Experimental Biology in Transition: Harrison's Embryology, 1895–1910

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"The Experimental Ideal"

Idealism gave way to materialism in biology around 1900, Garland Allen has told us in his widely read textbook on the history of twentieth-century biology.[1] Young biologists rejected the idealism, phylogenetic concerns, and descriptive methods of their predecessors and turned to the physical sciences as a model, according to this view. This led to their endorsement of experimentation. "No biologist could long resist the temptation of such a promising method," William Coleman has proclaimed in his equally well-known textbook on nineteenth-century biology.[2] Especially in the United States, the cause of experimental analysis, as exemplified by Wilhelm Roux's "Entwickelungsmechanik," gained "almost immediate support," Allen has maintained.[3] The result, Allen and Coleman have agreed, was a revolt in biology away from traditional descriptive morphological science to experimentation as the ideal.[4]

This picture of a generation of young rebels casting off the shackles of worn-out speculation and observation and embracing a brave new scientific method is appealing indeed. Unfortunately, the picture depends on boldly overdrawn distinctions, which I think that neither Allen nor Coleman would now support without further clarification.[5] In contrast, I therefore propose, by sketching the portrait of one central figure, to suggest an alternative picture of early twentieth-century biology that demonstrates evolving assumptions about, rather than revolutionary changes in, what proper methodology in biological investigation should be.

Specifically, I find that Ross Harrison's work in experimental embryology illustrates important methodological patterns and changes that exemplify developments in experimental biology generally. Above all,

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Harrison's work reveals that we must remain very clear about exactly what we mean by such terms as experimentation. Experimental science has obviously evolved since Bacon's and Descartes's time and has always meant different things to different people. Equally, experimentation varied for such noted "experimentalists" as Thomas Hunt Morgan or Frank Rattray Lillie, for example, and Harrison's case demonstrates that experimentation could develop in different ways even within one person's research.[6]

To help clarify discussion, I feel that it is essential to avoid adopting any single experimental standard but necessary to attempt to deal with the historical complexities. I suggest that there actually exists a continuum of experimentalisms, ranging from utilizing simple manipulative techniques to endorsing fully developed experimental hypothesis testing within a research program.[7] Harrison's evolving style, which exemplifies that of the "new experimenters," reveals such experimental options. In his earliest work, he did not seek causal explanations of embryonic development, as Roux did. Rather he wanted to delineate the developmental processes. It is thus important to recognize that there can be different types of experimentation and different problems or goals for which those different experimentations may be appropriate.

All levels of biological experimentation involve exercising control over organisms, but the nature and purpose of that control varies significantly. One can use a range of manipulative techniques beginning with simple disruption of normal conditions to elaborate construction of complex abnormal situations. The researcher can use the techniques to ask simply, "What will the organism do under such-and-such conditions?" Or the techniques can be applied to test hypotheses and thereby to address specific well-formulated questions with an experimental approach. If the hypothesis in question is embedded within a coherent research program, the experimental approach reaches its most complex form. In discussing whether early twentieth-century biology became experimental, we must be particularly alert to what we mean by that term.

The evolution of Harrison's work, as revealed through his published writings, demonstrates the way in which he came to endorse consciously an experimental approach within a research program and why he felt it important to do so.[8] Beginning with relatively simple experimental manipulations to obtain new data in his early work, he soon decided that his results were not satisfactory; he therefore articulated an experimental and theoretical context for his manipulations. His emerging endorsement of an experimental approach exemplifies what Coleman, Allen, and others have considered the heart of early twentieth-century biology. The facts in this one case will therefore reveal an alternative to Allen's and Coleman's understandings of the reasons for the endorsement of experimentation.

Ross Harrison's Medical Orientation

When Harrison began his early work, he confidently reported the results of his research as conclusive contributions to understanding development. In 1895, for example, his first major paper, which was his doctoral thesis, appeared in the *Archiv für Mikroscopische Anatomie*. Entitled "Die Entwicklung der unpaaren u. paarigen Flossen der Teleostier," it immediately followed a paper by Harrison's German mentor Moritz Nussbaum.[9] Harrison's concerns and his style paralleled Nussbaum's rather closely, which should not be surprising since the research was carried out at Nussbaum's suggestion and in his laboratory at Bonn. Harrison clearly had become a successful user of experimental manipulations. But he was operating within the context of traditional German medical school studies, with the goals of answering questions about anatomy and embryology in order to have a full description of each—for ultimately practical reasons. There is absolutely no evidence that he had given "almost immediate" support to Roux's experimental program of "Entwickelungsmechanik." Harrison did not seek to establish causal connections in development, as Roux did, nor did he endorse the "experimental ideal" of hypothesis testing in a more modern sense.

Harrison's background at the Johns Hopkins University, which historians of American science have liked to emphasize, played a less direct role in shaping the problems or methodology in his early dissertation work than it did later.[10] His graduate study and his undergraduate work at the same medically-oriented new American university did convince Harrison to go to Germany to study, but this was not unusual since most of his successful contemporaries also went.[11] While not denying that William Keith Brooks's and H. Newell Martin's biological influence on Harrison may have been significant in the long run, I think it did not shape his work as much as did his decision to study medicine in Germany. In Germany, Harrison settled in an anatomical institute in Bonn and completed his degree in medicine, which others of his contemporaries who became leading figures in biology did not. Why? And what influence did Harrison's decision to work on anatomical and embryological problems in a German medical context have on his later commitments?

In answering this question of Why?, we encounter the familiar and difficult problem of establishing influence. In the face of negligible clues from archival sources or published material, what can we conclude about influence? Did Harrison choose a medical context purposefully or by chance? Apparently, there was a certain measure of the latter, according to the only apparent extant source.[12] Chance placed him with Nussbaum at least, but interest in the problems of fin development in teleosts made him visit Bonn and Nussbaum in the first place to seek advice.

Perhaps Harrison felt comfortable with the fortuitous choice of a medical setting at Bonn because of his own prior medical orientation; according to reports, he had almost chosen medicine for his original course of study in America.[13] Neither Bonn nor Nussbaum was obscure scientifically, so Harrison's choice was quite reasonable. Bonn had become a famous medical center when Johannes Müller held the chairs of anatomy and physiology there, followed briefly by Hermann von Helmholtz. The subsequent tenure of Max Schultze as professor of anatomy and Ernst Pflüger as professor of physiology continued the tradition of excellence in medicine. Nussbaum studied under Schultze and Pflüger, then stayed in Bonn, progressing slowly through the ranks in physiology until 1907, when he was given a personal chair as Ordentlicher Professor in Biology and Histology. Thus Harrison's choice of Bonn and Nussbaum may not have been fully premeditated, but it was hardly an unlikely choice—given Harrison's medical orientation.[14] His choice of teleost fin development is more difficult to identify, though it is unlikely that his interest grew from his summer in 1890 at Woods Hole, as so many of his contemporaries' interests did. There he had worked on early oyster development—not a likely stimulus for fin investigation![15]

Whatever the reasons, it is clear that Harrison chose to pursue a medical degree self-consciously. He purposely did not spend much time at the Naples Zoological Station while in Europe, as his friend Morgan had done, and he similarly did not seek a mentor with evolutionary interests, as others of his colleagues from Johns Hopkins had.[16]

The second question remains. What difference did his choice of a basically medical context make to his later work? How did Harrison's career differ because he sought a medical degree rather than continuation of research for a doctorate in zoology while in Germany? Here again, the difficult problem of establishing influence arises. But this is a different type of influence, an assessment of which must begin by considering whether medicine and biology were substantially enough differentiated that it is legitimate to study the influence of one on the other.

There exists no clear dichotomy of medicine as absolutely distinct from biology. In fact, the two are now—and were then—clearly related and overlapping. Yet, despite the difficuties in identifying some work as either biological or medical, the fact remains that by 1890 many people *were* eager to distinguish the two fields.[17] As Coleman has stated,

> Sometime during the middle third of the eighteenth century those interested in the phenomena of life began to isolate and examine special problems for consideration and, knowingly or otherwise, to devise or articulate special techniques and viewpoints for prosecuting their examination. This process raced on undiminished throughout the nineteenth century. Its ultimate effect was to create a body of men who were recognizably biologists and whose subject, embracing a multitude of specialties, was biology. The creation of biology as a recognized

discipline thus followed with only brief delay upon the determination of the legitimate subject matter of the science.[18]

Also, the fact that the Johns Hopkins University had a medical school, with a department of anatomy, and a separate graduate school with a completely autonomous department of zoology, attests that there existed at least perceived differences between zoology (or biology) and medicine.

There are obvious grounds for distinction stemming from the fact that medicine deals with disease, focuses on diagnoses, and seeks therapy by way of clinical practice. As a result, the two areas were primarily distinguished by subject matter, as Coleman has suggested, and also by the type of result sought rather than by methodologies.[19] To help clarify any real distinctions, consider a range of problems from the very practical and precisely defined, i.e., concern with correcting specific structural or functional defects in humans, to the very theoretical and general, i.e., seeking careful descriptions and explanations for phenomena of life in general. In 1890, traditional medicine was identified with the former end of the range and the "new experimental biology" with the latter. Most biological, medical, and biomedical work belonged between the extremes, of course, but researchers did generally identify with one extreme or the other and therefore perceived themselves as either biologists or medical workers.

In 1890 there was an important constraint on biology, which restricted the type of explanations considered desirable or acceptable. From Darwin and Haeckel to Roux and the other advocates of experimentation and causal explanation, all stressed evolution. Biological results must not only conform to evolution theory, but it was agreed that evolution theory could help lead to desired explanations.[20] Thus even though Morgan won a Nobel Prize in Physiology and Medicine and even though much of this work lay in a middle ground between medicine and biology, such men as Edmund Beecher Wilson, Edwin Grant Conklin, Morgan, Lillie, Charles Manning Child, William Morton Wheeler, George Howard Parker, and Herbert Spencer Jennings all identified with evolution in some way and considered themselves biologists.

In significant contrast, Harrison both rejected evolutionary constraints on his work and sought a medical degree. He did not deny that life had evolved, but he felt the whole study of evolution too speculative to be studied scientifically.[21] Evolution should not be either a regulative or directive constraint on biological research, according to Harrison. This difference from his contemporaries who also became leaders in biology was basic to Harrison's ability to forge an experimental embryological program, a program that by 1910 he considered *biological* despite its absence of evolutionary constraints.[22] And this biological program represented a different biology than that of the 1890s.

His fellow students at Johns Hopkins and elsewhere had, like

Harrison, begun their research with describing embryological development, but all moved into other specialty areas of zoology. Because of Harrison's deep-rooted concern with embryology as at least partly a *medical* problem in the traditional anatomical sense, emphasizing careful description of each stage of development against a background hope for practical medical applications, Harrison's emerging *biological* concern with seeking explanations of developmental processes differed from his friends' work. Harrison came to be considered both a medical and a biological researcher by others, though by 1910 he considered himself more a zoologist and his program of experimental embryology an essentially biological program.[23] His description of zoology in 1914, at the dedication of the new Osborn Memorial Laboratories for Biology, at Yale, reveals the differences but also the close alliance he saw between biology and medicine:

> Biology embraces that whole group of sciences which deal with the living world. They had their origin in the practical needs of medicine and in the study of natural history, which was the expression of the desire of man to know something about his fellow beings, to name them and to classify them. This group of sciences is complex, and, being a growth in adaptation to various practical exigencies, its subdivisions are not altogether logical. In the broadest sense, zoölogy, which has to do with animal life, is half of biology, botany the other half. According as animals are studied with respect to their form and structure, their activities, or their condition in disease, we distinguish morphology or anatomy, physiology, and pathology; but these subjects, which constitute the immediate foundation of modern medicine, are studied so intensively with reference to man and his more closely related brethren that special laboratories are provided for their accommodation, and those who devote themselves to them would no doubt resent their being classed as mere subdivisions of zoölogy. There is, however, an immense field including the structure, functions, life histories and relationships of animals that is scarcely touched upon by the above-named subjects. This is zoölogy in the more restricted sense, and, together with the study of plants, is that which is usually known in the college curriculum as biology. The problems of zoölogy, however, are to a considerable extent similar to and even identical with the problems of anatomy and physiology. In other words, zoölogy speaks the language of anatomy and physiology, but besides this it has to have command of the dialects of those less organized regions where such subjects as animal behavior, geographical distributions, ecology or the adaptation of organisms to their environment, evolution, and heredity are cultivated.[24]

Zoology, in other words, was simply at one end of a continuum with medicine at the other. According to his biographer John S. Nicholas, Harrison "sometimes whimsically referred to medicine as applied biology."[25] The type of work he valued in embryology originally grew out of what was considered a medical environment; then it came to be considered biological. But the work actually lay between the traditional disciplines of biology and medicine, illustrating the evolving nature of disciplines as well as of experimental methodologies. Harrison's biology by 1910 was a new biology, different from that of the 1890s.

Harrison's career and his resulting embryological program depended in an essential way on his close identification of biology and medicine and on his choice to ignore evolution as an explanatory or directive factor in research, a commitment which likely influenced him to study nerve and muscle development and to go to an anatomical institute in Germany. His commitment was reinforced there by his participation in a medical, nonevolutionary environment as it would not have been had he studied instead at the Naples Zoological Station. The remainder of this paper illustrates Harrison's move from a more traditional descriptive approach that he considered medical to a more biological approach at Yale. It explains how Harrison's changing assumptions about appropriate experimental methodology and the related shift in the problems that he sought to address were essential to that move.

Harrison's Experimentation

Concerned at Bonn with tracing the role of cells rather than germ layers in development, Harrison described anatomical and successive embryonic stages with impressive competence.[26] Yet he felt a weakness because he could not give details of the development of nerves, a subject he found particularly interesting. Unfortunately, he wrote, "about the development of nerves in the unpaired fins, I could indicate nothing of significance. With the help of the usual embryological methods the particulars of development are not to be discovered."[27] These inadequate methods were based on experimental manipulations, designed to cut the organism into analyzable cell groups and to fix the action of normal development, and on description of the results of that intervention. They could not provide more data than observation of normal development allowed.

Although Harrison and Nussbaum wanted to understand the dynamic processes of development, their experimental methods did not involve the controlled hypothesis testing characteristic of more sophisticated experimentation and were not, like Roux's work, oriented toward achieving causal analysis of the processes. As if description of sequential stages of development would reveal the significant connections, Harrison, like the contemporary group of "cell counters" doing cell-lineage studies in Woods Hole in the 1890s, depended on observation and on description of embryonic stages to address a question of description: What happens during ontogeny? This work was experimental only in the most basic sense of using simple manipulations to produce and fix disrupted and hence necessarily abnormal specimens and thereby to gain control over observations. The method differed much more from the experimental approach Harrison endorsed soon afterwards than from the traditional manipulations used throughout the nineteenth century by German medical researchers in anatomy as well as in physiology. His use of particular cutting, fixing, and staining techniques represented typical descriptive medical research. Again we see that Harrison fit very well within his environment at the anatomical institute at Bonn. And his work did yield productive results for advancing anatomical description of stages of organic development. But Harrison had not lent support, either immediate or otherwise, to Roux's program of "Entwickelungsmechanik." There is, in fact, no evidence that he had at that time any interest in Roux's suggestions.[28]

Harrison's introduction to Gustav Born's special techniques for transplanting parts of embryos onto other embryos provided the basis for more analytical ways to address questions about nerve development, problems the old methods could not touch.[29] In a paper of 1898, in which he used Born's techniques, Harrison wrote that "in the method of grafting we have a means of experimentation for which no substitute is offered. Born's discovery that certain amphibian embryos lend themselves with readiness to such operations is of especial importance in that it renders the method applicable to the study of developmental problems."[30] Born's method allowed the researcher to graft togther parts from two differently pigmented species. The hybrid continued to develop as one organism with two differently colored areas, which could thereafter easily be followed throughout development. "By varying the region in which the parts are stuck together," Harrison enthused, "it thus becomes possible to trace out the mode of growth of individual structures or organs."[31]

Even though Harrison's presentation remained thoroughly formal, the reader can sense a certain excitement in his realization of the importance of Born's technique. Yet in 1898 Harrison used the remakable technique simply to describe in more detail than had previously been possible how cells act in development and regeneration (in this case the cells of frog tails). He saw the promise of the method as being the production of additional data for an anatomical understanding of organisms' development, not a tool for hypothesis testing. His grafting experiments provided data that could test the accepted view of, for example, "the individual constituents of the tail."[32] But such tests were really descriptive tests, answering "Is it true that what they say is really what happens?" Careful observation using Born's techniques, therefore, provided new data, not new explanations. The reader gains no sense from this paper of why Harrison—or anyone else—would want to know these facts except that they contributed small pieces to a descriptive picture of embryonic development. Nowhere did Harrison reveal a broader perspective or larger question that might have motivated his research. The problems for which he used his newfound experimental techniques still concerned careful anatomical and embryological description.

In retrospect, some historians have been tempted to regard this as less interesting than fuller use of an experimental approach and to consider the rise of experimental hypothesis testing as more important for turn-of-the-century biology. Yet this careful use of experimental techniques to develop descriptive data also represents an essential element of the "new experimental biology." Harrison's medical work, like his contemporaries' cell-lineage studies, reveals a fundamental commitment to asking narrowly defined questions and to obtaining definitive results. At the time, his seemingly more traditional medical approach, still within a medical context that sought to utilize research results, was definitely legitimate and important.

Furthermore, Harrison's use of Born's grafting techniques, although initially unexciting to retrospective judgment, did move him in a different direction than had his earlier concern with describing normal developmental stages. He began to use abnormal or contrived conditions to learn more about the normal progression of cellular changes and changes in groups of cells, thus emphasizing both cells and dynamic change. Born's method provided a practicable means for analyzing development into distinguishable smaller pieces so that one could obtain apparently definitive results. It was a pivotal innovative experimental technique for manipulating development and thus going beyond normal conditions.

After his introduction to Born's techniques, Harrison continued along his descriptive morphological way, refining his observations and his experimental manipulations to address various embryological questions. Then, for the first time, in a paper of 1903 on lateral line sense organs in amphibians, he compared his experimental results with "control" or normal development, to the extent that he knew the latter, and he closed with a brief but noteworthy "Schluss'" section which discussed current general theories of development.[33] He referred to the views of Hans Driesch and Roux on the then much-debated issue of self-differentiation and concluded that the "Anlage" of the lateral line are already represented in the germ and develop without additional impulses being necessary. But, he concluded, it is the mutual effect of embryonic parts, at an early developmental stage, that determines that certain cells will become lateral line cells. Though no experimental data had illuminated the processes to date, Harrison added, he hoped that Hans Spemann's efforts would show the nature of the determining factors and the moment that differentiation becomes fixed.[34]

Awareness of Spemann's early studies, which he cited, and of the issues of self-differentiation and of concern with dependent differentiation within the totality of the organism refocused Harrison's research—or at least his published presentation of that research.[35] He began to report his results in terms of general theories of development, thus moving beyond his previous purely descriptive account that simply states "here it is." Instead he laid out his results and went on to conclude that they supported self-differentiation—or almost.

No doubt reinforcing Harrison's apparently expanded awareness of general issues was his attendance at an important scientific meeting held in April 1904. The Anatomische Gesellschaft convened in Jena to discuss a variety of current topics, of which nerve fiber development was one of the most central.[36] Harrison participated in a session with Albert von Kölliker and Oscar Schultze, who argued respectively that sheath or Schwann cells do and do not play a crucial generative role in fiber development.[37] Harrison, drawing on his own experiments in which he had removed the source of the Schwann cells, argued that they could not play a primary role, since nerve fibers developed even without their presence; they must instead play a secondary role, if any role at all.[38]

This meeting seems to have initiated Harrison into high-powered verbal exchange regarding his research subject. One is tempted to suggest that his realization that people are obstinate and that experimental "proof" is more difficult to provide than he had thought led him to seek a more definitive approach in his research. However this may be, his attendance undoubtedly did shape the way he oriented his studies after 1904. And, perhaps more significantly, the way he used experimentation and the way he reported his results began to change subtly as he saw the inadequacy of previous attempts. From 1904 to 1910 Harrison sought to discover what he had to do to make his work convincing—for one of his assumptions was that one's work should be convincing (meaning conclusive, compelling others to accept it as definitive).[39]

During this period Harrison concentrated on establishing beyond doubt the way in which nerves develop and the role of the nervous system in development. At first, he did not question his assumptions; thus he did not ask why one would want to know about the development of nerves or why one would focus on cells in nerve development. This made sense within the context of his essentially descriptive interest in body processes, getting results, and answering questions about what happens to make up the final anatomical product. For these ends, Harrison urged, success depended on proper use of experimentation. "It is clear," he wrote, ". . . that the facts are insufficient to determine even the comparatively simple relations between the nervous system and the developing musculature." Thus the only effective approach "is by direct experimentation, but in devising experiments for this purpose it is necessary to formulate clearly just what is to be determined, for it is obvious . . . that the nervous system may possibly exert its influence in a variety of ways."[40]

Therefore Harrison reported experiments that were executed specifically "in order to determine the effect of [one factor or another] on normal development." He tested, for example, the effect of suspension of muscular activity by treating the embryo with acetone chloroform. This allowed him to determine how the embryo developed without normal functional stimuli. Clearly, then, the experiment provided a way of testing the role of functional development by isolating that factor and eliminating it. The experimental results provided data not obtainable from normally developing organisms alone. Thus the experimentally induced pathological specimens yielded new data, data that Harrison felt were useful, although others disagreed with the validity of the data since they were "abnormally derived."[41]

At least this experimental method, designed to test a particular question, was potentially conclusive. Two years later Harriosn wrote:

> Prior to the year 1904 all attempts to solve these problems were based on observations made upon successive stages of normal embryos. When one compares the careful analyses of their observations, as given by various authors, one cannot but be convinced of the futility of trying by this method to satisfy everyone that any particular view is correct. The only hope of settling these problems definitely lies, therefore, in experimentation.[42]

General recognition of the value of an experimental approach—whatever that meant to the principals involved—was acknowledged by the establishment of the *Journal of Experimental Zoology* in 1904, with Harrison as managing editor.

In his experiments reported in 1904, Harrison showed that the muscles developed even after removing the spinal cord and hence the nerve tissue. Therefore "this experimental demonstration of the independence of the developing muscular tissue may be regarded as crucial evidence against the general correctness of the view . . . that the first development of the muscles takes place under the influence of the nervous system."[43] The results reinforced Harrison's belief that Roux's view of development as involving a separate organ-forming stage and functional development stage must be misleading; he saw the two stages as really overlapping and complexly interrelated.[44]

Perhaps because he had seen the different ways the same descriptive evidence could be used within the traditional medical context, as it had been at the 1904 meeting in Jena, in 1904 Harrison recognized the value of using experimental techniques to achieve what he considered to be "crucial evidence" for addressing a clearly formulated question. Yet he also recognized that he had so far only contributed to "one phase" of understanding the general problem of neural influence in development. At last—from the retrospective point of view—he understood that he had a general problem and that to achieve useful results it was productive to attack smaller phases one at a time. The product was the emergence of a specialized embryological research effort.

This is not meant to suggest that Harrison's effort was unique, for Spemann, in Germany, certainly provided a notable parallel, but is meant to emphasize that Harrison's specialization in experimental embryology was different from contemporary biologists' specializations in cell-lineage studies, cytology, and genetics.

As he pursued his studies, Harrison began to realize that his experimentation could succeed best in producing results when very narrowly defined questions were posed. Still stimulated by discussions of details at the Jena meeting in 1904, Harrison felt the additional stimulus of obtaining definitive results to address increasingly well-defined and specific questions. From 1906 to 1910 Harrison no longer asked general anatomical questions about structures or development of whole nerves or nervous systems. Instead he asked more specific questions about the nature and processes of nerve parts. In particular: What is the constitution of the nerve fiber and how does it grow from its point of origin to the periphery of the organism?

Beginning with this problem, Harrison by 1907 had formulated the basic elements of a research program. He knew what questions he wished to answer and what the current theoretical answers were. He knew that an experimental approach was essential to achieve productive results and that he should concentrate on cells as the fundamental developmental units for experimental analysis. But he also felt that he should keep in mind the fact that the organism is a whole and that cell development also responds to changes in the cellular environment of the neighboring cells and of the whole organism.

Only with this preliminary articulation of his program did Harrison realize the productive power of an experimental approach. But only after a few false steps did he discover that merely presenting presumably definitive results did not immediately convince others that they were in fact definitive. At first he set out to prove specific points, an effort that failed to persuade opponents and that must have helped to shape his later ideas about effective methodologies.

One outstanding example of this failure occurred in 1907, when Harrison produced a very direct short paper.[45] Originally read before the Society for Experimental Biology and Medicine, this paper purported to "show beyond question that the nerve fiber develops by the outflowing of protoplasm from the central cells."[46] Harrison had used experimental techniques to transplant into an artificial culture medium a piece of embryonic tissue that normally gives rise to nerves; this constituted the first successful true tissue culture. But the technique, albeit ground-breaking, was not in itself what interested Harrison.[47] Rather, he sought to use this experimental transplantation technique to show how nerve material behaves outside the influence of its normal environment. If nerve fibers formed as usual, then he had demonstrated that they *could* develop without external influences and that hypotheses requiring such external influences (external to the nerve cell and fiber, that is, though they could still be inside the organism as a whole) were not defensible. This rather simple demonstration, Harrison held, provided a supposedly definitive experimental test of the various hypotheses about nerve fiber development: Do nerve fibers form by coagulation of nondifferentiated material, by growth along preestablished bridges, or by protoplasmic outgrowth?[48] Because the alternatives were disallowed, only one possible theory remained, the outgrowth, or neuron, theory. Furthermore, the experimental methods opened the way for addressing other carefully defined questions relating to nerve development, Harrison wrote:

> The possibility becomes apparent of applying the above method to the study of the influences which act upon a growing nerve. While at present it seems certain that the mere outgrowth of the fibers is largely independent of external stimuli, it is, of course, probable that in the body of the embryo there are many influences which guide the moving end and bring about the contact with the proper end structure. The method here employed may be of value in analyzing these factors.[49]

But one absolutely essential element was missing from Harrison's experimental approach, an approach that he hoped to make a definitive one: the use of controls and careful comparison of the experimental with the control specimens. This left him open to charges that his experimental results did not reveal anything about normal conditions. And those charges were indeed presented.[50] Thus others, with different points of view, rejected his conclusions. Direct demonstration and proof by disproof of alternatives did not work because opponents did not admit the results as disproofs.

By 1908, when he presented his summary lecture to the Harvey Society in New York, Harrsion had become an advocate of the experimental approach, with hypothesis testing and experimental techniques, but still without a full sense of the way to use his larger program to make this particular points compelling. Although by then he recognized that experimental results did not always succeed in convincing the opposition, he seems to have felt that what he needed to achieve compelling results was to define his experimental questions more carefully by using isolation experiments and to accumulate more evidence. He asserted that

> although my own work upon the normal development of the salmon and frog has led me to a decided opinion in favor of the cell-outgrowth theory, the attitude of many later investigators showed that we should never be able to obtain evidence from the study of normal development, that would convince everyone alike of the truth of either of the views just stated. A decisive answer to the question, it

seemed to me, could be obtained only by a more exact method of study, i.e., by the elimination, in turn, of each of the two conflicting elements.[51]

Thus he reported the results of two sets of experiments that had eliminated respectively the source of the Schwann cells (after which he found that nerve fibers developed anyway) and the source of the ganglion cells (after which fibers did not develop). This led him to conclude that only ganglion and not Schwann cells are essential for nerve fiber development. But, he continued, "unfortunately for the purpose of devising a clear-cut and crucial experiment, the antithesis between the two views [about nerve fiber development] is not complete. . . . The first experiments of my own . . . were not crucial." Going on to report the results of his tissue culture experiments, he finally summarized that "we have in the foregoing a positive proof of the hypothesis first put forward by Ramon y Cajal," that nerve fibers develop by protoplasmic outgrowth.[52]

Yet at the end, his tone became more cautious with respect to his ability to "prove" his results; instead he discussed placing the neuron theory "upon the firmest possible basis,—that of direct observation." Although he still thought his work had delivered the needed proof, he recognized that others might not think so and that even a seemingly "crucial experimental test" of a hypothesis would perhaps not be definitive. Thus he chose his words carefully, calling the "attractive" alternative "untenable" and concluding, "The embryological basis of the neurone concept thus becomes more firmly established than ever."[53] Firmly established it may have been, but not "proven."

Several factors help to explain Harrison's increasing appreciation of what it takes to convince others who hold different assumptions about appropriate methodologies, problems, or results. First, on the practical level, the experimental test of hypotheses had not worked. Opposition to the neuron theory continued. Given Harrison's commitment to making his work definitive, he had to seek new methods of making his results accepted. Second, Harrison had moved from The Johns Hopkins University Anatomy Department to Yale University, as Bronson Professor of Comparative Anatomy, a joint position in the Sheffield Scientific School, Yale College, and the Graduate School. There he had assumed the position of a biologist rather than a medical school anatomist. This, I suspect, was critical to his changing attitudes. For although he still addressed medical audiences, he also had to communicate with a different general scientific and university audience, which saw the traditional medical problems from a different perspective. This audience regarded the old anatomical problems of delineating how the adult nerves get the way they are from the perspective of such biological problems as establishing the dynamics of how a single egg cell becomes a complex organism, the current rage in biology. This new audience would have been most interested in the general aspects of Harrison's work: in his use of tissue culture, in his ability to isolate parts of an embryo experimentally, in his testing of hypotheses and presenting answers to questions about what happens in development. After his move to Yale, Harrison became more directly concerned with biological processes as well as patterns of development and the anatomical end product. Perhaps most significant, the importance of articulating and making effective a research program had become more urgent to Harrison as the highly acclaimed first University Professor at the traditionally oriented Yale University, since he wished to attract students and to create a research institute of the German style.[54]

Of course, a change of attitude in itself cannot effect results. The fact that his conclusions were still not acceptable to everyone was manifested by the continued publication of opposing views. Therefore, in 1910, Harrison launched a full attack on the opposing nerve development theories that required more than protoplasmic outgrowth from ganglion cells. Specifically, he countered Hans Held's protoplasmic bridge theory. As a result, in 1910 Harrison produced two papers of quite different natures. The first, published in Roux's *Archiv*, provided his final statement within the context and with the style of the descriptive anatomical/embryological debate about nerve development.[55] This paper paralleled earlier experiments to show that nerve fibers grow out into an artificial medium, namely clotted lymph, and that the ganglion cell alone is crucial for nerve fiber growth and development. Furthermore, he cited his results, discussed earlier, that functional activity cannot play a necessary role in nerve development because experimentally inactivated nerves do develop in any case.[56]

The second paper, often cited as Harrison's "crucial" paper, appeared in the American *Journal of Experimental Zoology*, which Harrison edited.[57] This paper drew upon many of the same research results that he had discussed before, but it presented the case for the neuron theory within the context of a *biological* research program. Harrison now outlined his broader research program to uncover experimentally the details and mechanics of embryonic development. He argued within the context of current biological theories about mechanisms and causal features in development, theories influenced especially by Gustav Born, Wilhelm His, Roux, and their contemporaries arguing for experimental embryology, the physiology of development, or "Entwickelungsmechanik."[58] With this paper emerged a fully articulated presentation of the research program that Harrison had been developing. This program soon formed the fruitful basis of an identifiably biological research school centered around Harrison in Yale Unversity's new Osborn Zoological Laboratory.[59]

This second paper of 1910 is an unquestionable masterpiece, one that appears to have silenced even the most stubborn remaining opposition to the neuron theory.[60] By amassing all available evidence from experimental tests, claims by opponents, and counterdemonstrations, Harrison certainly weakened the case for the opposition. Most important, however, he abandoned the claim for a crucial, decisive test between the two major theories—the protoplasmic bridge and the neuron theories. In a sense he abandoned or moved beyond a naive sense of definitive hypothesis testing. Rather, he argued that the two theories were not so obviously opposed as they might seem but were in many ways complementary.[61]

He thus defused opposition and went on to argue for his own research program. He had showed that cellular protoplasmic outgrowth could produce nerve fibers, which he demonstrated were just like normal fibers in the controls; thus he used his controls effectively. "In order to discover the factors which influence the formation of the nerve paths," Harrison wrote, "we must, therefore, in the first instance take into consideration this property of protoplasmic movement. This is of the utmost importance, and any theory of nerve development which fails to do this is sure to be misleading."[62] Further, he claimed that the protoplasmic development into nerve fibers falls "within Roux's definition of self-differentiation, by which is meant, not that the process is entirely independent of external conditions, but simply, as Roux . . . in first defining the concept pointed out, that the changes in the system, or at least the specific nature of the change, are determined by the energy of the system itself."[63]

What these experiments and their interpretation confirmed was the role of protoplasm and cells in nerve growth.[64] Harrison acknowledged that he did not know how the nerve makes its connection with the periphery, but he did indicate how one might explore those connections in future work:

> In studying the secondary factors which influence the laying down of the specific nerve paths of any organism, we are concerned, therefore, primarily with the laws which govern the direction and intensity of protoplasmic movement, and it is the analysis of these phenomena to which students of the ontogenetic and regenerative development of the nervous system must now direct their attention. The present discussion will not have been in vain if it makes clear that the protoplasmic movement concept is no less capable of rational analysis than is development in general.[65]

This was an extremely fertile paper, exciting in it suggestions for future work and in the example it provided in attitude and approach for carrying out that future work. As I have demonstrated elsewhere, Harrison was perceived as a leader in American experimental biology partly because of this work.[66] He had succeeded in making his work convincing—even if not logically definitive.

Conclusion

I have argued that Harrison's experimental methodology evolved and that it did so in response to both internal and external factors. Inspired by the commitment to making his work conclusive, Harrison's early use of the most basic experimental manipulations gave way to rigorous hypothesis testing using those techniques and ultimately to the formulation of a research program based on an experimental approach. Commitment to experimental techniques, hypothesis testing, and specialization of research program made it possible to achieve results that the emerging larger embryological community could accept.

Acceptance of an experimental ideal—as distinguished from "naturalist" or "observational" methodologies—may well have occurred widely in biology shortly after 1900, as Coleman and Allen have suggested. Harrison's case shows, however, that he at least did not endorse a fully experimental approach in conscious opposition to alternative techniques or approaches. Neither did he adopt experimental techniques or an experimental approach because they were obviously promising and hence a priori tempting. Further, there is absolutely no evidence that he endorsed experimentation at any level because of seeking to emulate the physical sciences or because he rejected the old morphological and descriptive approaches of his predecessors, as Allen has suggested Harrison's generation of biologists did.[67]

What, then, is an alternative explanation for Harrison's adoption of experimentation, and what does this one case study tell us about the emergence of American experimental biology generally? The real problem is in posing the question in this form: it is misdirected, as is the popular question about why early twentieth-century biology became experimental. It makes no sense to ask *why* Harrison, or his contemporaries, adopted experimentation before asking *whether* he adopted experimentation. Asking "Why experimentation?" already assumes that there is a distinguishable differentiation of experimentation from something else, some nonexperimentation. But Harrison's case shows that what we now call experimental biology, or the experimental ideal, or an experimental approach, or whatever, actually emerged slowly. Although Harrison called his work of 1903 and thereafter "experimental," we would have to mean something different by that word to ask why he accepted experimentation at each stage. Experimental science evolved, therefore, and indeed continues to evolve. The type of experimentation Harrison did in 1910 differed from his experimental manipulations of 1903 and after just as the type of experimentation done today in biology laboratories differs from that done at the turn of the century.

Certainly, it is interesting to explore how experimentation changed or to observe that the evolving understanding of what an experimental approach could do seemed to be accelerated shortly after 1900. But that study is interesting because it is symptomatic of a general complex of changes—in scientific methodology and subject matter, in the arts and philosophy, in politics, and generally.

Surely the emergence of special studies such as embryology as separate from medical studies and the emergence and acceptance of various successful specialized *biological* research programs by 1910 must be as fundamental as the incorporation of experimental methodologies by these research programs when experimentation helped them to achieve results. Those biological programs sought to understand both causal and descriptive aspects of life in their own right. The concern with problems considered to be biological and the institutional acceptance of that commitment in the United States—in universities, journals, and research laboratories—involved much more than a wholesale and "almost immediate" endorsement of an isolable experimental ideal in biology.

Around 1900, in fact, there was no such fully developed ideal but only a complex of changing commitments. Even those who thought they were endorsing Roux's experimental program of "Entwickelungsmechanik" did not immediately adopt what they came to endorse as an experimental approach and what Coleman and Allen have termed the experimental ideal. Some of these investigators began with cell-lineage studies which at first simply employed basic experimental manipulations to give the observer control over his specimens. With such noted "experimental biologists" as Wilson, Lillie, and Conklin, for example, we see an evolution, similar to Harrison's, in the style of experimentation thought to be desirable. Morgan's work also demonstrates a parallel evolution from use of experimental techniques in his early regeneration studies to later hypothesis testing and an experimental approach.[68]

Thus, the experimental ideal did not exist as an ideal until investigators realized how experimentation could be used within specialized biological research programs to achieve results. That a number of Americans did produce research programs with experimental methodologies demonstrates their concern with achieving significant results with regard to narrowly defined questions—for which experimentation works well—and the existence of institutional and social support systems for such programs. To produce a recognizable portrait of the emergence and acceptance of American experimental biology that conforms to and seeks to explain the historical data, therefore, it will be useful to draw accurate descriptive pictures and rigorously illustrated analyses of shifting individual and then group assumptions.

NOTES

1. Garland Allen, *Life Science in the Twentieth Century* (New York: John Wiley & Sons, 1975), esp. pp. xix–xxiii.

2. William Coleman, *Biology in the Nineteenth Century* (New York: John Wiley & Sons, 1971).

3. Allen, *Life Science*, p. 34.

4. Allen, *Life Science*, chaps. 2 and 3: "Revolt from Morphology," I and II, esp. pp. 21–72; Coleman, *Biology*, p. 162.

5. This claim is supported by personal conversations with both men.

6. For discussion of ideas of experimentation see: Jane Maienschein, "Problems of Individual Development: Experimental Embryological Morphology," paper delivered at meeting of the History of Science Society, New York, December 1979, and "Crucial Experiments" and "Development" in *Dictionary of the History of Science* (1981). Also Edward Manier, "The Experimental Method in Biology," *Synthese* 20 (1969): 185–205.

7. "Research program" is not used as a theory-laden philosophical term here, but within the context of general usage of the early twentieth century.

8. The published material provides the bases for this study, since I am interested in changes in how Harrison presented his work rather than in the genesis of that work.

9. Ross Harrison, "Die Entwicklung der unpaaren u. paarigen Flossen der Teleostier," *Archiv für Mikroscopische Anatomie* 46 (1895): 500–578; and Moritz Nussbaum, "Zur Mechanik der Eiablage bei Rana fusca," *Archiv für Mikroscopische Anatomie* 46 (1895).

10. For example: Dennis McCullough, "W.K. Brooks's Role in the History of American Biology," *Journal of the History of Biology* 2 (1969): 411–38; Jane Maienschein, "American Biology Comes of Age," paper delivered at The Johns Hopkins University, History of Science Department, January 1981, and Arizona State University, Zoology Colloquium Series, September 1981.

11. Laurence Veysey, *The Emergence of the American University* (Chicago: University of Chicago Press, 1965), esp. pp. 130–31.

12. John S. Nicholas, "Ross Granville Harrison," *National Academy of Sciences Biographical Memoirs* 35 (1961): 132–62, esp. p. 137.

13. Nicholas, "Harrison," p. 132.

14. Ross Harrison, "Moritz Nussbaum," essay (March 16, 1920) in Harrison Collection, Yale University Manuscripts and Archives, New Haven, Conn.

15. Nicholas, "Harrison," p. 134.

16. Edmund B. Wilson went to Naples in 1882–83 and reported the importance of the "new vistas of scientific work" there, as discussed in Thomas H. Morgan, "Edmund Beecher Wilson," *National Academy of Sciences Biographical Memoirs* 21 (1941): 315–42. Morgan spent time there during 1894–95 and said that his Naples experience was a turning point for him scientifically. He became involved in the controversy over half embryos, for example: Thomas H. Morgan, "The Formation of One Embryo from Two Blastulae," *Archiv für Entwickelungsmechanik der Organismen* 2 (1895): 65–71; Harrison, in contrast, spent only a brief time in 1896 and made no reference to the importance of the visit, while he often mentioned Bonn as critical.

17. As demonstrated by the labeling in journals, university departments, and research institutes, for example.

18. Coleman, *Biology*, p. 15.

19. Coleman, personal communication.

20. Interest in evolution was manifested in various ways, not necessarily the same for each of the individuals and not necessarily in Haeckel's extreme sense, which tends to be identified with the period. Careful study of each individual will help illuminate this important factor.

21. For example, Harrison's description of biology in 1914, to be quoted in this essay, implies the acceptability of evolution. In 1922 he wrote that "in my opinion there are no Geologists or Biologists of note who do not believe in the correctness of the evolution theory" (Harrison to Mabel Moore, December 8, 1922, Harrison Collection). And numerous exchanges with his evolution-minded friend Edwin G. Conklin reveal Harrison's belief in evolution. Yet Harrison never discussed evolution in his research papers. Neither phylogenetic nor other evolutionary factors had a place in laboratory work, according to Harrison, because it was impossible to study evolution "scientifically." This interpretation of Harrison's attitudes was reinforced by personal conversation with Evelyn Hutchinson, February 2, 1977.

22. See Jeffrey Werdinger, "Embryology at Woods Hole: The Emergence of a New

American Biology," Ph.D. dissertation, Indiana University, Bloomington, 1980. Werdinger discusses what he terms the "internal" and the "external" critiques of previous phylogenetic traditions in embryology. I do not mean to suggest that medicine is antievolutionary in any way; rather evolution provided no essential constraints or directive influence for medicine around 1900.

23. For example, in 1914 Harrison was offered a position as head of the anatomy department in the medical school at Johns Hopkins; in 1924 he was offered a similar position in the newly organized Columbia University Medical School. Instead he chose to stay at Yale as Sterling Professor of Biology. Nicholas, "Harrison," esp. p. 146, discusses other medical-biological connections during his career at Yale.

24. Ross Harrison, "The Osborn Memorial Laboratories, I: The Zoölogical Laboratory," *Yale Alumni Weekly* 23 (1914): 668–69.

25. Nicholas, "Harrison," p. 146.

26. Harrison, "Die Entwicklung." While not concerned with tracing the course of individual cells, Harrison concentrated on cellular changes in later embryonic stages rather than on the germ layers Haeckel and others had emphasized. In this he was like his contemporary American cell-lineage investigators.

27. Harrison, "Die Entwicklung," p. 527. Original: "Über die Entwicklung der Nerven in den unpaaren Flossen, vermag ich nichts Wesentlicher anzugeben. Mit Hülfe der gewöhlicher embryologischen Methoden sind die Einzelheiten der Entwicklung nicht ausfinden zu machen."

28. I feel certain that Harrison would have known of this work because of his study in Germany and his time spent in Woods Hole and at the Marine Biological Laboratory, Woods Hole, Massachusetts. He probably knew of Roux's ideas, therefore, but found other work more interesting, with different goals and different assumptions. Undoubtedly he knew of Roux's introduction to his journal, *Archiv für Entwickelungsmechanik*, translated by William Morton Wheeler as "The Problems, Methods, and Scope of Developmental Mechanics," *Biological Lectures* (Boston: Ginn & Co., 1894), pp. 149–90.

29. Gustav Born, "Über Verwachsungsversuche mit Amphibienlarven," *Archiv für Entwickelungsmechanik* 4 (1896): 349–465; 517–623.

30. Ross Harrison, "The Growth and Regeneration of the Tail of the Frog Larva," *Archiv für Entwickelungsmechanik* 7 (1898): 430–85, esp. p. 430.

31. Harrison, "Growth and Regeneration," p. 430.

32. Harrison, "Growth and Regeneration," p. 435.

33. Ross Harrison, "Experimentelle Untersuchungen über die Entwicklung der Sinnesorgane der Seitenlinie bei den Amphibien," *Archiv für Mikroscopische Anatomie* 63 (1903): 35–149.

34. Harrison, "Experimentelle Untersuchungen," pp. 142–43.

35. The Harrison Collection at the Yale University Manuscripts and Archives has only a few items such as notebooks from Harrison's earlier years, but even the material available reflects nothing different than the publications. It would be desirable to know more about why this change came in 1903. Maybe Harrison had simply become aware of other work and theories, maybe the impending 1904 anatomy meeting at Jena provided the crucial stimulus; the reasons simply are not clear.

36. Sally Wilens, Introduction to *Organization and Development of the Embryo*, by Ross Harrison (New Haven: Yale University Press, 1969), p. xiii.

37. Sheath cells could be seen, using microscopic techniques, surrounding the nerve axon as soon as anatomists could see nerves. They could not tell, therefore, whether the sheath cell caused (that is, was antecedent to), was caused by, or was completely independent of the fiber it surrounded.

38. Ross Harrison, "Nachtrag zu der Diskussion zu den Vorträgen von Schultze and v. Kölliker," *Verhandlung d. Anatomische Gesellschaft, 80 Versammlung*, Jena, 1904, p. 52. It would be enlightening to know more about this meeting. The papers were fairly descriptive, presenting data to support the preferred conclusions. But reports suggest that theory and methods were also vigorously discussed.

39. There are, of course, other meanings, some philosophically loaded, but this seems to have been what Harrison meant.

40. Ross Harrison, "An Experimental Study of the Relation of the Nervous System to

the Developing Musculature in the Embryo of the Frog," *American Journal of Anatomy* 3 (1904): 197–220, esp. pp. 199–200.

41. There was considerable discussion in the 1890s, especially in German anatomical journals, about the distortions caused by manipulations. Oscar Schultze and Hans Held were leading disputants on the issue of nerve fiber development in particular.

42. Ross Harrison, "Further Experiments on the Development of Peripheral Nerves," *American Journal of Anatomy* 5 (1906): 121.

43. Harrison, "Experimental Study," p. 216.

44. Harrison, "Experimental Study," p. 218.

45. Ross Harrison, "Observations on the Living Developing Nerve Fiber," *Anatomical Record* 1 (1907): 116–18.

46. The Society for Experimental Biology and Medicine, according to discussions in the Harrison Collection at Yale University, was an attempt to bridge those two subjects by coordinating experimental studies in both.

47. Jane Oppenheimer, "Ross Harrison's Contributions to Experimental Embryology," *Bulletin of the History of Medicine* 40 (November–December 1966): esp. p. 525 establishes the greater importance of Harrison's questions than his techniques.

48. For further discussion see Jane Maienschein, "Ross Harrison's Crucial Experiment as a Foundation of Modern American Experimental Embryology," Ph.D. dissertation, Indiana University, Bloomington, 1978, esp. chaps. 1 and 3.

49. Harrison, "Observations," p. 118.

50. For example, Hans Held, *Die Entwicklung des Nervengewebes bei den Wirbeltieren* (Leipzig: Verlag Johann Ambrosius Barth, 1909).

51. Ross Harrison, "Embryonic Transplantation and Development of the Nervous System," *Anatomical Record* 2 (1908): 391.

52. Harrison, "Embryonic Transplantation," pp. 397 and 409.

53. Harrison, "Embryonic Transplantation," p. 410.

54. This interest is reflected in various archival sources in the Harrison Collection at Yale University and is summarized in an undated document, "Program for an Institute for Research in Experimental Embryology and Related Fields."

55. Ross Harrison, "The Development of Peripheral Nerve Fibers in Altered Surroundings," *Archiv für Entwickelungsmechanik* 30 (1910): 15–33.

56. Harrison, "Development," p. 30.

57. Ross Harrison, "The Outgrowth of the Nerve Fiber as a Mode of Protoplasmic Movement," *Journal of Experimental Zoology* 9 (1910): 787–846.

58. Frederick Churchill, *Wilhelm Roux and a Program for Embryology*, Ph.D. dissertation, Harvard University, 1966, esp. chap. 2.

59. Maienschein, "Ross Harrison's Crucial Experiment," chap. 4.

60. Even the archopponent of the neuron theory, Held, published no further rebuttals on the subject.

61. Harrison, "Outgrowth," p. 830.

62. Harrison, "Outgrowth," p. 832.

63. Harrison, "Outgrowth," p. 833.

64. Harrison, "Outgrowth," p. 840.

65. Harrison, "Outgrowth," pp. 840–41.

66. Maienschein, "Ross Harrison's Crucial Experiment."

67. Allen, *Life Science*, esp. pp. xvii–xix.

68. Jane Maienschein, "Shifting Assumptions in American Biology: Embryology, 1890–1910," *Journal of the History of Biology* 14 (Spring 1981): 89–113.