repressor to alter its state. Setting aside an enormous amount of crucial detail, this is the conceptual core of the models of the operon developed out of the collaborative exploration of the demonstrable similarities between the *lac* and λ systems. Among the conceptual difficulties that had to be overcome to reach this point was resistance to the idea that regulation could occur at the level of the gene. Because it had been classically held that genes could only be altered by mutation, it was commonly believed (by Monod among others) that genes were sacrosanct and could not participate in ordinary cellular transactions (85, 94, chapter 7). The break with this classical view, we suggest, begins the final stage of making genes into fully physiological entities. This step, when completed, marks the demise of the old charge, so influential in the early resistance to genetics in France, that genes are only formal entities and that hypotheses that base doctrines of heredity on genes should be dismissed as unphysiological. The rapid acceptance of the operon theory in molecular biology thus reflects (as a side effect) the full-fledged entry of French genetics into the international

mainstream and the acceptance in that mainstream of the fruits of a line of physiological investigation deeply rooted in older, nongenetic and antigenetic French traditions.

The full statement of the operon theory in 1961 (86, 87) marks a major turning point in the history of molecular genetics. The door was opened to an enormous suite of investigations across familiar domains and far beyond. A large number of investigators attempted to apply operon models to multicellular eukaryotes, not just for regulation of protein synthesis, but also for differentiation and morphogenesis. Closer to home, many investigations sought to elucidate and refine variant models of the operon or of particular operons. Thus, one issue was whether all operons involve a repressor, or whether some related control systems respond directly to inducing signals rather than derepression. Consideration of the possibilities for chromosomal rearrangement led to the crude beginnings of biotechnological operations—fusions of particular genes with particular operators were achieved (initially by deletions in diploid bacteria so as to avoid lethality) (84). Models in terms of cybernetic circuits were developed in profusion; Monod drafted a book manuscript, never published, entitled "La cybernetique enzymatique," now available in the archives of the Pasteur Institute. Monod also explored a range of major questions regarding the identification of repressors, their mode of action, and how they were altered in derepression. Of particular importance is his program of research concerning allostery, conformal alteration of repressor and other regulatory molecules by interactions at a second site, allowing chemically unrelated molecules to switch sophisticated metabolic systems on and off. This line of work shows that Monod retained his basic commitment to physiological biochemistry, but it also shows the penetration of questions from that background into the heart of molecular genetics. This is another symptom of the merging of the work of French molecular genetics into the international mainstream.

CONCLUSION: Distinctiveness of French Genetics?

We have had to ignore many domains of genetic investigation in France. Among the most important is human genetics, where the discovery of the roles of chromosomal aberrations in human disease by Lejeune & Turpin (98–101, 151) is worthy of serious investigation. This work, however, never made good contact with the work on which we have focused here (27). Similarly important, and perhaps better integrated into mainstream genetics, is the immunological genetics of Jean Dausset, honored with a Nobel Prize. There are many other lines of work—viral, fungal, mouse, and agricultural genetics, and much more—that deserve attention, many of them supported and facilitated by the network of scientists whose work we examined in this review. Nonetheless, we stop this review here, in the mid-1960s, because French treatments of heredity are no longer as distinctive, compared with those in other countries, as they were earlier in the century. To conclude, we offer a brief account of the salient distinctive features. For this purpose, we employ a

somewhat outmoded distinction between external (non-cognitive sociological and institutional) factors and internal (cognitive and experimental) factors.

Important external factors hindered French biologists from developing an active program of genetic research in the first three or four decades of this century. (*a*) The lack of contact between agricultural engineering and universities (plus elite research institutions) meant that practical breeding did not influence doctrines of heredity as much in France as it did in the countries in which Mendelism played a crucial role. [There was, of course, some interaction; see (22, 79)]. (*b*) French resistance to negative eugenic ideologies fostered resistance to Weismannism and doctrines of "hard" heredity, which, again, militated against acceptance, or even development, of Mendelism. (*c*) Given this climate, the high human cost of World War I and the demands placed on French youth to devote themselves to rebuilding their country made careers in genetics unattractive.

External factors also were important in forging the network of individuals who eventually provided the real foothold for genetics in France in the 1940s and 1950s. In the 1930s, the individuals concerned were connected through a small number of institutions. In this decade, they met regularly in the summers at the marine biological laboratory at Roscoff, enabling them to forge close personal contacts with one another as well as good working relationships with such foreign scientists as JBS Haldane and the young Jean Brachet. Two of the institutions where they were employed, the Institut de Biologie Physico-Chimique and the Pasteur Institute, protected "outsiders" unsuitable for university employment, thus enabling them to pursue idiosyncratic programs of research and avoid being implicated in the biological traditions of the universities. Teissier and L'Héritier, who worked in an elite teaching establishment, the Ecole Normal Supérieure, had very light teaching loads (mainly tutoring) and were allowed, as mathematicians, to develop original programs of biological research without depending on the "mandarins" of the University of Paris. Furthermore, Rockefeller Foundation funding allowed four of the key individuals to work abroad, thus providing them with the opportunity to develop genetic and biochemical alternatives to the main traditions in France. These external stimuli obviously also played an important role in shaping the directions their work took in the later 1930s and beyond.

Yet, turning to internal factors, the intellectual traditions of the universities and the four institutions just named also played a major role in shaping the research of the individuals in the network. Given the centrality of mathematics in French science, and its dominant role in the curriculum of the Ecole Normal Supérieure, it is not surprising that the individuals there who became interested in biology would employ mathematical tools in their research, far beyond those employed by typical university biologists. This is certainly true for Teissier and his pupils, as well as l'Héritier and Malécot. Teissier, in particular, before his collaboration with l'Héritier, developed a major program in laws of growth and allometry, a program, incidentally, that greatly influenced Monod's studies of the growth of bacterial cultures. Indeed, some of the analyses of competition in population cages were

built upon the same mathematics. And for the other figures, a crucial influence was the long French preoccupation with physiological causal analysis. The standards of adequate explanation of the transmission and development of traits developed by the figures we have studied here were inescapably rooted in these traditions. The requirements of physiological understanding help explain the focus on nucleocytoplasmic relations and infectious heredity, and the strong dependence on kinetic studies, employed far more readily as tools for genetics in the 1930s and 1940s by the French workers than by most workers in other countries.

The emphasis on physiology was clearly fostered by long intellectual traditions, including specifically medical interests and training. Briefly put, France was not only the country of Lamarck (who became the emblem of resistance to the penetration of genetics), but also that of Bernard and Pasteur. Bordet, d'Hérelle, all three Wollmans, Monod, Jacob, and Lwoff worked in the Pasteur Institutes of Brussels and Paris, and Jacob, Lwoff, and Elie Wollman all had medical degrees. Although none of these last three were practicing physicians, this part of their background fits very well with our claim that the distinctive interest in the physiological basis for the transmission of traits (and their development within the organism) formed a crucial intellectual background for the founders of genetics in France. French workers were, of course, not unique in this regard. Still, the founders of genetics in England, Germany, Sweden, the United States, and even Russia were far more likely to have connections with issues regarding breeding and practical agriculture than the French scientists studied here, and did not draw as extensively on physiological or medical backgrounds as did the French.

This said, it is virtually impossible to disentangle the interactions of the external and internal factors that we have separated here for purposes of analysis. Institutional support (some of it medical) for physiological investigations in the Pasteur Institute and the Institut de Biologie Physico-Chimique both reinforced the importance of physiological studies and offered protection for esoteric investigations of phenomena that proved to be important in the study of heredity. Such opportunities were simply not available within the universities. The biologists thus supported were encouraged to draw on the great intellectual and institutional strength of the Pasteurian and Bernardian traditions, but left to find their own way to link them to international developments in genetics. Thus, the extra-university institutions involved fostered the research that produced the largely physiological tools that proved especially valuable when they were applied to issues in regulatory genetics. Of obvious relevance here are studies of phage, lysogeny, enzymatic adaptation, and cytoplasmic inheritance of respiratory competence in yeast, but it is an artefact of our selection of work to examine that we have not provided more examples.

The mixed consequences of physiological interests are readily seen in the careers of Cuénot and Guyénot. Cuénot, the only biologist who pursued fundamental Mendelian research in the first decade, had a significant physiological orientation himself. He was the first to propose that genes control enzyme formation (39), and he devoted the last eight of his experimental papers in genetics to the effect

of Mendelian factors on susceptibility to cancer in mice (45). The resistance of the universities to Mendelism was deeply motivated by the resistance of university biologists to approaches that seemed unlikely to provide a "physiological theory of heredity" [taken from the title of (138)]. This is, surely, part of the reason for which Cuénot steered his doctoral students away from genetics. And it helps explain the consequences of Guyénot's unsuccessful attempt to show that Morgan's mutations arose from a failure to control the nutrition of his flies and the antiseptic conditions in which they were raised. That exercise, one of the most remarkable systematic attempts to put a Lamarckian hypothesis to the test, was exactly what his mentors called for—and his failure to accomplish what he set out to do meant that he had no career in France. His project, successful from the perspective of Morgan, was a failure according to the standards of Bernardian physiology and Pasteurian microbiology.

Finally, one last lesson from external history concerns the entry of genetics into university curricula in the period just after World War II. It is clear that the strong research achievements of Ephrussi, L'Héritier, and Teissier played an important role here. In the early 1930s, there was no one of sufficient stature working in genetics to merit consideration, let alone appointment, to a university professorship. It is clear that the physiological and mathematical strengths of these individuals were of help in gaining them support. But their scientific accomplishments alone were not enough to make reform possible. Political considerations were at least equally important. The biologists of the Sorbonne strongly opposed a professorship for Ephrussi (20), and it was only with considerable international support and the assistance of politically and scientifically powerful allies among the physicists and mathematicians, many of them active in the Resistance, that Ephrussi's appointment was secured. Even given the excellence of the research done by the principal figures whose work we have examined, the question remained open whether it was the sort of work to earn a professorship and to justify the investment in new French disciplines (population and microbial/general genetics) by the CNRS. Given the political climate within biology, the answer was by no means automatic. External alliances were required to accomplish the needed reforms, to establish Ephrussi's professorship, and to secure the CNRS's material support. Even the most significant scientific accomplishments require reasonably stable and reliable material support, and that support can never be safely taken for granted.

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NOTE ADDED IN PROOF

At p. 333, we ascribe the discovery of Hfr factors to Hayes (82). As Hayes (82, 166) and Jacob & Wollman (93, 166) explicitly acknowledged, the first Hfr factor was found by LL Cavalli-Sforza (1950, La sessualità nei batteri, *Boll. 1st sierotera*. Milan 29:1–9). Jacob & Wollman (93, pp. 57–59) describe the history of these discoveries and explain the advantages of using Hayes's Hfr, which arose as a spontaneous mutant of Cavalli-Sforza's. Hayes's Hfr was used in virtually all of Jacob and Wollman's work with strains carrying Hfr factors.

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