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The Experimental Life Sciences in the Twentieth Century

By Daniel J. Kevles* and Gerald L. Geison**

THE LIFE SCIENCES have entered a wholly new era during the twentieth century, in terms of scale, institutional visibility, claims on resources, and social consequences. Above all, experimental biology has come to be seen as the most powerful force in the modern reconception of the nature of life and in the radical transformation of medical practice. This transformation had diverse sources, but none was more telling than the attempt to subject issues in late-nineteenth century evolutionary and developmental biology to experimental scrutiny. That general research program led to the emergence of new disciplines such as embryology, cytology, endocrinology, the reproductive sciences, and genetics, which rapidly took on lives of their own, independent of evolutionary debates, and produced a wide range of conceptual and utilitarian triumphs.¹

Experimental biology has been widely hailed for its role in unpacking the riddles of heredity, notably through the introduction of Mendelian and molecular genetics, and for its contribution to the production of newly vigorous agricultural crops, newly specific preventive measures in public health, and newly efficacious therapies in medical practice. Its practitioners and advocates could point to such utilitarian results in agriculture as hybrid corn and the green revolution; or to such benefits in medicine as antiseptics, vaccines, serum therapies, replacement therapies like vitamins, insulin, and other hormones, and above all antibiotics like penicillin and other specific remedies for infectious diseases.

Since the discovery of the double-helix structure for DNA, in 1953, the most spectacular achievements of modern experimental biology have derived from molecular biology. Examples include the use of genetic mapping with restriction fragment length polymorphisms to identify diagnostic markers for genes that figure in disease and to track down those genes for the purpose of sequencing and analyzing them; the deployment of recombinant DNA techniques to construct transgenic animals to study gene function by observing their effects when they are inserted into foreign organisms; and the introduction of foreign genes into plants to improve features

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¹ See, e.g., Adele E. Clarke, "Embryology and the Rise of American Reproductive Sciences, circa 1910-1940," in *The Expansion of American Biology*, ed. Keith Benson, Jane Maienschein, and Ronald Rainger (New Brunswick, N.J.: Rutgers Univ. Press, 1991), pp. 107-132; and Jane Maienschein, "History of Biology," *Osiris*, 1985, 1:147-162.

ranging from disease resistance to market qualities. Some of the utilitarian promise implicit in this research has begun to be realized—for example, in genetically engineered organisms that produce unprecedented yields of milk, proteins, insulin, or human growth hormone, and very recently in the first efforts to apply gene therapy to human victims of genetic diseases.²

Such striking results in both “pure” and “utilitarian” work in the experimental life sciences could hardly go unnoticed by historians. On the basic biological side, we now have valuable studies of several major developments in the history of twentieth-century physiology, embryology, biochemistry, classical genetics, and molecular genetics. On the utilitarian, institutional, and social side of the story, we also have a growing body of work in the history of agricultural research and a very large, if not always distinguished, body of literature on the history of modern medical institutions, problems, and practices. In fact, the history of diseases has lately become a sort of growth industry, with major studies of such afflictions as cholera, tuberculosis, yellow fever, polio, and even the new scourge AIDS, to speak only of the more obviously somatic diseases.

However, a vast terrain remains to be explored in the technical history of molecular biology and its disciplinary relatives, where thus far scientist-participants (often with the help of journalists) have set a largely whiggish tone and agenda, celebrating successes while ignoring twists, turns, and failures. Equally important, the historiography of the experimental life sciences is, like the sciences themselves, enormously diverse and disparate. Works in the history of the medically related sciences, for example, take little cognizance of those involved with agriculture, while the development of molecular biology has been treated as something of a force unto itself, disconnected (until recently) from the rest of modern biology. Indeed, some of the richest, most accessible, and most significant needs and opportunities for historians of modern life science lie in explorations of the interplay between basic experimental biology and agricultural or medical practices.

How is the history of such a rich and diverse domain of twentieth-century science to be written? To unify our study of the rise of the experimental life sciences and make it easier to understand, we have imposed a common analytic framework on the disparate fields that constitute them. Our framework is based on the following three clusters of categories: goals, patronage, and institutions; concepts and research programs; and methods, instruments, and materials devised within a discipline or imported from without. We will first discuss these categories schematically, then briefly illustrate how they can be used to structure and clarify the history of two major areas of research in the experimental life sciences. Most of our discussion concerns developments in the United States, but we believe that our framework is applicable to the history of the modern experimental life sciences elsewhere. Of course, our illustrative subjects and themes deserve much fuller historical and multinational analysis.

Our aim here is not to challenge prevailing historiographic interpretations. In fact, there are no overarching interpretive schools in the historiography of twentieth-

² See, e.g., Diana Long Hall, “Physiological Identity of American Sex Researchers between the Two World Wars,” in *Physiology in the American Context, 1850–1940*, ed. G. L. Geison (Bethesda, Md.: American Physiological Society, 1987), pp. 263–268; and Daniel J. Kevles and Leroy Hood, eds., *The Code of Codes: Scientific and Social Issues in the Human Genome Project* (Cambridge, Mass.: Harvard Univ. Press, 1992).

century biology. Nor do we presume to be comprehensive: the corpus of historical studies in modern biology is as vast as it is disparate. We seek only to draw attention to the large number of subjects that warrant historical investigation within this domain and to suggest how our framework might help to reveal their commonalities.

I. THE ANALYTIC FRAMEWORK

The goal of understanding, preventing, and finding therapies or cures for the diseases that beset people, animals, and plants has generated an enormous amount of experimental biological research. So has the effort to improve nutrition, growth, and fitness or quality in all three types of organisms. These broad utilitarian goals have given rise to abundant patronage. There are the large philanthropic foundations, like the Rockefeller and Carnegie foundations and the Wellcome Trust; the numerous eleemosynary agencies concerned with general medicine, like the Markey Foundation; and the still more numerous single-disease philanthropies, like the former National Foundation for Infantile Paralysis (now the March of Dimes Birth Defects Foundation), the Cystic Fibrosis and Multiple Sclerosis foundations, and the Muscular Dystrophy Association. In the United States key government agencies include state departments of public health and, at the federal level, the Food and Drug Administration, the U.S. Department of Agriculture, and the National Institutes of Health; the Atomic Energy Commission (now the Department of Energy) and its national laboratories such as that at Oak Ridge, Tennessee; several military agencies, notably the Office of Naval Research; and the National Science Foundation. The Medical Research Council has been an essential patron in Britain, as has INSERM (Institut National de la Santé et de la Recherche Médicale) in France. Utilitarian goals have also played a major role in the proliferation of diverse and numerous institutions where experimental life science research has been conducted: private research centers such as the Rockefeller Institute for Medical Research or the Pasteur Institute, as well as a host of public and private medical schools, agricultural schools, veterinary schools, bacteriological laboratories, and university departments of biology, biochemistry, and molecular biology.³

But if purposes and patronage did much to shape the orientations and problem choices of the research carried out in these institutions, the work itself took place within a conceptual space occupied by a set of inherited and evolving research programs that sometimes competed with one another. Among the most obvious of the defining concepts were and are those associated with Darwinian evolution through natural selection, the germ theory of disease, Mendelian genetics, structural biochemistry, and the genetic code.

The specific research programs pursued within these conceptual frameworks posed inherent technical challenges. Their resolution often hinged on innovations in methods, the identification or construction of appropriate biological materials, and the invention of new instruments. In physiology, for example, investigators of human

³ Jane S. Smith, *Patenting the Sun* (New York: William Morrow, 1990), makes clear the value of studying foundations devoted to disease research. See also George W. Corner, *A History of the Rockefeller Institute, 1901-1953: Origins and Growth* (New York: Rockefeller Institute Press, 1964); Robert E. Kohler, *Partners in Science: Foundations and Natural Scientists, 1900-1945* (Chicago: Univ. Chicago Press, 1991), esp. pp. 265-391; Michael Morange, ed., *L'Institut Pasteur: Contributions à son histoire* (Paris: Editions la Découverte, 1991); and the works cited in note 16 below.

reproduction sometimes arranged with local physicians to gain access to discarded embryos, ova, and ovaries from miscarriages, tubal pregnancies, and hysterectomies;⁴ studies of intermediary metabolism were transformed by the micromanometer in the hands of Hans Krebs (of Krebs cycle fame);⁵ embryology, developmental biology, and immunology found powerful new resources in the techniques of tissue culture and transplantation;⁶ and neurophysiology attained a new level of sophistication through the use of such biological material as the giant squid axon and new instruments such as the string galvanometer (forerunner of the electrocardiograph) for recording and amplifying biological signals.⁷

Virtually every branch of modern experimental biology came to rely on standardized biological materials and carefully constructed "laboratory animals," whether supplied by commercial firms that arose to meet the need or produced in on-site laboratory colonies of *Drosophila*, yeast, slime molds, rats, mice, or guinea pigs among other organisms.⁸ The infiltration of experimental biology by physicists, chemists, and their techniques helped foster the development of important new instruments. The ultracentrifuge, chromatography, electrophoresis, X-ray diffraction, and electron microscopy collectively opened the door to isolating and analyzing biological substances and ultimately understanding their structure and function.

The inherent technical challenges were often common across institutions and research programs. The difficulty of separating biological substances, determining protein structure, or assessing chromosomal and genetic features, for example, was the same whether the substances or proteins or chromosomes or DNA derived from a bacterium, a bee, or a bull. Cytogenetics was transformed by the advent, in the 1950s, of methods that permitted the clear karyotyping of chromosomes and, in the 1960s, of still other methods that allowed the identification of chromosomes by the pattern of bands they displayed upon treatment with a fluorescent chemical.⁹ And

⁴ Adele Clarke, "Research Materials and Reproductive Science in the United States, 1910-1940," in *Physiology in the American Context*, ed. Geison (cit. n. 2), pp. 332-335.

⁵ Frederic L. Holmes, "Manometers, Tissue Slices, and Intermediary Metabolism," in *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences*, ed. Adele Clarke and Joan Fujimura (Princeton: Princeton Univ. Press, 1992), pp. 151-171.

⁶ See, e.g., Frederick B. Bang, "History of Tissue Culture at Johns Hopkins," *Bulletin of the History of Medicine*, 1977, 51:516-537.

⁷ See, e.g., G. H. Bishop, "My Life among the Axons," in *The Excitement and Fascination of Science: Reflections by Eminent Scientists*, 2 vols (Palo Alto, Calif.: Annual Reviews, 1965), pp. 3-20; Louise Marshall, "The Fecundity of Aggregates: The Axonologists at Washington University, 1922-1942," in *Perspectives in Biology and Medicine*, 1983, 26:613-636; Marshall, "Instruments, Techniques, and Social Units in American Neurophysiology, 1870-1950," in *Physiology in the American Context*, ed. Geison (cit. n. 2), pp. 351-369; Robert G. Frank, Jr., "The Joseph Erlanger Collection at Washington University School of Medicine, St. Louis," *Journal of the History of Biology*, 1979, 12:193-201; and Frank and Judith H. Goetzl, "The Alexander Forbes Papers," *J. Hist. Biol.*, 1978, 11:429-435.

⁸ See Garland Allen, "The Introduction of *Drosophila* into the Study of Heredity and Evolution: 1900-1910," in *Science in America since 1920*, ed. Nathan Reingold (New York: Science History Publications, 1976), pp. 226-277; Robert E. Kohler, *Lords of the Fly: Drosophila Genetics and the Experimental Life* (Chicago: Univ. Chicago Press, 1994); Clarke, "Research Materials and Reproductive Science in the United States" (cit. n. 4), pp. 323-350; Clarke and Fujimura, eds., *The Right Tools for the Job* (cit. n. 5); H. L. Foster, "The History of Commercial Production of Laboratory Rodents," *Laboratory Animal Science*, 1980, 30:793-798; and Michael Lynch, "Sacrifice and the Transformation of the Animal Body into a Scientific Object: Laboratory Culture and Ritual Practice in the Neurosciences," *Social Studies of Science*, 1988, 18:265-289.

⁹ See T. C. Hsu, *Human and Mammalian Cytogenetics: An Historical Perspective* (New York: Springer-Verlag, 1979).

material, methodological, and instrumental innovations developed in one branch of experimental biology were often transferred advantageously to other branches.

It is well known that microbiology and molecular biology profited from new concepts and methods that came their way through cross-disciplinary interactions with physics and chemistry. Less well recognized is the benefit that physiology and microbiology have derived from the experimental materials provided by other disciplines, including notably physics, whose particle accelerators produced radioactive isotopes in abundance beginning in the 1930s. The isotopes first served as markers for tracking the course of chemicals through the body.¹⁰ In recent years they have become *sine qua non* in molecular biological research, serving as tags for fragments of DNA employed for purposes ranging from basic gene analysis to forensic genetic fingerprinting.

Although some of the topics mentioned above have been the subjects of historical study, many more await their historians. Like agricultural experiment stations or the Pasteur Institute, chromosomal banding, restriction enzymes, or the polymerase chain reaction, they merit historical treatment in and of themselves. And in our judgment, all of these topics would benefit from integrated consideration of our categories. We illustrate the point here with two examples—neurobiology and animal virology, focusing in both cases on research conducted in the United States after World War I.

II. NEUROBIOLOGY

An important recent book on the history of “neuroscientific concepts” does not even bother to enter the twentieth century, boldly claiming that “by 1850 the foundations of modern neuroscience had been laid.”¹¹ That claim would surely be disputed by those who have participated in the development of twentieth-century neurobiology. At a very general conceptual level, to be sure, some or even most of the basic issues had been posed and vigorously pursued by the mid-nineteenth century, but no stable consensus had emerged about several central problems, and a huge amount was yet to be learned about the details of the structural and functional features of the nervous system.

Even by the turn of this century, two or three of the most fundamental concepts in modern neurobiology were still under dispute or not yet fully developed. At the anatomical level, more than a few physiologists still preferred the “reticular” theory of the nervous system as a continuous cytoplasmic network rather than the ultimately triumphant “neuron” theory, according to which the nervous system was a complex arrangement of discrete individual cells—the latter theory being associated above all with Santiago Ramon y Cajal, the first (and so far only) Spanish recipient of the Nobel Prize in physiology or medicine.¹² Even among those who accepted the neuron theory by about 1900, its functional implications and significance had just

¹⁰ J. L. Heilbron and Robert W. Seidel, *Lawrence and His Laboratory: A History of the Lawrence Berkeley Laboratory*, Vol. I (Berkeley: Univ. California Press, 1989), pp. 156–157, 34–39, 219.

¹¹ Edwin Clarke and Louise S. Jacyna, *Nineteenth-Century Origins of Neuroscientific Concepts* (Berkeley: Univ. California Press, 1987), p. 1.

¹² See, e.g., Susan M. Billings, “Concepts of Nerve Fiber Development, 1839–1930,” *J. Hist. Biol.*, 1971, 4:275–306; and Santiago Ramon y Cajal, *Recollections of My Life* (Philadelphia: American Philosophical Society, 1937).

begun to be explored, notably by the English physiologist Charles Scott Sherrington, another future Nobel laureate. It was Sherrington who introduced the now universally accepted terms for the functional units of the cellular nervous system—axon, dendrite, and synapse—and who focused on the synapse, the junction between separate nerve cells, as the physiologically most significant unit. In 1907, after a decade of delicate animal experiments, notably on decerebrated cats, Sherrington advanced his famous, if highly complicated, theory of the “integrative action of the nervous system.”¹³

During the next half century neurophysiologists pursued a rich variety of specific problems and developed several major new concepts with the aid of sophisticated new techniques, electronic instruments, and recording devices. Far from being a stagnant field whose foundations had already been laid by 1850, neurophysiology continued to attract highly talented scientists, including a disproportionate number of future Nobel laureates. Until the rise of structural biochemistry and molecular biology, no branch of the experimental life sciences enjoyed such favor with the Nobel committee.¹⁴

Like biochemistry and molecular biology, neurophysiology attained its privileged status partly by demonstrating the fertility of the mechanistic approach to biological problems—specifically, by showing the extent to which extremely complex events in the nervous system could be explained by or “reduced to” electrical-chemical and other basic physical concepts. Only after World War II did the once glorious success of “classic” neuromuscular physiology begin to fade. The analytic categories outlined above offer a way of beginning to understand both the prolonged success of twentieth-century neurophysiology as such and its eventual diversification into such new fields as endocrinology, central nervous system physiology, and information or cognitive science—into, in short, “neuroscience” writ large.

Goals, Patronage, and Institutions

Given the crucial role of the nervous system in the distinctive features of animal and human life, neurophysiology has always held a special place among the branches of physiology. It might seem that generous patronage would have come to a field that sought insight into the mechanisms of locomotion and reflexes, the five special senses, and sensation in general—perception, paralysis, passion, and pain. Who could deny the appeal of a subject with such profound implications for the grandest philosophical issues of all—the “seat” of the mind, the interplay between mind and body, and the very nature of thought or the soul itself?

Yet the very pertinence of neurophysiology to these and other central human concerns could be a burden as well as a boon. At least through the mid-nineteenth century, experimental research on the nervous system could and did expose its practitioners to charges of atheistic “materialism,” and the results of such research were sometimes seen as dangerous to established beliefs, authorities, and institutions. During our more secular century neurophysiologists have had rather less to fear from

¹³ C. S. Sherrington, *The Integrative Action of the Nervous System* (New Haven: Yale Univ. Press, 1907). See also Judith P. Swazey, *Reflexes and Motor Integration: Sherrington's Concept of Integrative Action* (Cambridge, Mass.: Harvard Univ. Press, 1969).

¹⁴ See D. M. Fox, M. Meldrum, and I. Rezak, eds., *Nobel Laureates in Medicine or Physiology: A Biographical Dictionary* (New York: Garland, 1990).

such philosophical and religious objections (even though, like other experimental biologists, they have continued to face widely publicized charges of cruelty to animals). In the secularized and specialized twentieth-century Western world the goals of experimental neurobiology became more narrowly defined and much less controversial. But abundant patronage did not then flow automatically to the field. Its claims to attention and resources were now assessed according to a different set of criteria: like most branches of the biomedical sciences, neurobiology was obliged to articulate its goals and to seek patronage in terms that met the shifting needs or demands of medical education and medical practice.

For that reason the most important force in the development of experimental neurobiology during the past century has been the general ascendance of "scientific" medicine, based on the premise that experimental biology would yield benefits for medical education, clinical practice, and human welfare that were at least commensurate with its high costs. Leaving aside for now the question of how fully this ideology of scientific medicine was or is justified by the actual results of basic research in various branches of the biomedical sciences—a crucial issue woefully neglected by historians and other analysts—there can be no doubt that the ideology is widely accepted by the medical profession, private philanthropies, government agencies, and the public in general.¹⁵

In the United States, the first really large-scale patrons of scientific medicine were the Carnegie and Rockefeller foundations, especially the latter. The Rockefeller Foundation contributed not only directly through the Rockefeller Institute for Medical Research and fellowships for a host of individual research projects across the country and indeed around the world, but even more importantly through its crucial role in the radical transformation of American medical education after 1910. Taking its lead from the famous "Flexner Report" of that year on medical education in the United States and Canada, the General Education Board of the Rockefeller Foundation indicated its readiness to distribute tens of millions of dollars to medical schools throughout the country on the condition that they adopt "Flexnerian" programs of reform.¹⁶ The Carnegie Foundation for the Advancement of Teaching, although its support for similar goals was less sustained and less extensive in scale, was in fact the official sponsor of the Flexner Report. And in the year the report was published, 1910, the Carnegie Foundation gave \$2,000,000 to the Washington University Medical School in St. Louis so that it could be reorganized along the lines of Flexner's recommendations.¹⁷

The Flexner Report, citing the German university system and the Johns Hopkins University as its models, called for eliminating the worst of the numerous proprietary medical schools then common throughout the United States and transforming the rest into university-based institutions that emphasized the "preclinical" sciences, laboratory training, and the research ethos of the German universities. Medical

¹⁵ See Gerald L. Geison, "'Divided We Stand': Physiologists and Clinicians in the American Context," in *The Therapeutic Revolution: Essays in the Social History of American Medicine*, ed. Morris Vogel and Charles E. Rosenberg (Philadelphia: Univ. Pennsylvania Press, 1979), pp. 67-90; and John Harley Warner, "Science in Medicine," *Osiris*, 1985, 1:37-58.

¹⁶ Abraham Flexner, *Medical Education in the United States and Canada* (New York: Carnegie Foundation, 1910); E. Richard Brown, *Rockefeller Medicine Men: Medicine and Capitalism in America* (Berkeley: Univ. California Press, 1979); and Kenneth M. Ludmerer, *Learning to Heal: The Development of American Medical Education* (New York: Basic Books, 1985).

¹⁷ Marshall, "The Axonologists at Washington University" (cit. n. 7), p. 613.

schools enticed by the enormous funds dangled before their eyes by the Carnegie Foundation and especially the Rockefeller Foundation thus found themselves encouraged or obliged to recruit research-oriented experimental scientists, often Ph.D.s instead of clinically-oriented M.D.s, to teach the preclinical subjects. The upshot, already clear by the 1920s, was a sudden move toward a nationally standardized approach to medical education and research remarkably similar in structure to the one that still prevails today.¹⁸

Whatever the general virtues and defects of the Flexner model—and it has been the target of increasing criticism during the past two decades or so—it indisputably opened huge new opportunities for experimental research in the life sciences. Medical schools everywhere in the United States created positions for the newly ascendant practitioners of experimental biology and erected veritable laboratory Xanadus in which they could conduct their own research as well as teach experimental science to aspiring physicians. Happily for physiologists, the Flexner Report called physiology “the central discipline of the medical school,”¹⁹ and physiologists, including not least neurophysiologists, were among the major early beneficiaries of the Flexnerian revolution in medical education.

In fact, a preliminary scan of the general history of American physiology suggests that the period between the Flexner Report and World War II may have been a golden age for American neurophysiology. During those four decades, American neurophysiologists continued to enjoy their traditional dominance within the discipline—a dominance institutionally ratified, so to speak, when “all five of the papers at the first annual meeting of the [American Physiological] Society, in 1888, were on neural topics.” By the 1913 annual meeting of the society, the proportion of papers on neurophysiological topics had “declined” to 36 percent, while at the 1930 meeting fully 42 percent of the papers presented had something to do with the nervous system.²⁰ During the first half of this century only cardiovascular physiology—then considered a closely related specialty in any case—came close to challenging the hegemony of neurophysiology within American physiology and its official society.

The highwater mark, perhaps, for American neurophysiology was the decade of the 1930s. That decade began with the formation of a highly influential, if small and informal, group known as the “Axonologists,” a sort of dining club for self-appointed disciplinary leaders that met at the same time as, though separately from, the American Physiological Society. This practice did not always endear them to outsiders from other branches of the discipline, one of whom later reported that, at annual meetings of the society during the 1930s, the “Axonologists were the important people, and almost strutted through the corridors, dominated the meetings, being very conscious that they alone were in the frontiers of physiological discovery.”²¹

If the Axonologists or other American neurophysiologists really did prance about during the 1930s, it is not hard to understand why. Almost all were fairly young, in their thirties or forties, and they were flush with the acknowledged success of the

¹⁸ Flexner, *Medical Education in the United States and Canada*; and Ludmerer, *Learning to Heal* (both cit. n. 16).

¹⁹ Flexner, *Medical Education in the United States and Canada*, p. 63.

²⁰ Marshall, “Instruments, Techniques, and Social Units in American Neurophysiology” (cit. n. 7), pp. 354 (quotation), 358.

²¹ *Ibid.*, pp. 358 (quotation), 359; and Marshall, “The Axonologists at Washington University” (cit. n. 7).

precise results that flowed from their new techniques for amplifying and recording electrical signals from biological materials. Neurophysiology was also then a special favorite of the Rockefeller Foundation. Thus during the mid 1930s a small but significant contingent of Axonologists at Washington University in St. Louis received generous Rockefeller funding for their expensive cathode-ray oscillographs. As early as 1923 one of them, the future Nobel laureate Herbert Gasser, had "without his seeking it" received a fellowship from Abraham Flexner and the Rockefeller Foundation for a two-year leave of absence to travel abroad.²²

After World War II, as the Rockefeller Foundation reassessed its priorities and as its funding for medical research was vastly outstripped by the infusion of governmental support from the National Institutes of Health and other agencies, neurophysiology lost some of its prewar swagger. For a while neurophysiologists continued to dominate the councils and publications of the American Physiological Society, which now included the *Journal of Neurophysiology*, founded in 1937. As late as 1958, in a remarkable survey of the discipline commissioned by the American Physiological Society with support from the National Science Foundation, Ralph Gerard—himself a leading neurophysiologist who had convened the first meeting of the Axonologists—estimated that "two-thirds of all laboratory experiments [within physiology] are in neural and circulatory physiology."²³

By then, however, Gerard and other neurophysiologists who had once dominated the annual meetings of the American Physiological Society had begun to display a more subdued, almost wistful tone about the place of their specialty within the discipline of physiology and experimental biology more generally.²⁴ Historians of modern physiology have not yet fully explored the impact of World War II on the field, including how it may have moved neurophysiology away from its classical focus and reshaped its relations with other disciplines.

Concepts and Research Programs

To the general historian of scientific ideas or culture, surely the most familiar concept in twentieth-century neurophysiology is Ivan Pavlov's notion of the conditioned reflex, especially as deployed by behavioral psychologists like B. F. Skinner. Much less attention has been paid to the details of spinal reflex physiology, even as elaborated by C. S. Sherrington in his general theory of the "integrative action of the nervous system." Another central concept, at once related to and yet very different from prevailing ideas in neurophysiology, was Walter B. Cannon's notion of "homeostasis," as popularized in his 1932 book *The Wisdom of the Body*. Not surprisingly, given its seemingly clear links to such ideas as evolution, adaptation, and equilibrium—and thus, more broadly, to American social theory—Cannon's concept of homeostasis has already attracted a fair amount of historical attention.²⁵ For similar

²² Marshall, "The Axonologists at Washington University," pp. 618–619.

²³ Ralph W. Gerard, *Mirror to Physiology: A Self-Survey of Physiological Science* (Washington, D.C.: American Physiological Society, 1958), p. 231.

²⁴ See, e.g., *ibid.*; Bishop, "My Life among the Axons" (cit. n. 7); and Ralph W. Gerard, "The Organization of Science" (1952) in *The Excitement and Fascination of Science* (cit. n. 7), pp. 149–160.

²⁵ On Cannon, homeostasis, and equilibrium or functionalist models in American social thought see Walter B. Cannon, "Organization for Physiological Homeostasis," *Physiological Reviews*, 1929, 9:399–431; Cannon, "The Autonomic Nervous System, and Interpretation," *The Lancet*, 1930, 1:1109–1115; Cannon, *The Wisdom of the Body* (New York: Norton, 1932); Saul Benison, A. Clifford

reasons there is a steadily increasing body of historical literature on the theory of hormones, a theory that encompassed both the effects of nervous action on hormonal secretions and the role of hormones (or "chemical messengers") in the transmission of nervous impulses at the synaptic junction between neurons. English and American physiologists contributed the important work on homeostasis and hormones, which Continental physiologists were relatively slow to accept.²⁶

These wide-ranging ideas may seem more exciting than the "list of the major themes and concepts in twentieth-century physiology" that we owe to Louise Marshall, a neuroscientist-cum-historian: "(1) The central nervous system localization for control of hormonal secretion and body homeostasis, (2) the identification of control of movement at several levels of the higher brain centers, (3) the characterization of the elements of the compound action potential, (4) the forces influencing neuronal regeneration, and (5) the electrochemical theory of nervous transmission."²⁷ This otherwise valuable list also omits the "all-or-none law," according to which a given fiber from any sort of tissue either responds maximally or not at all, the strength of the response being independent of the strength of the stimulus. First advanced in the case of cardiac tissue in the late nineteenth century, the all-or-none law was extended to ordinary skeletal muscle by World War I, and then to peripheral nerves and finally the central nervous system by World War II.²⁸

Marshall's list of "major themes and concepts" could also be challenged on the grounds that it minimizes theoretical issues and seems skewed toward central nervous control at the expense of peripheral, decentralized "autonomy" in the form of ganglia or circulating chemical substances (in a word, hormones).²⁹ Although Marshall acknowledges elsewhere the importance of the chemical theory of nervous transmission and its challenge to central nervous control, adding these and other controversial issues might have led to a list that better revealed how pertinent twentieth-century neurophysiology is to broader philosophical and ideological concerns. And it is not merely politically fashionable to suggest that historians of neurobiology might have paid closer attention to controversies over the site of control of particular neurophysiological functions. At least for the outsider, a discussion of such controversies would also help to clarify the *technical* issues at stake.

Barger, and Elin L. Wolfe, *Walter B. Cannon: The Life and Times of a Young Scientist* (Cambridge, Mass.: Belknap Press of Harvard Univ. Press, 1987); Stephen J. Cross and William Randall Albury, "Walter B. Cannon, L. J. Henderson, and the Organic Analogy," *Osiris*, 1987, 3:165-192; Donald Fleming, "Walter B. Cannon and Homeostasis," *Social Research*, 1984, 51:609-640; and C. E. Russett, *The Concept of Equilibrium in American Social Thought* (New Haven: Yale Univ. Press, 1968).

²⁶ See Gerald L. Geison, *Michael Foster and the Cambridge School of Physiology: The Scientific Enterprise in Victorian Society* (Princeton: Princeton Univ. Press, 1978), esp. the discussion of national styles on pp. 331-355. See also *ibid.*, pp. 311-321, 353-354, and the sources cited there. On the closely related topic of reproductive physiology and sex research see, e.g., Merriley Borell, "Organotherapy and the Emergence of Reproductive Endocrinology," *J. Hist. Biol.* 1985, 18:1-30; Diana Long Hall, "Biology, Sex Hormones, and Sexism in the 1920s," *Philosophical Forum*, 1974, 5:81-96; Hall, "Physiological Identity of American Sex Researchers" (cit. n. 2); and Clarke, "Research Materials and Reproductive Science in the United States" (cit. n. 4).

²⁷ Marshall, "Instruments, Techniques, and Social Units in American Neurophysiology" (cit. n. 7), p. 359.

²⁸ See Robert G. Frank, Jr., "Instruments, Nerve Action, and the All-or-None Principle," *Osiris*, 1994, 9:208-235; and G. L. Geison, "Keith Lucas," in *Dictionary of Scientific Biography* (New York: Scribners, 1970-1980), Vol. III, pp. 532-535.

²⁹ Cf. Geison, *Michael Foster and the Cambridge School of Physiology* (cit. n. 26), *passim*.

Methods, Instruments, and Materials

Forty years ago the American physiologist Walter Fenn wrote that "the whole history of physiology could be written in terms of new tools for research." Fenn, like many experimental scientists, did not need historians, philosophers, or sociologists to teach him about the importance of techniques and experimental systems, or "the right tools for the job," in the production of the conceptual knowledge that has been the traditional concern of historians and philosophers of science.³⁰ His point about the centrality of "new tools for research" in the development of physiology, though surely exaggerated, is especially apt in the case of twentieth-century neurophysiology.

Every account of twentieth-century neurophysiology makes it clear that conceptual developments in the field were so closely bound up with advances in methods, instruments, and materials that it seems almost artificial to draw a distinction between its conceptual and its technical sides. This point emerges with special clarity when one recognizes the intimate link between particular instruments and specific research programs in the field. Even before World War I several leading neurophysiologists made their mark chiefly through their technical skill, one prominent example being the Cambridge physiologist Keith Lucas. Though once described as "essentially an engineer," Lucas laid much of the groundwork for the extension of the all-or-none law from cardiac muscle to other tissues, a research program that was further pursued by his student, the future Nobel Laureate Edgar Douglas Adrian. The next generation of neurophysiologists expressed admiration for Lucas's technical skills, tinged with regret that he had died—in 1916, in an airplane crash—before he could profit from the new physiological instruments that became available after, and indeed largely because of, World War I.³¹

The crucial common feature of postwar instruments was their capacity to amplify and record bioelectrical phenomena without the distortion produced by the recording levers in such traditional instruments as the kymograph (a revolving smoked cylinder that inscribed traces of muscular contraction). During World War I a few American physiologists, notably Alexander Forbes of Harvard, became aware of the potential utility for physiological research of amplified electronic waves, as exemplified by the radio compass. Increasingly refined versions of instruments based on this principle reached sophisticated expression in the cathode-ray oscillograph devised by Herbert Gasser and his associates at Washington University. Their device helped clear the way for a newly precise analysis of the effects of individual fiber size and other features of nervous tissue. In 1944 Gasser and his senior colleague Joseph Erlanger were awarded the Nobel Prize "for their work on 'the highly differentiated functions of single nerve fibers,' [but] the award implicitly recognized Erlanger and Gasser's seminal role in developing the single most important instrumental tool in modern neurophysiology, the amplifier *cum* cathode ray oscillograph."³²

Much more could and should be said about the process by which the amplified

³⁰ Fenn as quoted in Gerard, *Mirror to Physiology* (cit. n. 23), p. 245. Cf. Clarke and Fujimura, *The Right Tools for the Job* (cit. n. 5).

³¹ See Frank, "All-or-None Principle" (cit. n. 28).

³² Frank, "The Joseph Erlanger Collection" (cit. n. 7), p. 195. See also Frank, "All-or-None Principle" (cit. n. 28); and Frank and Goetzl, "The Alexander Forbes Papers"; Marshall, "The Axonolo-

cathode-ray oscillograph was developed—not least because it both represents a striking example of the importance of “tinkering” and manual skills in science and draws our attention to the relations between experimental physiologists and industrial corporations such as Western Electric. Several other examples along the same lines could be drawn from the history of modern neurophysiology, and in fact Louise Marshall has already emphasized the extent to which research programs and groups in the field were associated with the exploitation of instruments, including the micro-electrode in Gerard’s laboratory at the University of Chicago.³³

Not all neurophysiologists welcomed this full-blown “instrumentalization” of the field. By 1952 Gerard himself offered the following admonitory comment:

What is important, and a change in kind, is that the users of instruments are increasingly not their masters. Once, any physiologist could tinker a kymograph into good behavior and even make or have one made in the shop in the basement. Few today dare open the crinkle-finish black boxes purchased from some “radio” firm, and, even of those who do, a small number indeed could carry on without the services of an expert electronics engineer. This may be unfortunate, but it is certainly inevitable. Not only do instrument societies flourish now, but a formal discipline of instrumentology is rapidly becoming established—indeed, becoming subdivided into new specialties—so that a self-respecting physiology laboratory can hardly limp along with only (besides technicians) glass blower, mechanic and electrical factotum.³⁴

III. ANIMAL VIROLOGY

Like neurobiology, virology has become a broad, central subject in twentieth-century experimental life science. Fundamentally important in and of itself, it links a number of essential branches of biology—in the early decades of the century, botany, plant pathology, human and veterinary medicine, and bacteriology; in the later ones, genetics, protein chemistry, cytology, and molecular biology. The field comprises three main branches—bacterial, plant, and animal virology. A few popular and scholarly studies have attempted to deal with the overall history of the subject; the best scholarly study is that by the British virologist A. P. Waterson and the historian Lise Wilkinson.³⁵ However, these studies are of necessity introductory, not least because only one branch of the field—bacterial virology—has been well studied historically.

The mid-century history of bacterial virology has received abundant historiographic attention because of the key role it played in the development of molecular genetics. A good deal is known about the work at its principal centers, notably the Pasteur Institute in Paris, Cambridge University, and the amorphous American phage school that formed in the mid 1940s around the study of phage—the term for viruses that prey on bacteria—as a means of getting at the physical and chemical

gists at Washington University”; and Marshall, “Instruments, Techniques, and Social Units in American Neurophysiology” (all cit. n. 7).

³³ Marshall, “Instruments, Techniques, and Social Units in American Neurophysiology.”

³⁴ Gerard, “The Organization of Science” (cit. n. 24), p. 153.

³⁵ A. P. Waterson and Lise Wilkinson, *An Introduction to the History of Virology* (Cambridge: Cambridge Univ. Press, 1978). See also Sally Smith Hughes, *The Virus: A History of the Concept* (New York: Science History Publications, 1977), most of which is concerned with the period before 1900, and Peter Radetsky, *The Invisible Invaders: The Story of the Emerging Age of Viruses* (New York: Little, Brown, 1991), a pioneering popular account.

basis of genetics. The phage group's founders and guiding spirits were Max Delbrück, Salvador Luria, and Alfred D. Hershey. The trio were at different institutions—Delbrück at the California Institute of Technology, Luria at Indiana University, Hershey at Washington University—but they conjoined during summers at the Cold Spring Harbor Laboratory on Long Island, to do research and teach about phage to new recruits. The phage group's scientific hallmarks included using simple, uniform biological systems—for example, bacteria and phage isolated and bred to have standard characteristics—and studying them with quantitative experimental techniques. The crucial role of phage research in the early development of molecular biology was signified by the award of the Nobel Prize in physiology or medicine in 1969 to Delbrück, Luria, and Hershey.³⁶

The principal object of historiographic attention in plant virology has been the tobacco mosaic virus, again because of its connection with the development of molecular genetics. Identified in the late nineteenth century, tobacco mosaic virus emerged as a model plant virus in the 1920s and was much studied thereafter. It provided information that illuminated bacterial and animal virology later on, the most dramatic being, as Wendell Stanley demonstrated in 1935, that it could be crystallized and thus analyzed as a physicochemical substance.³⁷ However, historians have written little about plant virology apart from the tobacco mosaic virus, and they have devoted still less study to animal virology.

Thus plant and animal virology are rich with historiographic opportunity. So, we would claim, is bacterial virology, for historians to date have tended to emphasize conceptual developments—the interplay between ideas and concepts on the one side and experiment and technique on the other. With some exceptions, it is generally acontextual, inattentive to features of the research environment—local, national, and international—that gave rise to fundamental advances or allowed them to occur.³⁸ While Waterson and Wilkinson emphasize conceptual accomplishment, they also point out that virology raises a variety of issues, including how new disciplines arise and scientific institutions are rearranged, how scientific research has been related to medical practice, and how it can depend heavily on instruments and methods.³⁹

In all, virology is a prime subject for the type of treatment outlined in the analytical framework we have advanced. To illustrate the value of the framework and the historiographic needs and opportunities in the field, we here focus on its least studied branch—animal virology—while attending to plant and bacterial virology as

³⁶ See Ernst Peter Fischer and Carol Lipson, *Thinking about Science: Max Delbrück and the Origins of Molecular Biology* (New York: Norton, 1988), pp. 148–166; Robert C. Olby, *The Path to the Double Helix* (Seattle: Univ. Washington Press, 1974), pp. 225–226, 238–240; and Horace F. Judson, *The Eighth Day of Creation: The Makers of the Revolution in Biology* (New York: Simon & Schuster, 1979), p. 70.

³⁷ Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), p. 120.

³⁸ Prominent exceptions include Prina G. Abir-Am, "The Discourse of Physical Power and Biological Knowledge in the 1930's: A Reappraisal of the Rockefeller Foundation's 'Policy' in Molecular Biology," *Soc. Stud.*, 1982, 12:341–382; Abir-Am, "Essay Review: How Scientists View Their Heroes: Some Remarks on the Mechanism of Myth Construction," *J. Hist. Biol.*, 1982, 15:281–315; Abir-Am, "The Biotheoretical Gatherings: Transdisciplinary Authority and the Incipient Legitimation of Molecular Biology in the 1930's: New Perspective on the Historical Sociology of Science," *History of Science*, 1987, 25:1–70; Lily E. Kay, "Cooperative Individualism and the Growth of Molecular Biology at the California Institute of Technology, 1928–1953" (Ph.D. diss., Johns Hopkins University, 1987); and Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology* (New York: Oxford Univ. Press, 1991).

³⁹ Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), pp. viii–xii.

necessary and appropriate. Although ranging through much of the twentieth century, our discussion is centered on the period from the late 1920s, when animal virology was a nascent field at best, extremely limited not only in knowledge but in numbers of practitioners and arsenal of basic methods, to the 1960s, when it emerged as one of the leading fields of microbiology.

Goals, Patronage, Institutions

Animal viruses were often investigated because they cause disease in animals and human beings, particularly infectious diseases such as rabies, equine encephalitis, foot and mouth disease, yellow fever, influenza, and polio. An eagerness to deal with viral diseases (in plants as well as animals) prompted the establishment of patronage and institutions for viral research—for example, the Potato Virus Research Station at Cambridge University, first funded privately by the biologist R. N. Salaman; the viral research institution that the German Ministry of Agriculture created in 1910, placing it on the island of Riems so as to isolate the work from mainland farm communities; and the Division for Plant Pathology that the Rockefeller Foundation funded at Princeton in 1931, which counted Wendell Stanley among its first staff recruits.⁴⁰ No doubt research in plant and animal virology went on in many other agricultural research institutions, public and private, whose development and research programs expressed concern with the particular vulnerabilities of local crops and animal breeds.

Work on viruses threatening to human beings was naturally pursued in the medical arena. A key institutional locus was the Rockefeller Institute for Medical Research in New York City, where important attention was given to common infectious diseases. There Peyton Rous suggested in 1911 that cancer might result from viral infection, demonstrating that a nonfilterable agent, as viruses were initially termed, would transmit sarcomas in chickens. Between the 1930s and the mid 1950s the principal sources of funds for research and training in animal virology were philanthropic agencies concerned with combating infectious diseases. The Rockefeller Foundation, for example enlarged its long-standing concern with international health and development to include investigations in viral diseases transmitted by insects, among them yellow fever, dengue, and encephalitis; and the American Cancer Society came to play a role in virology after it began supporting research in 1948.⁴¹

The program of the National Foundation for Infantile Paralysis (NFIP) exemplifies the significance of such philanthropic agencies in fostering advances in animal virology. Established in 1938 by Basil O'Connor, Franklin Delano Roosevelt's former law partner and ongoing confidant, the NFIP raised money each year through its March of Dimes campaign—enough to provide an annual operating budget of almost \$3 million in 1940, close to \$20 million in 1945, and more than \$50 million in 1953. Committed to fighting and eventually eliminating the disease of poliomyelitis, the NFIP used its money to explore the nature of the disease and to develop defenses against it.⁴²

⁴⁰ *Ibid.*, pp. 122, 130, 143.

⁴¹ See *The President's Review from the Rockefeller Foundation Annual Report, 1956* (New York: Rockefeller Foundation, 1956), p. 29; and James T. Patterson, *The Dread Disease: Cancer and Modern American Culture* (Cambridge, Mass.: Harvard Univ. Press, 1987), pp. 171–172.

⁴² Smith, *Patenting the Sun* (cit. n. 3), pp. 82, 161.

In formulating and developing its program, the NFIP consulted biological and medical experts. The experts were well aware that poliomyelitis was caused by an animal virus that attacked the cells of the nervous system, but that little was understood about the virus itself or how to proceed in dealing with the disease. They apparently advised NFIP officials to mount a two-pronged attack: award research grants to advance knowledge of the polio virus in particular and of animal viruses in general; and give postdoctoral fellowships to promising young scientists so as to increase the number of trained practitioners in the field. The magnitude of its activities is suggested by the fact that even in 1953, when the National Institutes of Health (NIH) made microbiology an explicit commitment of its external grants program, providing some support for work in polio, the NFIP spent more than twenty-five times as much on polio research as did NIH, which then devoted the largest share of its grant money to cancer research. Between 1938 and 1956 the NFIP awarded 322 postdoctoral fellowships in virology and other fields related to polio, including 97 in microbiology. An official at the foundation estimated in 1956 that no fewer than one third of the virologists under 45 in the United States had been trained under NFIP fellowships.⁴³

In the twenty years after 1938 NFIP grants went for work of pathbreaking significance across a broad spectrum of microbiology. By 1956, 1,870 papers had been published that acknowledged its assistance: roughly 10 percent were in basic biochemistry, 14 percent in basic physiology, and 20 percent in viruses and viral diseases other than polio. The foundation's grants included sizable subventions to Linus Pauling at the California Institute of Technology for research into the structure of proteins, nucleic acids, and their components, and to Wendell Stanley, who had moved to Berkeley, for inquiries into the physical and chemical properties of plant, animal, and bacterial viruses. Its postdoctoral awards included a fellowship to James D. Watson that supported him during the year he puzzled out the structure of DNA with Francis Crick.⁴⁴

Concepts and Research Programs

The fight against polio involved research into the epidemiology of the disease, the isolation and identification of its causative viral strains, and the development of a vaccine against it. How other viral diseases have been approached awaits systematic historical investigation. One wonders what constituted basic research in animal viruses in the pre-molecular era, what concepts were brought to it, and what advances such research yielded.

Peyton Rous's demonstration that cancer might be an infectious viral disease led others to investigate that possibility in animals other than chickens. The research

⁴³ In 1953 the NIH polio research budget was \$72,000; the NFIP's, \$2 million. See Smith, *Patenting the Sun* (cit. n. 3), p. 249; and T. E. Boyd, memo to Basil O'Connor, "Contributions to Science in the Field of Poliomyelitis," March of Dimes Birth Defects Foundation Archives, White Plains, New York, [1956], pp. 19-20.

⁴⁴ Boyd, memo to Basil O'Connor, pp. 23-24, 21-22, 31-32; and James D. Watson, *The Double Helix* (New York: Atheneum, 1968), p. 132. The NFIP awarded grants for work on the encephalitis virus at Berkeley; on human viral diseases at Harvard, some of which monies were given to Enders; and on animal and plant viruses and biophysical properties of viruses at the University of Pittsburgh, where the program was stimulated by the arrival of Salk in 1947. Boyd, memo to Basil O'Connor, pp. 20-22.

program apparently followed Rous's: attempt to stimulate tumor growth in a healthy animal by injecting a nonfilterable extract obtained from a malignancy in a cancerous one. The program failed: for twenty years after Rous's initial experiment, neither Rous nor anyone else was able to transmit tumorous growths by inoculation in mammals. (In 1908 two Danish pathologists had isolated a nonfilterable agent that induced fatal leukemia in chickens. However, since leukemia at the time was not considered to be a form of cancer, their results were not thought relevant.⁴⁵) Where and how these experimental attempts were conducted and why they failed requires investigation.

Whoever did them, the failures led to widespread rejection of the idea that cancer had much if anything to do with viruses; yet the concept and the research program that accompanied it remained alive at the Rockefeller Institute. In 1931 a member of the Institute staff named R. E. Shope examined a freshly shot rabbit with tumorlike growths and showed that the condition was transmissible in rabbits by a nonfilterable agent. In 1932 Shope investigated a papilloma found among the wild rabbit population in Iowa and Kansas, demonstrating that this too was caused by a nonfilterable agent. Indeed, upon injection with the wild rabbit agent, domestic rabbits developed papillomas that were at first benign but then became malignant.⁴⁶

Shope's results by no means moved theories of oncogenesis in a viral direction. Scientists by and large looked elsewhere for the causes of cancer, entertaining a variety of theories and pursuing diverse research programs in consequence. Like the Rockefeller research program, these theories and research programs deserve historical scrutiny. Among the plausible theories was the idea that cancer had something to do with genes. Indications of a genetic basis for cancer came from several notable clusters of evidence: The disease often ran in families, which suggested some hereditary predisposition to it; particular cancers occurred with high frequency in certain lines of mice; malignant cells multiplied into more malignant cells; and mutagenesis (for example, by radiation) could lead to malignancies. To the end of exploring the genetic theory of cancer, biologists at the Jackson Laboratory in Bar Harbor, Maine, bred pure strains of mice differing from one another in their frequency of cancer, hoping to find a clue to oncogenesis through the classical Mendelian methods of crossing and backcrossing. In a recent book the Swedish biologist George Klein recounts that the program produced a startling result: "The hybrid offspring from a cross between a high-breast cancer strain and a low-cancer strain developed breast cancer at a relatively high frequency if the mother belonged to the high-incidence strain and the father to the low-incidence strain, but the offspring had a low incidence of cancer if the opposite was the case." In 1936 John Bittner at the Jackson Laboratory traced the phenomenon to the transmission from mouse mother to child of what he called a "milk factor," which later was termed the mouse mammary tumor virus (MMTV). At the time Bittner was actually convinced that the milk contained a virus that increased risk of breast cancer in the mouse but was not sufficient to give the disease. (While 90 percent of the maternal strain of mice contracted breast cancer, no more than 30 percent of the offspring did, which suggested that susceptibility to cancer, arising perhaps from hormones, might be of comparable importance to viruses in generating the disease.) According to Klein, Bittner used the term "milk

⁴⁵ Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), p. 159.

⁴⁶ *Ibid.*, p. 160.

factor" instead of "virus" because he was reluctant to challenge the prevailing orthodoxy that cancer had nothing to do with viruses, explaining, "If I had called it a virus, my grant applications would automatically have been put into the category of 'unrespectable proposals.' As long as I used the term 'factor,' it was respectable genetics."⁴⁷

The viral role in oncogenesis nevertheless continued to attract at least some biologists in the 1930s (it would be useful to know which of them and with what research consequences). One of them was Emory Ellis, a biologist at the California Institute of Technology, and the research consequences of his innovation were considerable. Ellis had trained as a physical chemist and began to work with viruses when he received a fellowship for cancer research. He was aware that specific viruses caused diseases in plants, lysis in some bacterial species, and some cancerous growths in animals, and that the malignancies seemed to require both the presence of the right virus and the susceptibility of the cell. Ellis expected that learning more about the nature of viruses would help one understand such malignancies and perhaps those of other origins.⁴⁸ How to acquire that knowledge—what model system to adopt—was the question.

Ellis and his colleagues were reluctant to work with an animal virus like that responsible for rabbit papilloma because of the care, time, and money required when working with a large animal colony. The cost of investigating a plant virus such as the tobacco mosaic virus would be lower but still significant. To Ellis, it seemed clear that the most advantageous model system to use was bacteriophage, which required virtually no care, occupied little laboratory space, would yield results in a matter of hours, and would—lending themselves to a technique developed by the French biologist Félix d'Hérelle, to whom Ellis acknowledged a debt—make their activity known by the production of readily observable plaques on a Petri-dish bacteria lawn.⁴⁹

Ellis recalled that there also "appeared to exist some formal similarities in the processes of bacteriophage, fertilization of egg-cells by sperm and infection in virus diseases." He added, "If these do indeed have common aspects, even though taking place in substrates as different as man and bacteria, then study of the process in the system lending itself to quantitative study seemed likely to be the most rewarding." The similarities as well as obvious differences among the three processes motivated his detailed study of bacteriophage, Ellis remembered. "We hoped that once we understood it, we would be in a better position to understand virus-induced malignancies. It was this argument which led us to start work on bacteriophage."⁵⁰

The arrival of Max Delbrück at Caltech in 1937 soon broadened the work on phage into what became the phage school, which reworked the original program into one of bacterial genetics as such. However, historians ought to remember the original argument that brought Ellis to adopt bacteriophage as his model system.

⁴⁷ George Klein, *The Atheist and the Holy City: Encounters and Reflections*, trans. Theodore and Ingrid Friedman (Cambridge, Mass.: MIT Press, 1990), pp. 120–122, quoting from pp. 121, 122. See also Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), p. 161.

⁴⁸ Emory L. Ellis, "Bacteriophage: One-Step Growth," in *Phage and the Origins of Molecular Biology*, ed. John Cairns, Gunther Stent, and James D. Watson (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory of Quantitative Biology, 1966), pp. 53–54. See also Fischer and Lipson, *Thinking about Science* (cit. n. 36), p. 114; and William C. Summers, "How and Why Bacteriophage Came to Be Used by the Phage Group," unpublished MS in D. J. Kevles's possession, 1991, pp. 2–4.

⁴⁹ Ellis, "Bacteriophage," pp. 54–56.

⁵⁰ *Ibid.* See also Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), p. 103.

The argument locates an important root of the phage school not only in the genius and philosophical commitments of Delbrück but in the ongoing tradition of inquiry into the causes of disease, particularly the school of viral oncogenesis that goes back to Peyton Rous.

Techniques, Instruments, Materials

What prompted Ellis to reject work with animal viruses—the need to use live animals—was a major problem for animal virology. It had long been recognized that viruses would not grow outside the living cell, which meant that the most convenient place for growing them was live animals. The best live animals for the purpose were those that, like mice or rabbits, were small and reproduced relatively quickly. In the early 1930s mice were indeed adapted for the study of the human influenza virus. But many animal viruses could be not be cultivated in mice. The polio virus, for example, could only be grown in monkeys, which were employed early in the century to demonstrate that polio was a viral disease of the central nervous system. In the 1930s the only effective means of cultivating polio virus was to inject it into monkeys, let it grow, then harvest it by killing the animals. Even when small animals could be used, the *in vivo* constraints made studies of animal viruses in the laboratory expensive, time consuming, and cumbersome, largely beyond the kind of controlled experiments that might permit analyses of how viral infection or oncogenesis worked, how viruses reproduced, even what they comprised. Animal cultures compelled the virologist to try to deduce from the animal's reaction to infection some information on the properties and the nature of viruses.

As early as World War I scientists tried to get around the difficulty by resorting to tissue culture—in vitro accumulations of living and reproducing cells—as a medium for growing animal viruses. Much is known about the early history of tissue culture. Between 1907 and 1911 the Yale biologist Ross G. Harrison pioneered a fundamental type of the technique—the so-called hanging-drop method—for studying the development of nerve fiber tissue. However, Harrison's method did not provide tissue cultures suitable for animal viruses, and for reasons that historical study might expose, developing such cultures was not a simple matter.⁵¹

In Manchester in 1928, for example, H. B. Maitland and his wife, Mary Cowan Maitland, introduced a technique that kept cells viable for a short time and, though growth was minimal, allowed them to express enough activity to multiply certain viruses for study. Max Theiler used the Maitlands' technique when developing a yellow fever vaccine. However, the technique could not be used for isolation of a virus from a test material. In the years bracketing World War I, Alexis Carrel at the Rockefeller Institute devised ingenious methods of tissue culture that could be adapted to the *in vitro* cultivation of animal viruses. In 1927 he and his collaborator Tom Rivers exclaimed that "one finely pulped chicken embryo might be capable of producing as much vaccine as a calf." Still, Carrel's methods were extremely complicated, particularly the intricate set of procedures required to keep the culture free from bacterial contamination. Years later a professor at the Royal Caroline Insti-

⁵¹ In 1928 Alexis Carrel, in "Tissue Culture in the Study of Viruses," part of the classic text *Filterable Viruses*, edited by Tom Rivers (London: Ballière, Tindall, & Cox, 1928), ascribed the lack of progress to reliance on "the comparatively crude procedure . . . derived . . . from the experiments of Harrison." Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), pp. 72–73.

tute in Sweden would note that Carrel's was "a complicated ritual. . . . Tissue culture developed almost into a tissue cult, a mystery the secret rites of which were revealed only to a narrow circle of inaugurates with Carrel as their high priest."⁵²

In 1931 A. M. Woodruff and E. W. Goodpasture reported an advantageous method: growing animal viruses on the sheets of cells formed by the extraembryonic membranes of the chick embryo inside the fertilized egg. Their method was comparatively successful and widely used during the 1930s. One of the leading pioneers in animal virology, F. Macfarlane Burnet in Australia, succeeded in growing the influenza virus in the developing egg, for example. As Waterson and Wilkinson note, "The egg can be seen as a particularly cheap and convenient experimental animal; by a stretch of imagination (and definition) it can perhaps also be seen as a very sophisticated kind of tissue culture, carrying its own medium, by the same token that W. Roux's frog embryo experiments are often seen as the beginnings of tissue culture."⁵³

For all their utility, chicken embryos were not a suitable host for all animal viruses of interest. In 1936 Albert Sabin and Peter K. Olitsky tried to grow polio virus in chicken embryos and failed. They also failed to grow it in Maitland cultures of mice and monkeys. They succeeded only with human embryonic brain tissue. The result fostered the idea, mistaken as it eventually turned out, that the polio virus was strictly neurotropic; it also discouraged follow-up of that particular culture technique because human embryonic tissue was an unsuitable medium for culturing viruses that might be used in vaccinations.⁵⁴ The National Foundation for Infantile Paralysis remained eager to find a culture that was suitable for the polio virus. In the late 1940s it awarded funds for research to John Enders, a medical research scientist at the Boston Children's Hospital, where he headed a small group at work on tissue-culturing infectious viruses.

Enders became interested in the viral culturing problem while on the staff of the Harvard Medical School during the 1930s. His research was interrupted by the war, but in 1947 he resumed exploration of tissue culture in collaboration with Thomas H. Weller, who as a Harvard medical student had assisted him just before the war, and Frederick C. Robbins, Weller's roommate at medical school. Enders, Weller, and Robbins soon succeeded in growing mumps virus in cultured chicken cells with their innovative technique of continuous culture, periodically replacing the nutritive medium while leaving the viral culture intact. The collaborators then sought to apply their technique to the cultivation of varicella (chicken pox) virus in cultures of its natural host, human embryonic skin and muscle tissues. In 1948, appropriating some of these cultures, they managed to cultivate the polio virus, an achievement that was to earn them the 1954 Nobel Prize in physiology or medicine.

They originally had no intention of experimenting with the polio virus, but were aware of the mounting evidence that it might not be a strict neurotrope. They and

⁵² "Physiology or Medicine 1954: Presentation Speech by Professor S. Gard, member of the Staff of professors of the Royal Caroline Institute," *Nobel Lectures in Physiology or Medicine, 1942-1962* (Amsterdam: Elsevier, 1964), p. 444. See also *ibid.*, p. 445; and Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), pp. 144 (Maitlands), 68-73 (Carrel).

⁵³ Waterson and Wilkinson, *Introduction to the History of Virology*, pp. 76, 138-139.

⁵⁴ Gard, "Physiology or Medicine 1954" (cit. n. 52), p. 445. Earlier, MacFarlane Burnet and A. V. Jackson in Australia had reported growing polio virus under similar conditions, but neither they nor anyone else had followed up the breakthrough: Boyd, memo to Basil O'Connor (cit. n. 43), p. 30.

others found it difficult to see, for example, how the nervous system alone could produce the abundant quantities of polio virus found in the feces of many patients. They also had in a laboratory freezer a sample of the Lansing strain of polio virus sent them some time earlier by the NFIP. As they reported in their Nobel address, "Thereupon it suddenly occurred to us that everything had been prepared almost without conscious effort on our part for a new attempt to cultivate the agent in extraneural tissue." According to a later account by a member of the NFIP, Weller had prepared too many tubes of culture medium for the experiment with the chicken pox virus, so Enders suggested that he seed the cultures with some polio virus from the laboratory freezer.⁵⁵

The demonstration that polio virus could be grown in non-nerve cell tissue cultures was a stunning part but not the whole of the Enders group's achievement. With the mumps virus, their technique involved growing cells suspended in fluids; for polio, they developed methods for growing them in a solid layer. They also devised methods for keeping track of the multiplication of the virus and for using cell cultures containing the virus to test for poliomyelitis antibodies. Perhaps even more significant, they made it possible to recover usable polio virus from feces or spinal cord suspensions by suppressing the bacterial contamination of these sources with the newly available antibiotics, penicillin and streptomycin, then centrifuging the sample. They thus eliminated the need to obtain polio virus via the laborious and time-consuming procedure of intracerebral inoculation of monkeys.⁵⁶

The feat of the Enders group not only transformed polio virus production, emancipating it from the expensive use of live monkeys and pointing the way to large-scale production of a polio vaccine; it also promised to revolutionize animal virology by liberating the field in general from the grip of Carrel's tissue cult. It provided methods for growing animal viruses reliably and efficiently *in vitro* and for acquiring them in abundance. As Enders, Weller, and Robbins noted in their Nobel address, the application of antibiotics had made it "possible to apply tissue culture to the routine isolation of viruses from materials heavily contaminated with microorganisms" and "to use them under conditions and in numbers which in the past would have been quite unthinkable."⁵⁷

Tissue culture was thus revolutionized by the Enders group's work. In short order many new animal viruses were discovered, including, by the mid 1950s, at least eighteen different immunologic types of the human adenoviruses.⁵⁸ It would seem obvious that this revolution in tissue culture and its consequences warrants historical investigation. The role of the new antibiotics in the revolution also raises the historiographic question of the effect of World War II on the postwar development of the life sciences. Many medical researchers went off to war. During the war Enders was

⁵⁵ John F. Enders, Frederic Robbins, and Thomas H. Weller, "The Cultivation of the Poliomyelitis Viruses in Tissue Culture" (Nobel Lecture, 11 Dec. 1954), in *Nobel Lectures in Physiology or Medicine* (cit. n. 52), pp. 448-467, on p. 451; and Boyd, memo to Basil O'Connor (cit. n. 43), p. 30.

⁵⁶ "John F. Enders," in *Nobel Prize Winners: An H. W. Wilson Biographical Dictionary*, ed. Tyler Wasson (New York: H. W. Wilson, 1987), pp. 300-302; and Enders, Robbins, and Weller, "Cultivation of the Poliomyelitis Viruses in Tissue Culture," p. 457.

⁵⁷ Smith, *Patenting the Sun* (cit. n. 3), pp. 135-137; Boyd, memo to Basil O'Connor, p. 30; and Enders, Robbins, and Weller, "Cultivation of the Poliomyelitis Viruses in Tissue Culture," pp. 458-459.

⁵⁸ Enders, Robbins, and Weller, "Cultivation of the Poliomyelitis Viruses in Tissue Culture," p. 465.

a consultant on epidemic diseases to the secretary of war, and Weller, a member of the Army Medical Corps, was stationed at the Antilles Medical Laboratory in Puerto Rico, where he headed the Departments of Bacteriology, Virology, and Parasitology. One wonders how the war changed the outlooks of biological practitioners and affected their research programs.

Certainly the war affected the materials and instruments available to animal virologists. Although radioactive tracers were produced by cyclotrons before the war, the nuclear piles of the Manhattan Project and then the Atomic Energy Commission yielded them in still greater variety and abundance. In the postwar era such tracers exercised "enormous impact across the whole spectrum of biological research," to cite the judgment of Waterson and Wilkinson. They were indispensable, for example, to Alfred Hershey and Martha Chase in their classic demonstration that the viral protein coat is adsorbed on the surface of the host cell by its tail, which then injects the DNA of the virus into the cell.⁵⁹

One instrument that benefited the study of animal viruses, which are too small to be seen under the ordinary light microscope, was the electron microscope—invented before the war for use in physics. In 1940 RCA funded (at \$3,000 a year) a National Research Council fellowship for the purpose of exploring the instrument's biological applications, and the young biologist appointed to the fellowship, Thomas F. Anderson, began using the microscope to photograph the tobacco mosaic virus and bacteriophage. During the second year of his fellowship Anderson began to work with Salvador Luria, who had visited RCA to explore the possibility of using the electron microscope to check the size of some bacteriophages which he and a collaborator had just estimated from X-ray cross sections. In 1942 Max Delbrück joined the electron picture-taking.⁶⁰

Perhaps the most important visual evidence that the electron microscope provided during the war years was that phage particles multiply inside the cells, rather than at their surfaces; until lysis occurs, the number of particles visible at the surface remains constant. This constancy also means that very few, if any, of the particles enter the cell, an observation that seemed to Delbrück to be of the "greatest consequence" and led him to revise his thinking about how phage reproduced. According to Anderson's later reflections, the electron microscope brought to the fore "the deeper mysteries of how the particles are organized, what the function of each part might be, and why the particles appear to remain on the surface of the host instead of diving into it like a respectable parasite. The resolution of these mysteries has been shown to require the intelligent application of additional methods of research—the microscope can only suggest solutions, not confirm them."⁶¹

After the war, as its technology and resolution improved, the electron microscope became an increasingly valuable adjunct to virological research, widely used in all three branches of the field. It revealed viruses as concrete objects to think about, permitted them to be distinguished from one another morphologically, and provided visual tests of theories concerning viral properties and behavior that were

⁵⁹ Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), p. 108.

⁶⁰ *Ibid.*, pp. 105–106.

⁶¹ Thomas F. Anderson, "Electron Microscopy of Phages," in *Phage and the Origins of Molecular Biology*, ed. Cairns, Stent, and Watson (cit. n. 48), pp. 63–64, 67, 77 (long quotation). See also the obituary of Anderson, *New York Times*, 13 Aug. 1991, p. C19.

arrived at by other means.⁶² This bare outline of accomplishments suggests that the precise role of the electron microscope in virology and other branches of experimental biology deserves systematic historical analysis. Certainly it awaits historical scrutiny.

IV. CONTEXT AND CONTINGENCY

In 1969, we are told, there was "a good deal of handwringing by some members of the American Physiological Society" when a new group of "Young Turks" established the independent and interdisciplinary Society for Neuroscience.⁶³ The anxiety was not merely "institutional," in the narrow sense that the old guard in the American Physiological Society feared a loss of members to the new and independent group. Conceptual issues and prospects for future funding were also at stake. Neuroscience was concerned mainly with aspects of brain function instead of classical neuromuscular topics. As such, it reached out toward such nascent fields as cybernetics and cognitive science instead of the traditional and clinically oriented specialties of neuroanatomy, neurology, neurosurgery, and psychiatry.

In this new context some of those who had flourished during the golden age of "classical" neurophysiology might have begun to doubt the wisdom of the Faustian bargain they had made with the utilitarian goals of medicine as conceived between the two world wars. Like cardiology, which relied on similar kinds of noninertial graphical recording instruments, neurophysiology was more than a little unsure about its immediate clinical utility.⁶⁴ Some of the less arcane results of neurophysiological research did seem to have implications for neurological *diagnoses*, but its direct *therapeutic* benefits were hard to see or even imagine—with the possible exception, it was sometimes supposed, of the guidance it gave to neurosurgeons performing lobotomies and related operations. In the face of such doubts about the direct clinical utility of their research, "classical" neurophysiologists could no longer rely so confidently on the "pure" intellectual excitement that their work had once aroused. Even in the "purely" intellectual arena, if not only there, enthusiasm was shifting toward the new interdisciplinary field called neuroscience.

The case was quite different in animal virology. The field received increasing attention during the 1950s, partly because the electron microscope revealed the presence of viruses in animal tumor cells, partly because during the decade a number of viruses were demonstrated to stimulate malignancies. One such virus, found to generate several types of tumors in mice, rats, and hamsters, was named the polyoma virus in recognition of its multiple potencies. (Why biologists found so much viral

⁶² Anderson, "Electron Microscopy of Phages," p. 77; and Waterson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), p. 155. See also Boyd, memo to Basil O'Connor (cit. n. 43), pp. 2–3.

⁶³ Marshall, "Instruments, Techniques, and Social Units in American Neurophysiology" (cit. n. 7), p. 359.

⁶⁴ On cardiology see the superb studies by Robert G. Frank, Jr., "The Telltale Heart: Physiological Instruments, Graphic Methods, and Clinical Hopes, 1854–1914," in *The Investigative Enterprise: Experimental Physiology in Nineteenth-Century Medicine*, ed. W. Coleman and F. L. Holmes (Berkeley: Univ. California Press, 1988), pp. 211–290; and Joel Howell, "Cardiac Physiology and Clinical Medicine? Two Case Studies," in *Physiology in the American Context*, ed. Geison (cit. n. 2), pp. 279–292. See also Geison, "Physiologists and Clinicians in the American Context" (cit. n. 15).

oncogenesis, as the phenomenon had come to be called, in the 1950s when they could not find it in the 1920s and 1930s is another puzzle for historians to explain.)⁶⁵

Animal virological research was also accelerated in the 1950s by the merger of innovations in tissue culture with the quantitative, plaque-counting methods developed in bacterial genetics. A principal locus of the merger was the California Institute of Technology, where animal virology came to occupy several biologists in a group headed by Renato Dulbecco (and partially supported by the National Foundation for Infantile Palsy). Dulbecco, who had learned phage-group methods in the laboratory of Salvador Luria, devised ingenious methods for culturing animal viruses in monolayers of human or animal tissue spread out on a flat dish. The methods made cellular degeneration arising from viral infection visible as a plaque. Applying the techniques of phage analysis to such cultures, Dulbecco and his collaborator Marguerite Vogt were able to pursue the type of genetic analysis of animal viruses, including polio viruses, that had been brilliantly accomplished with bacteriophage.⁶⁶

The research of Dulbecco's group—which included Howard Temin and Harry Rubin—helped to establish animal viral genetics as an exciting field in its own right. It also suggested that the distinction between viral and genetic theories of oncogenic action was fuzzy, not least because Dulbecco and Vogt observed that the polyoma virus transformed—that is, caused to divide without restraint—hamster cells cultured in a laboratory dish. They also found that the virus quit reproducing in the transformed cells, which suggested, by analogy with the behavior of temperate phage, that its DNA had been incorporated into the genome of the cell itself, thus accounting for the transformation.⁶⁷

By the 1960s, not only could viral genetics be pursued quantitatively in cell culture, but so also could animal-tumor virology—with the result, as James Watson later said, that “for the first time, thinking at the molecular level could begin.” Tumor virology was additionally boosted by reports from a number of laboratories that the Rous sarcoma virus would induce tumorous growths not only in fowl but also in mammals, including mice, rats, hamsters, rabbits, and monkeys. Research on animal tumor viruses flourished, enlarging the texts published about them, forming a major branch of basic medical and biological science. In a sense the field had come full circle, moving from the seemingly dubious work of Peyton Rous into bacteriophage, then turning back to animal viruses via Dulbecco, among others. In 1966 the completion of the circle and the vitality of the field were recognized when Rous, at age eighty-five, shared the Nobel Prize in physiology or medicine.⁶⁸

⁶⁵ Watson and Wilkinson, *Introduction to the History of Virology* (cit. n. 35), p. 162; Ludwik Gross, *Oncogenic Viruses*, 2nd ed. (Oxford: Pergamon Press, 1970), pp. 10–13, 106, 264; W. Ray Bryan, “Peyton Rous,” *Science*, 1966, 154:364–365; “Peyton Rous,” in *Nobel Prize Winners Biographical Dictionary* (cit. n. 56), pp. 889–890; J. Michael Bishop, “Oncogenes,” *Scientific American*, 1982, 246:81; and Natalie Angier, *Natural Obsessions: The Search for the Oncogene* (Boston: Houghton Mifflin, 1988), p. 5.

⁶⁶ Boyd, memo to Basil O'Connor (cit. n. 43), p. 31.

⁶⁷ Harry Rubin, “Quantitative Tumor Virology,” in *Phage and the Origins of Molecular Biology*, ed. Cairns, Stent, and Watson (cit. n. 48), pp. 294–295; and Marguerite Vogt and Renato Dulbecco, “Virus-Cell Interaction with a Tumor-Producing Virus,” *Proceedings of the National Academy of Sciences*, 1960, 46:365–370.

⁶⁸ James D. Watson, “Foreword,” in *Viral Oncogenes* (Cold Spring Harbor Symposia on Quantitative Biology, 44) (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1980), pt. 1, p. xviii;

The scientific prospects of animal tumor virology helped generate a degree of boosterism for the field—a crash research program might find cures for cancer—and proclamations of that kind figured importantly in the creation of the so-called war on cancer in 1971, during the administration of President Richard M. Nixon. That war led to neither immediate therapies nor cure, but the huge investment of funds (several billion dollars) in the field accelerated the development of molecular biology and DNA technology in ways that are understood in outline but beg for systematic historical analysis.⁶⁹ Unlike the case with classical neurophysiology and neuroscience, what the cancer war did not realize in one way, it yielded in others, notably clinical payoffs such as DNA diagnostics and the immense stimulus that the molecular biological advances of the 1970s provided to the biotechnology industry. Then, too, animal virology as such has continued to flourish because of the role that viruses play in infectious disease and because practitioners in the field can point to unalloyed successes such as the polio vaccine and to dark challenges, notably the AIDS epidemic.

V. CONCLUDING REMARKS

We hope that our flexible analytic framework will be useful in accounting for the post-1960 transmutation of neuroscience and the further development of animal virology, as well as for other fields in the experimental life sciences. We wish to emphasize the importance of one category of that framework, the role of methods, instruments, materials. Until recently, it had been the topic most neglected by historians of the modern life sciences, perhaps because it has increasingly involved technological imports from other disciplines.⁷⁰ Here the historians were once in good company with those biologists whose resistance to recognizing the importance of materials and instrumentation was proportional to the sophistication of the instruments and materials on which they relied. Thus Professor Sven Gard, of the Royal Caroline Institute in Sweden, when, in 1954, he presented Enders, Robbins, and Weller for their Nobel Prize:

Gross, *Oncogenic Viruses* (cit. n. 65), pp. 136–139; “Rous, Francis Peyton,” *McGraw-Hill Modern Scientists and Engineers*, 3 vols. (New York: McGraw-Hill, 1980), Vol. III, pp. 48–49; and Robert J. Huebner and George J. Todaro, “Oncogenes of RNA Tumor Viruses as Determinants of Cancer,” *Proceedings of the National Academy of Sciences*, 1969, 64:1087–1088. Rous shared the Nobel prize with Charles B. Huggins, who had demonstrated the role of hormones in the treatment of cancer, especially cancer of the prostate.

⁶⁹ Klein, *The Atheist and the Holy City* (cit. n. 47), p. 128.

⁷⁰ This long-standing neglect is now rapidly being rectified. See, e.g., Bruno Latour and Steve Woolgar, *Laboratory Life: The Construction of Scientific Facts* (Princeton: Princeton Univ. Press, 1987); Merrile Borell, “Extending the Senses: The Graphic Method,” *Medical Heritage*, 1986, 2:114–121; Borell, “Instruments and an Independent Physiology: The Harvard Physiological Laboratory, 1871–1906,” in *Physiology in the American Context*, ed. Geison (cit. n. 2), pp. 293–321; Borell, “Instrumentation and the Rise of Modern Physiology,” *Science & Technology Studies*, 1987, 5:53–62; Timothy Lenoir, “Models and Instruments in the Development of Electrophysiology, 1845–1912,” *Historical Studies in the Physical and Biological Sciences*, 1986, 17:1–54; Lenoir, “Helmholtz and the Materialities of Communication,” *Osiris*, 1994, 9:185–207; Frank, “All-or-None Principle” (cit. n. 28); Alberto Cambrosio and Peter Keating, “‘Going Monoclonal’: Art, Science and Magic in the Day-to-Day Use of Hybridoma Technology,” *Social Problems*, 1988, 35:244–260; Lynch, “Sacrifice and the Transformation of the Animal Body into a Scientific Object” (cit. n. 8); R. J. Greenspan, “The Emergence of Neurogenetics,” *The Neurosciences*, 1990, 2:145–157; and esp. Clarke and Fujimura, eds., *The Right Tools for the Job* (cit. n. 5), including their extensive bibliography.

The electronics, radioactive isotopes, and complicated biochemistry of our age has threatened to turn medical science into something dangerously resembling technology. Now and again we need to be reminded of its fundamental biological elements. Against this background we express our admiration of the biological common sense, characterizing your approach to important medical problems, and of the wonderful simplicity of the solutions you have presented.⁷¹

Applied to our two case studies, our framework also calls attention to two important general points concerning the ascent and descent of disciplines. First, the rise and relative decline of "classical" neurophysiology indicates that the interplay between basic experimental biology and agriculture or medicine is not always marked by steady progress or uniformly effective results. Once-favored disciplines or specialities in the biomedical sciences can slip from their lofty perch if their clinical utility comes into doubt, and perhaps even more readily if they become intellectually less exciting than other specialties always ready to take their place. Second, the case of animal virology suggests that it is a mistake to think of medical or agricultural practices as "applied" experimental biology; in fact, the interplay has gone both ways, and medical or agricultural interests have often been essential to shaping developments in so-called basic research. Further, substitutes for a lack of immediate clinical payoff can be found in the richness of new intellectual programs and in the reward of unexpected utilitarian dividends. History is not only contextual; it is also contingent.

⁷¹ Gard, "Physiology or Medicine 1954" (cit. n. 52), p. 447.