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THE MODERN EXPERIMENTAL LIFE SCIENCES: NEEDS AND OPPORTUNITIES FOR HISTORICAL RESEARCH

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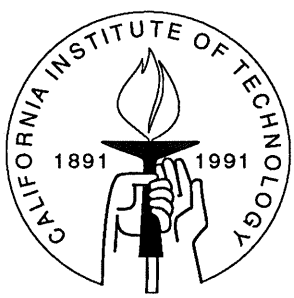

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The Modern Experimental Life Sciences
Needs and Opportunities for Historical Research

During the past century, advances in the experimental life sciences have come from experimental biology as such, from medical and agricultural research, and from the interplay between the two. Like the physical sciences, they have been stimulated by both a desire to know for its own sake and for the sake of utility. Nothing new in kind marked either these motivations or interactions, but during the past century experimental biology has entered a wholly different era in terms of its scale, institutional visibility, claims on resources, and social consequences. In particular, it 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.

Post-1900 experimental biology sprang from diverse parentage, but none was more powerful than the attempt to subject issues in late-nineteenth century evolutionary and developmental biology to experimental scrutiny. That general research program contributed mightily to the emergence of disciplines such as embryology, cytology, endocrinology, the reproductive sciences, and genetics, which rapidly took on lives of their own, independent of evolutionary debates, and which marched to 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, anti-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 centered on 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 employment 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 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 achievements 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 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 and ignoring twists, turns, and failures. Equally important, the historiogaphy of the experimental life sciences is, like the sciences themselves, enormously diverse and disparate. Works in the history of, for example, the medically related sciences take little cognizance of those involved with agriculture, while the development of such fields as 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.

Some unification and, hence, better understanding, of the rise of the experimental life sciences is likely to come from consideration of that interplay -- from imposing on the disparate fields that comprise these sciences a common analytic framework. To our minds, the framework should should include (though it may not be limited to) three clusters of categories: (1) goals, patronage, and institutions; (2) concepts and research programs; and (3) methods, instruments, 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 needs and opportunities in the history of the experimental life sciences elsewhere. Our illustrative subjects and themes deserve much fuller historical and multi-national analysis.

Of necessity, our aim here is not to challenge prevailing historiographic interpretations: there are no overarching interpretive schools in twentieth-century biology. Nor do we presume to be comprehensive: the corpus of historical studies in modern biology is as vast as it is disparate. Our purpose is to be substantively suggestive, with regard both to the large number of subjects that warrant historical investigation and to how an analytical framework might assist in illuminating their commonalities.

* * *

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 -- for example, the Rockefeller and Carnegie Foundations and the Wellcome Trust; the numerous eleemosynary agencies like the Markey Foundation, that are concerned with general medicine; 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 or Multiple Sclerosis Foundations, and the Muscular Dystrophy Association. There are the government agencies like the early Food and Drug Administration, the U.S. Department of Agriculture, and state public health agencies; and obviously the now dominant National Science Foundation and National Institutes of Health in the United States, the Medical Research Council in Britain, and INSERM 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 were sometimes in competition 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 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 organ 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 EKG) 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 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 profited from new concepts and methods that came its 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 spit out radioactive isotopes in revolutionarily cheap 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 various topics schematized 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. Yet at least as pregnant with historiographic opportunities are any number of broad, fundamental areas of experimental biology that would benefit from integrated consideration of all or most of our categories. We illustrate the point here with two examples -- neurophysiology and animal virology, focusing in both cases on research conducted in the United States after World War I.

Neurophysiology

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 participated in the development of twentieth-century neurophysiology. 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 neurophysiology 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 mainly with Ramon y Cajal, the first (and so far ony) 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 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" in a book with that title.[13]

During the next half century, neurophysiologists successfully 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 (about which a bit more below). 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 -- in its case, more 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 insight into both the prolonged success of twentieth-century neurophysiology and its eventual decline.

1. Goals, Patronage, and Institutions

Not surprisingly, 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 even seem that the goals of research in neurophysiology are of such obvious interest and importance that its practitioners must always have enjoyed generous patronage. What patron could resist the claims of 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 it should not be forgotten that 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 the past century, of course, neurophysiologists have had less to fear from such philosophical and religious objections (though, like other experimental biologists, they have continued to face widely publicized if mostly impotent charges of cruelty to animals). In the secularized and specialized twentieth-century Western world, the goals of experimental neurophysiology became more narrowly defined and much less controversial. But that is not to say that abundant patronage then flowed automatically to the field. Its claims to attention and resources were now to be assessed according to a rather different set of criteria. Like most branches of the biomedical sciences, neurophysiology was now 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 neurophysiology during the past century has been the general ascendance of "scientific" medicine, which has been premised on the assumption 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 that has been woefully neglected by historians and other analysts --

there can be no doubt as to its widespread acceptance 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, 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 it was published, 1910, 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 the elimination of the worst of the numerous proprietary and "didactic" medical schools then common throughout the United States, and for the transformation of the rest into university-based institutions that emphasized the "preclinical" sciences, laboratory training, and the research ethos of the German universities. Medical schools enticed by the enormous funds dangled before their eyes by the Carnegie and, more often, the Rockefeller Foundations 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 1920's, 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 Flexnerian 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 ascendent 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 leading 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 sort of golden age for neurophysiology. During those four decades, American neurophysiologists continued to enjoy their traditional dominance within the discipline -- a dominance that had been 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."[20] By the 1913 annual meeting of the Society, the proportion of papers on neurophysiological topics had "declined" to 36%, while at the 1930 meeting fully 42% of the papers presented had something to do with the nervous system.[21] During the first half of this century, only cardiovascular physiology -- 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 1930's. 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.[22] 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 1930's, the "Axonologists were the important people, and almost strutted through the corridors, being very conscious that they alone were in the frontiers of physiological discovery."[23]

If the Axonologists or other American neurophysiologists really did prance about during the 1930's, 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 precise results that flowed from their new techniques for amplifying and recording electrical signals from biological materials. Perhaps for that very reason, neurophysiology was also then a special favorite of the Rockefeller Foundation. Thus, at Washington University in St. Louis during the mid-1930's, a small but significant contingent of Axonologists 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.[24]

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 seems to have lost some of its pre-war swagger. For a while, of course, 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."[25]

By then, however, Gerard and other neurophysiologists who had once strutted about the corridors at annual meetings of the American Physiological Society had began to display a more subdued, almost wistful tone about the place of their specialty within the discipline of physiology and experimental biology more generally.[26] Among what remains for historical investigation is 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.

2. Concepts and Research Programs

To the general historian of scientific ideas or culture, surely the most familiar concept in twentieth-century neurophysiology is Pavlov's notion of the conditioned reflex, especially as deployed by behavioral psychologists like B.F. Skinner. For good reasons, much less attention has been given to the details of spinal reflex physiology, even as elaborated by Sherrington in his general theory of the "integrative action of the nervous system." Another central concept, at once related to and yet in significant ways very different from prevailing ideas in neurophysiology, was Walter B. Cannon's notion of "homeostasis," as popularized in his book of 1932, *The Wisdom of the Body*. Not surprisingly, given its seemingly clear links to such ideas as evolution, adaption, and equilibrium -- and thus, more broadly, to American social theory -- Cannon's concept of homeostasis has already attracted a fair amount of historical attention.[27] For similar 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.[28] It is curious, but not altogether mysterious, that English and American physiologists should have contributed so importantly to these ideas, which continental physiologists were relatively slow to accept.[29]

At least at first sight, these wide-ranging ideas seem more exciting than the following "list of the major themes and concepts in twentieth-century physiology" that we owe to the neuroscientist-cum-historian Louise Marshall: "(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."[30] To some students of twentieth-century neurophysiology, this otherwise valuable list will seem oddly incomplete, if only because it 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.[31]

Quite apart from this omission, Marshall's list of "major themes and concepts" could also be challenged on the grounds that it is theoretically reticent and seems to be skewed toward central nervous control at the expense of peripheral, decentralized "autonomy" in the form of ganglia or even circulating chemical substances (in a word, hormones).[32] Elsewhere, to be sure, it is clear that Marshall fully appreciates the importance of the chemical theory of nervous transmission and its challenge to central nervous control. But more explicit attention to these and other controversial issues might have led to a list that better revealed the extent to which twentieth-century neurophysiology can be seen as pertinent to broader philosophical and ideological concerns. And it is not merely "politically" fashionable to suggest that closer attention could have been paid to controversies over the site of control of particular functions. At least for the outsider, a discussion of such controversies would also help to clarify the *technical* issues at stake.

3. 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."[33] Fenn, like many experimental scientists, did not need historians, philosophers, or sociologists to teach him about the importance of technique, or the "the right tool for the job," in the production of the conceptual knowledge that has been the traditional concern of historians and philosophers of science.[34] By no means for the first time, a scientist-participant thus anticipated, however briefly, a theme that has lately become a central issue for historians and other analysts of scientific activity.

Fenn's point about the centrality of "new tools for research" in the development of physiology, though surely a bit exaggerated, is perhaps especially apt in the case of twentieth-century neurophysiology. Every account of twentieth-century neurophysiology makes 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 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, who was once described as "essentially an engineer," though he nonetheless 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.[35] The next generation of neurophysiologists expressed admiration for Lucas' 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.

The crucial common feature of the post-war 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 preserved 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.[36] Increasingly refined versions of instruments based on this principle reached highly sophisticated expression in the cathode-ray oscillograph devised by Herbert Gasser and his associates at Washington University, St. Louis. Their device helped clear the way for a newly precise analysis of the effects of individual fiber size and other features of nervous tissue.[37] 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."[38]

Much more could and should be said about the process by which this instrument was developed, not least because it represents a striking example of the importance of "tinkering" and manual skills in science, while also drawing our attention to the relations between experimental physiologists and industrial corporations such as Westinghouse. Several similar examples 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 microelectrode in Gerard's laboratory at the University of Chicago.[39]

Interestingly, not all neurophysiologists welcomed the full blown "instrumentalization" of the field. By 1952, even Gerard would offer the following rather admonitory remarks on the subject:

> 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.[40]

Animal Virology

Virology is one of the central subjects in twentieth-century experimental life science. Fundamentally important in and of itself, its development 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 *An Introduction to the History of Virology* (Cambridge: Cambridge University Press, 1978), by the British virologist A.P. Waterson and the historian Lise Wilkinson.[41] 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 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 -- Delbruck, at the California Institute of Technology; Luria, at Indiana University; Hershey, at Washington University, in St. Louis -- 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 an emphasis on the use of simple, uniform biological systems -- for example, bacteria and phage isolated and bred to have standard characteristics -- and the study of 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 Delbruck, Luria, and Hershey.[42]

It seems that 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 physico-chemical substance.[43] 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 as well, the historiography of which has 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, omitting to account for features of the research environment -- local, national, and international -- that gave rise to or allowed the fundamental advances to occur.[44] While Waterson and Wilkinson's pioneering multibranch history is conceptual in emphasis, they also recognize that virology encompasses issues historiographically beyond conceptual accomplishment. Indeed, they point out that it 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.[45]

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 necessary and appropriate. While 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.

1. Goals, Patronage, Institutions

Much investigation in animal viruses has been prompted by the diseases they cause in animals and human beings, particularly infectious diseases such as rabies, equine encephalitis, foot and mouth disease, fowl plague, 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, which was first funded privately by the biologist R. N. Salaman; the viral research institution that the German Ministry of Agriculture created, in 1910, on the island of Riems so as to isolate the work from mainland farm communites; and the Division for Plant Pathology, which the Rockefeller Foundation funded at Princeton, in 1931, and which counted Wendell Stanley among its first staff recruits.[46] 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 and where, in 1911, Peyton Rous suggested that cancer might result from viral infection, demonstrating that a non-filterable agent, as viruses were initially termed, would transmit sarcomas in chickens. Between the 1930s and the mid-1950s, the principal source of funds for research and training in animal virology were philanthropic agencies concerned with combating infectious diseases. The Rockefeller Foundation enlarged its longstanding concern with international health and development to include investigations in viral diseases -- for example, yellow fever, dengue, and encephalitis -- transmitted by insects; and the American Cancer Society came to play a role in virology after, in 1948, it inaugurated the support of research. Historians have much to learn about both developments.[47]

The significance of these philanthropic agencies in fostering advances in animal virology is perhaps exemplifed by the program of the National Foundation for Infantile Paralysis. Established in 1938 by Basil O'Connor, Franklin Delano Roosevelt's former law partner and ongoing confidant, the National Foundation was run from a national headquarters on the eleventh floor of 120 Broadway, in New York City, just a few floors away from O'Connor's offices. Lacking an endowment, it raised money each year through its March of Dimes campaign, enlisting celebrities, President Roosevelt and his family, about three thousand local chapters, and some two million volunteers. Checks poured in along with the dimes, 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 National Foundation used its money to explore the nature of the disease and to develop defenses against it.[48]

In formulating and developing its program, the National Foundation 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 its 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 practioners 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 National Foundation 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 National Foundation 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 National Foundation fellowships.[49]

In the twenty years after 1938, National Foundation 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% were in basic biochemistry, 14% in basic physiology, and 20% in viruses and viral diseases other than polio.[50] 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.[51]

2. 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 comprised basic research in animal viruses in the pre-molecular era, what concepts were brought to it, and what advances such research yielded.

Peyton Rous' demonstration that cancer might be an infectious viral disease prompted a good deal of investigation of that possibility in animals other than chickens. The research program apparently followed Rous' example -- attempt to stimulate tumor growth in a healthy animal by injecting a non-filterable extract obtained from a malignancy in a cancerous one. The program failed: for twenty years after Rous' 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 non-filterable 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 taken to be relevant to Rous'.[52]) Where and how these experimental attempts were conducted and why they failed remains a prime subject for historical inquiry.

Whover 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 -- sufficiently alive to warrant historical study. In

1931, a member of the Institute staff named R.E. Shope examined a freshly shot rabbit with tumor-like growths and showed that the condition was transmissible in rabbits by a non-filterable 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 non-filterable agent. Indeed, upon injection with the wild rabbit agent, domestic rabbits developed papillomas that were at first benign but then became malignant.[53]

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. What these theories and research programs were deserve historical scrutiny. Among the plausible theories was the idea that cancer had something to do with genes because the disease often ran in families, which suggested some hereditary predisposition to it. To the end of exploring the genetic theory of cancer, scientists 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.[54] 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, a scientist at the laboratory named John Bittner 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 that 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 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 aplications would automatically have been put into the category of 'unrespectable proposals.' As long as I used the term 'factor,' it was respectable genetics."[55]

The viral role in oncogenesis nevertheless continued to compel the attention of at least some biologists in the 1930s (it would be useful to know which of them and with what research consequences). The identity of one of them -- Emory Ellis -- is certain and the research consequences of his innovation were considerable. A biologist at the California Institute of Technology, Ellis, a physical chemist, had started to work with viruses upon receipt of a

fellowship for cancer research.[56] 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 more knowledge regading the nature of viruses would be helpful in understanding such malignancies and perhaps those of other origins.[57] 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 such a program would require the care and expense in time and money of working with a large animal colony. The cost of investigations with 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 make their activity known by the production of readily observable plaques on a Petri-dish bacteria lawn.[58]

Ellis recalled that there also "appeared to exist some formal similarities in the processes of bacteriophagy, fertilization of egg-cells by sperm and infection in virus diseases," adding, "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 provided the reasons for commencing study in detail of the process of bacteriophagy, 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."[59]

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. The argument locates the Caltech start 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.

3. 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. However, many animal viruses could be not be cultivated in mice. For example, the polio virus could only be grown in monkeys, which had been 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 available for cultivating polio virus was to inject it into monkeys, let it grow, then harvest it by killing the animals. Even if small animals were 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 had begun trying to get around the difficulty by attempting to grow animal viruses in tissue culture, *in vitro* accumulations of living and reproducing cells. 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 the purpose of studying the development of nerve fiber tissue. However, Harrison's method did not provide tissue cultures suitable for cultivating animal viruses, and, for reasons that historical study might expose, it was not a simple matter to develop tissue cultures appropriate for animal virus research.[60]

For example, in 1928, in Manchester, a couple named 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 and study them. The Maitlands' technique was used in development of Theiler's yellow fever vaccine. However, the technique could not be used for isolation of a virus from a test material.[61] At the Rockefeller Institute in the years bracketing World War I, Alexis Carrel had, of course, devised ingenious methods of tissue culture that could be adapted to the *in vitro* cultivation of animal viruses. In 1927, Carrel and his collaborator Tom Rivers enthused that possibly "one finely pulped chicken embryo might be capable of producing as much vaccine as a calf." Still, Carrel's methods were extremely complicated, particularly with regard to an intricate set of procedures that they required to keep the culture free from bacterial contamination. Years later, a professor at the Royal Caroline Institute in Sweden would note that

Carrel's was "a complicated ritual," continuing, "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."[62]

In 1931, A. M. Woodruff and E.W. Goodpasture reported an advantageous method for growing animal viruses the invention, perfection, and uses of which merit historical investigation. It consisted of growing the viruses on the sheets of uniform cells of the whole developing chicken embryo, that is, inside the fertilized egg. (Waterson and Wilkinson have noted, "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.") Woodruff and Goodpasture's method was comparatively successful and widely used during the 1930s. For example, in Australia, F. Macfarlane Burnet, one of the leading pioneers in animal virology, succeeded in growing the influenza virus in the developing egg.[63]

For all their utility, chicken embryos were not a suitable host for all animal viruses of interest, including the polio virus. In 1936, Albert Sabin and Peter K. Olitsky tried to grow polio virus in chicken embryos and failed. They also failed in attempts 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.[64] 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 the tissue-culturing of infectious viruses.

Enders had become interested in the viral culturing problem during the 1930s while he was on the staff of the Harvard Medical School. In 1947, his research having been interrupted by the war, he resumed exploration of tissue culture in collaboration with Thomas H. Weller, who had assisted him just before the war while he was a Harvard medical student, and Frederick C. Robbins, who had been Weller's medical school roommate. 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 would earn them the 1954 Nobel Prize in physiology or medicine.

They had not had any immediate intention of experimenting with the polio virus. However, they had been aware that evidence had been mounting that the virus might not be a strict neurotrope. Along with others, they 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 that had been sent them some time earlier by the National Foundation. In their Nobel address, they would recall, "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 an account by a member of the National Foundation staff only a short while later, Weller had prepared an excess of tubes of culture medium for the experiment with the chicken pox virus, so Enders suggested that he seed the cultures with some poliovirus from the laboratory freezer.)[65]

The demonstration that polio virus could be grown in non-nerve cell tissue cultures was a stunning part of but not the whole of the Enders' group's achievement. With the mumps virus, their technique involved growing cells suspended in fluids; for the 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 poliomyelitis antibodies. Perhaps 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 necessity of obtaining polio virus via the laborious and time-consuming procedure of intracerebral inoculation of monkeys.[66]

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 micro-organisms" and "to use them under conditions and in numbers which in the past would have been quite unthinkable."[67]

Tissue culture was thus revolutionized by the work of the Enders group. In short order, many new animal viruses were discovered, including, by the mid-1950s, at least eighteen different immunologic types of the human adenoviruses.[68] 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 what role World War II

played in the postwar development of the life sciences. Many medical researchers went off to war. Enders was a consultant to the secretary of war on epidemic diseases and Weller, a member of the Army Medical Corps during the war, was stationed at the Antilles Medical Laboratory, in Puerto Rico, wher 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, of course, 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.[69]

The electron microscope was not a product of the war, but the study of animal viruses, which are too small to be seen under the ordinary light microscope, benefited from the development of this instrument from quantum physics. Invented before the war, the microscope had been used in 1940 to photograph the tobacco mosaic virus and bacteriophage. That year, a young biologist named Thomas F. Anderson was appointed to a National Research Council Fellowship that RCA had funded at $3000 a year for the purpose of exploring the microscope's potential biological applications.[70] 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.

During the war years, electron microscopy appears to have revealed a good deal about phage processes. Perhaps the most important visual evidence they provided was that phage particles multiply inside the cells, rather than at their surfaces; until lysis occurred, the number of particles visible at the surface remained constant. This constancy also meant that very few, if any, of the particles entered 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.[71] 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 miscroscope can only suggest solutions, not confirm them."[72]

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 arrived at by other means.[73] 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.

Concluding Reflections

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.[74] 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 those goals were perceived during the period between the two world wars. Like cardiology, which relied on similar kinds of non-inertial graphical recording instruments, neurophysiology was more than a little unsure about its immediate clinical utility.[75] For if some of the less arcane results of neurophysiological research did seem to have implications for neurological diagnoses, 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. The arena of enthusiasm was shifting toward the new inter-disciplinary 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 oncogensis, as the phenomeon had come to be called, in the fifties when they could not find it in the twenties and thirties is a puzzle for historians to explain.)[76]

Animal virological research was also whirled ahead in the 1950s as a result of the merger of innovations in tissue culture with the quantitative methods that had been 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 Paryalysis). Dulbecco was a postwar Italian immigrant who had come to Caltech, in 1949, at the invitation of Max Delbrück via the laboratory of Salvador Luria, from whom he learned phage-group methods. Dulbecco 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.[77]

The research of Dulbecco's group -- which included Howard Temin and Harry Rubin -- helped mightily to establish animal viral genetics as an enormously 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 that its DNA had been incorporated into the genome of the cell itself, thus accounting for the transformation.[78]

By the 1960s, not only could viral genetics be pursued in cell culture quantitatively 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 -- and writing a remarkable record for historians to assess. In a sense, the field had come full circle, moving from the seemingly dubious work of Peyton Rous into bacteriophage, and turning back to animal viruses via Dulbecco among others. In 1966, the completion of the circle and the vitality of the field were recognized by the shared award to Peyton Rous, age eighty-five, of the Nobel prize in physiology or medicine.[79]

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 mightily in the creation, in 1971, of President Richard M. Nixon's War on Cancer. That war led to neither 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.[80] Unlike the case with classical neurophysiology, the failure to fulfill the clinical promise with cancer has been offset by clinical payoffs of other types -- DNA diagnostics, for example -- and by 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.

We expect that our flexible analytic framework would be helpful in accounting for the post-1960 transmutation of neurophysiology and development of animal virology, just, as we suggested at the outset, it captures important features in the evolution of other fields in the experimental life sciences. We also wish to emphasize the importance of one category of that framework, the role of methods, instruments, materials. It is the subject most neglected by historians of the modern, especially post-1940, life sciences, perhaps because it has come increasingly to involve technological imports from other disciplines.[81] Here the historians seem to have good company among those biologists whose resistance to recognizing the importance of materials and instrumentation (as distinct from methods) has been proportional to the sophistication of the instruments and materials on which they rely. Gerard's tone of regret was echoed in exemplary fashion by Professor S. Gard, of the Royal Caroline Institute, in Sweden, when he presented Enders, Robbins, and Weller for their Nobel prize:

> 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."[82]

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 specialties 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 one or another of the specialties that are always ready to take their place. Second, the case of animal virology declares 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.

References

1. See, for example, Adele E. Clarke, "Embryology and the Rise of American Reproductive Sciences, circa 1910-1940," in Benson, Maienschein, and Rainger 1991, 107-32; Maienschein 1985.

2. See, for example, Hall 1987; Kevles and Hood 1992.

3. Smith 1990 makes clear the value of studying foundations devoted to disease research. For the Rockefeller Institute, see Corner 1964. The Pasteur Institute awaits its historian.

4. Clarke 1987, 332-335.

5. Holmes 1992.

6. See, e.g., Bang 1977.

7. See, e.g, G .H.Bishop, "My Life Among the Axons," in Annual Reviews, Inc., 1965. *Excitement and Fascination of Science*, pp.3-20; Marshall 1983; Marshall 1987; Frank 1978b, 1979.

8. See Allen 1976; Clarke 1987; Clarke and Fujimura 1992; Foster 1980; and Lynch 1988.

9. For cytogenetics, see Hsu 1979.

10. Heilbron and Seidel 1989, pp. 156-57, 34-39, 219.

11. Clarke and Jacyna 1987, p. 1.

12. See, e.g., Billings 1971; Ramon y Cajal 1937.

13. Sherrington 1907; Swazey 1970.

14. See Fox, D. et al 1990. *Nobel Laureates.*

15. See Geison 1979; Warner 1985.

16. Flexner 1910; Brown 1979; Ludmerer 1985.

17. Marshall 1983, p. 613.

18. Flexner 1910; Ludmerer 1985.

19. Flexner 1910, p. 63,

20. Marshall 1987, p. 354.

21. Marshall 1987, pp. 354, 358.

22. Marshall 1983; Marshall 1987, pp. 358-359.

23. Marshall 1987, p. 358.

24. Marshall, 1983, pp. 618-619.

25. Gerard 1958, p. 231.

26. See, e.g., Gerard 1958, passim; and the essays by Bishop and Gerard in Annual Reviews, Inc. *Excitement and Fascination of Science*, 1965, pp. 3-23, 149-160.

27. On Cannon, homeostasis, and equilibrium or functionalist models in American social thought, see Cannon 1929, 1930, 1932; Benison et al. 1987; Cross and Albury 1987; Fleming 1984; Russett 1968.

28. See Geison 1978, pp. 311-321, 353-354 and the sources cited there. Even more historical attention has been devoted to the closely related topic of reproductive physiology and sex research. See, e.g., Hughes, 1977; Borell 1985; Hall 1974, 1987; Clarke 1987.

29. See esp. discussion of "national styles" in physiology in Geison 1978, pp.331-355.

30. Marshall 1987, p. 359.

31. For a skeletal discussion, see Geison 1973.

32. Cf. Geison 1978, passim.

33. As quoted by Gerard 1958, p. 245.

34. Cf. Clarke and Fujimura 1992.

35. See, for introductory discussion, Geison 1973.

36. See Frank 1978b; Marshall 1983, 1987.

37. Marshall 1983, 1987; Frank 1979.

38. Frank 1979, p. 195.

39. Marshall 1987.

40. R.W. Gerard, "The Organization of Science" [1952], in Annual Reviews Inc., *Excitement and Fascination of Science*, pp. 149-160, quote on p. 153.

41. See also Hughes 1977, most of which is concerned with the period before 1900, and Peter Radetsky 1991, a pioneering popular account.

42. Fischer and Lipson 1988, pp. 148-66; Olby 1974, pp. 225-26, 238-40; Judson 1979, p. 70.

43. Waterson and Wilkinson 1978, p. 120.

44. Prominent exceptions include the work of Abir-Am 1982a, 1987 and Kay, 1987, 1991.

45. Waterson and Wilkinson 1978, pp. viii-xii.

46. *Ibid.*, pp. 122, 130, 143.

47. *The President's Review from the Rockefeller Foundation Annual Report, 1956* (New York: The Rockefeller Foundation, 1956), p. 29; Patterson 1987, pp. 171-72.

48. Smith 1990, pp. 82, 161.

49. In 1953, the NIH polio research budget was $72,000; the National Foundation's, $2 million. Smith 1990, p. 249. Boyd 1956, pp. 19-20.

50. Boyd 1956, pp. 23-24.

51. *Ibid.*, pp. 21-22, 31-32; Watson 1968, p. 132. The National Foundation awarded grants for work on the encephalitides virus at Berkeley; on human viral diseases at Harvard, some of which monies were given to Enders; 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, pp. 20-22.

52. Waterson and Wilkinson 1978, p. 159.

53. *Ibid.*, p.160.

54. They had, for example, high-cancer mouse strains showing more than 90 percent incidences of the type of cancer that had been selected, including "strains with high incidences of breast cancer, leukemia, lung tumors, and adrenal-gland tumors. The frequency of all cancers among the low-incidence strains was reduced to less than 0.01 percent, whereas in an unselected population about 5 percent of mice get cancer. These experiments led to the important conclusion that there is no general cancer disposition, but rather that there are different genes that can influence tumor development in various tissues." Klein 1990, pp. 120-21.

55. Klein 1990, pp. 121-22; Waterson and Wilkinson 1978, p. 161.

56. The fellowship had been established by the mother of Seeley Mudd, a recent graduate of the Harvard Medical School, and benefactor of Caltech. Fischer and Lipson 1988, p. 114; Summers 1991, pp. 2-4.

57. Emory L. Ellis, "Bacteriophage: One-Step Growth," in Cairns, Stent, and Watson eds. 1966, pp. 53-54.

58. *Ibid.*, pp. 54-56.

59. *Ibid.* See also Waterson and Wilkinson 1978, p. 103.

60. In 1928, Alexis Carrel wrote in a chapter entitled "Tissue Culture in the Study of Viruses," in the classic text on filterable viruses that Tom Rivers edited: "Through the rudimentry techniques of the early days of tissue culture . . . it was demonstrated that tissues kept *in vitro* can be utilized in the investigation of the properties of viruses. Although fourteen years have elapsed since this work was undertaken, the method of tissue culture has not greatly increased our knowledge of the heterogeneous group of filterable pathogenic principles. . . ." Carrell continued, "This must be partly attributed to the fact that pathologists are far from having

mastered the techniques for the cultivation of tissues. Most of them have used the comparatively crude procedure which was derived immediately from the experiments of Harrison." Waterson and Wilkinson 1978, pp. 72-73.

61. "Physiology or Medicine 1954: Presentation Speech by Professor S. Gard, member of the Staff of professors of the Royal Caroline Institute," *Nobel Lectures . . . Physiology or Medicine, 1942-1962*, p. 445. See also Waterson and Wilkinson 1978, p. 144.

62. Waterson and Wilkinson 1978, pp. 68-73; "Physiology or Medicine 1954: Presentation Speech by Professor S. Gard," p. 444.

63. Waterson and Wilkinson 1978, pp. 76, 138-39.

64. "Physiology or Medicine 1954: Presentation Speech by Professor S. Gard," p. 445. Earlier, Burnet and Jackson, in Australia, had reported growth of poliovirus under similar conditions, but neither they nor anyone else had followed up the breakthrough. Boyd 1956, p. 30.

65. Enders, Robbins, and Weller 1954, p. 451; Boyd 1956, p.30.

66. "John F. Enders," in Wasson, ed. 1987, pp. 300-302; Enders, Robbins, and Weller 1954, p. 457.

67. Smith 1990, pp. 135-37; Boyd 1956, p. 30; Enders, Robbins, and Weller 1954, pp. 458-9.

68. Enders, Robbins, and Weller 1954, p. 465.

69. Waterson and Wilkinson 1978, p. 108.

70. *Ibid.*, pp. 105-6.

71. Thomas F. Anderson, "Electron Microscopy of Phages," in Cairns, Stent, and Watson, eds. 1966, pp. 63-64, 67. See the obituary of Anderson, *New York Times*, Aug. 13, 1991, p. C19.

72. Thomas F. Anderson, "Electron Microscopy of Phages," in Cairns, Stent, and Watson 1966, p. 77.

73. Thomas F. Anderson, "Electron Microscopy of Phages," in Cairns, Stent, and Watson 1966, p. 77; Waterson and Wilkinson 1978, p. 155. In the judgment of T.E. Boyd, of the National Foundation for Infantile Paralysis, the electron microscope "eventually made it possible to see and photograph virus particles over the entire range of known sizes. Although each species studied is uniform in shape and dimensions, these are generally not distinctive enough to permit recognition of virus particles dispersed in a heterogeneous field. Visual study has virtually been limited to fields in which the presence and identity of the viruses concerned has already been ascertained by other means." Boyd 1956, pp. 2-3.

74. Marshall 1987, p. 359.

75. On the development of graphical recording instruments in cardiology and the issue of their clincial utility, see the superb studies by Frank 1988 and Howell 1987. Cf. also Geison 1979.

76. Waterson and Wilkinson 1978, p. 162; Gross 1970, pp. 10-13, 106, 264; W. Ray Bryan, "Peyton Rous," *Science*, 154(Oct. 21, 1966), 364-65; "Peyton Rous," in Wasson, ed. 1987, pp 889-90. Bishop 1982, p. 81; Angier 1988, p. 5.

77. Boyd 1956, p. 31. Enders, Robbins, and Weller noted in their Nobel address: "Dulbecco and Vogt in a series of inegenious experiments have devised methods to obtain *in vitro* isolated plaques of cellular degeneration analogous to those produced by bacteriophage and have presented evidence indicating that each plaque represents the effect of a single infective unit of virus. According to their procedure cell suspensions are prepared by exposing tissues to trypsin. Kidney cells obtained in this manner when planted in flat dishes, yield homogeneous sheets of growth. After inoculation, the cells are covered with a thin layer of agar, thus limiting the spread of the cytopathogenic virus. This technique provides a new method for the more accurate assay of viral activity. Of greater importance is the means it offers of establishing clones of virus in connection with the search for variants possessing altered pathogenic properties." Enders, Robbins, and Weller 1954, p. 461.

78. Rubin 1966, pp. 294-95; Vogt and Dulbecco 1960, pp. 365-70. In 1974, Dulbecco remarked that "one of the most useful and encouraging results in the study of transformation was that it could be obtained in cell cultures." Dulbecco 1975, pt. 1, p. 1.

79. Watson 1979, pt. 1, p. xvii; Gross 1970, pp. 136-39; "Rous, Francis Peyton," *McGraw-Hill Modern Scientists and Engineers* (3 vols.; New York, McGraw-Hill, 1980), vol. 3, 48-9; Huebner and Todaro 1969, pp. 1087-88. The first edition of Gross' *Oncogenic Viruses*, published in 1961, came to about 400 pages; the second edition, of 1970, totaled almost 1,000 pages. 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.

80. Klein 1990, p. 128.

81. Although it deserves emphasizing that this long-standing neglect is now rapidly being rectified. See, e.g., Latour and Woolgar 1987; Borell 1986, 1987a, 1987b; Lenoir 1986; Cambrosio and Keating 1988; Lynch 1988; Greenspan 1990; and esp. Clarke and Fujimura 1992, including their extensive bibliography.

82. "Physiology or Medicine 1954: Presentation Speech by Professor S. Gard," p. 447.

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