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Before There Were Standards: The Role of Test Animals in the Production of Empirical Generality in Physiology

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Abstract. After 1900, the selective breeding of a few standard animals for research in the life sciences changed the way science was done. Among the pervasive changes was a transformation in scientists' assumptions about relationship between diversity and generality. Examination of the contents of two prominent physiology journals between 1885 and 1900, reveals that scientists used a diverse array of organisms in empirical research. Experimental physiologists gave many reasons for the choice of test animals, some practical and others truly comparative. But, despite strong philosophical differences in the approaches they represented, the view that it was best to incorporate as many species as possible into research on physiological processes was widespread in both periodicals. Authors aimed for generality, but they treated it as a conclusion that would or would not follow from the examination of many species. After 1900, an increasing emphasis on standardization, the growth of the experimental method and the growing industrialization of the life sciences led to a decline in the number of species used in research. In this context, the selective breeding of animals for science facilitated a change in assumptions about the relationship between generality and diversity. As animals were increasingly viewed as things that were assumed to be fundamentally similar, scientific generality became an *a priori* assumption rather than an empirical conclusion.

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In 1975, the Nobel prize winning physiologist Hans Krebs named what is now known as the August Krogh principle, one of the few explicit rationale for the choice of test organism in the contemporary life sciences.[1] Introduced in 1929, as Krogh bemoaned the increasing paucity of zoological knowledge in physiology, his most concise statement of the principle goes as follows: "For a large number of problems there will be some animal of choice . . . on which it can be most conveniently studied."[2] The principle acknowledges that beyond practical matters of access, cost, adjustment to captivity, etc., some species

[1] Krebs, 1975.
[2] Krogh, 1929, p. 247.

have unusual characteristics that give scientists a special empirical handle on the problem at hand. Krogh warned that only through close attention to zoological diversity would physiologists happen on these valued organisms.

Today the principle is often cited to emphasize the importance of maintaining diversity in experimental research. Examples such as *Drosophila*'s giant chromosomes, the squid axon and *Aplysia*'s giant nerve cells are among the clear success stories that attest to the value of the idea in experimental biology. Indeed, in the article in which he named the principle, Krebs enshrined it to echo Krogh's emphasis on the importance of zoological diversity in experimental physiology. Yet embedded in Krebs' characterization of the principle is an assumption that reflects a modern bias in the relationship between diversity and generality in experimental research. While championing the principle, Krebs maintained that its application would advance science because: ". . . a relatively minor modification of a standard situation may present great advantage in studying a phenomenon without affecting basic principles. ... Since the materials chosen are still representative of basic principles, they are examples rather than 'models'."[3]

Krebs' statement clearly assumes that diversity is an exception amid a background of presumed generality. The change in the species chosen is a "minor modification;" that "minor" change is somehow deviant: it is a modification of "a standard situation;" finally, and without question, the species difference represented in the unusual animal is still "representative" and will not, therefore, affect "basic principles." The concept of "model" traditionally implies some negative analogy. But Krebs explicitly ruled out any negative analogy by stating that his instances are not models, but "examples." One presumably needs the odd species because scientific understanding is incomplete. But, before the fact, before the completed empirical analysis, Krebs' statement assumes the generality of the process under study. The chosen species is somehow different; but behind the figure of diversity, he expected to find a ground of uniformity. Behind the uniqueness offered by these special situations stand unchanging "basic principles." As a result the general applicability of test results was treated as a presumption, not an *empirical question*. Indeed, this was one of the great strengths of the principle. One did not simply learn about *Drosophila*, for example, but, from *Drosophila*, about presumed universals of genetics.

The perception of diversity as a unique feature amid a background of generality is partly a result of the growth of a few standardized test animals that were developed for research in physiology after the turn of the twentieth century. After 1900, the selective breeding and increasingly widespread use of test animals such as rats, mice and fruit flies, led to a decline in the number of

[3] Krebs, 1975, p. 225.

species used in experiments. And the few increasingly common species that were adapted for science eventually were perceived as things with standardized features, "materials" (Krebs' word) in a laboratory system. I have shown, for example, that early in the twentieth century assumptions associated with the use of white rats as test animals changed. Though rarely used before 1900, once in common use, rats became carriers of generality.[4] They brought into the laboratory the presumption of uniformity, and their widespread use and ready availability were among the factors that led scientists to presume that results obtained on white rats reflected general processes.

But the presumption of generality was new. Prior to 1900, many scientists hoped for great generality, but it was not presumed. Rather, it had to be extracted from the manifest diversity thought to characterize life. Whether general processes could be found amid this diversity was itself an empirical question. Something of this older view can be seen in Krogh's original paper. Krogh was writing about several problems that had emerged with the huge growth of physiology from 1900 to the mid-1920s. One was a too close association between physiology and medicine. While important, he argued that this link had produced a "rather narrow" focus. He advised that a similarly close cooperation between general physiology and comparative physiology and zoology was just as important. "[T]he route by which we can strive toward the ideal [of generality] is by a study of the vital functions in all their aspects *throughout the myriad of organisms*. We may find out, nay, we will find out before very long the essential mechanisms of mammalian kidney function, but the general problem of excretion can be solved only when excretory organs are studied wherever we find them and in *all their essential modifications*."[5] The problem was general, but its manifestations were truly diverse. For Krebs, in contrast, diverse organisms were "minor modifications" of "a standard situation." Generality was presumed, and the occasional exception was a minor and transient oddity.

What was the nature of this change and how widespread was it? To understand it we need a clear picture of the situation that preceded this change. Krogh's statement was made in 1929, just after several of the most common standard laboratory animals had become entrenched in American

4 See Logan, 1999, 2001. Oudshoorn (1990) has developed the notion of knowledge "carriers," instruments of science that contribute to, but do not completely determine the acquisition of scientific knowledge. She uses this metaphor to trace a middle ground between a completely relativistic account of science and one that acknowledges that the processes of science can contact evidence that may violate categories constructed in the laboratory. I borrow her metaphor of the "carrier" to reflect the way in which test animals altered assumptions about the generality of laboratory findings.

5 Krogh, 1929, p. 247, italics mine.

laboratories.[6] Determining the basis and significance of the change requires an examination of the practices and assumptions guiding research prior to the development of standardized test animals. What reasons were given for the choice of organism prior to the widespread availability of convenient laboratory standards? What was laboratory life like before the standards were available, and scientists instead used whatever test animal they could find? Had a change really occurred, or did the presumption of generality precede the use of standard laboratory species? In what follows I explore the early use of test animals in physiology, focusing on the period between 1885–1900, just prior to the selective breeding of the first standardized species. Using the contents of two prominent physiology journals, I assess the types and numbers of animals used in experimentation and describe the kinds of reasons physiologists gave for their choice of test organism. I will show that between 1885 and 1900, a great variety of test animals was used in experimental physiology. Further, this variety was associated with quite different assumptions about the relationship between diversity and uniformity. Krogh's cautious implication that some generality *might* be extracted from a field of diversity was common, as what later was often considered superficial variety was taken quite seriously. I discuss the tension between the teleological approaches of "biological" physiology and the growth of experimentation, and I explore the ways in which proliferation of experimentation and experimental standards changed scientists' views of animals, transforming them from "organisms" to "things:" uniform "materials" that ensured generality.

Physiology at the End of the Nineteenth Century

The life sciences were in a state of flux in the end of the nineteenth century. Early attempts to integrate Darwin into anatomy and zoology, popular in the 1860s, were complicated in the 1890s by the eclipse of Darwinism. At the same time, the experimental method proliferated, creating new tensions between empirically successful mechanistic approaches and the teleological programs that attempted to frame a "new" biology served by controlled experimentation. Physiology matured in the midst of all of this. Arguably it led the way in the expansion of experimentation, and its development was deeply influenced by calls for a scientific medicine that placed scientific physiology at the core of modern approaches to human health.

Growth and success brought renewed tension between "general physiology" and the specialized disciplines of physiology that focused on

6 See Clarke and Fujimura, 1992; Clause, 1993; Fujimura, 1996a; Kohler, 1993; Logan, 1999; Rader, 1998.

the intensive examination of organ systems in the quest for medical utility. General physiology was descended from the synthetic and teleological traditions of German teleomechanism. It addressed the whole organism: the apparently purposeful integration of separate functions into a sustained and living being. Its goal was the discovery the laws of life itself, sometimes framed in explicitly evolutionary terms.[7] Special (or medical) physiology, on the other hand, was exemplified by a group of specialized problems that emerged between 1850 and 1920 addressing questions of human health. It focused on specific mechanisms of organ function – heart, stomach, brain, endocrine glands – and its organ focus eventually defined separate special disciplines such as cardiology, endocrinology, and neurology.

General physiology itself, however, was a very diverse enterprise, and its features differed as the opponents of an overly specialized medical focus also disagreed with one another. Nyhart describes the complex splintering of the animal sciences in Germany "in which physiology would be redefined from a general science of life to a science of animal function."[8] Approaches to function varied greatly, and by the 1870s, universities were dominated by the "new" physiology of the Berlin physicalist school, whose spokesmen, Emil du Bois-Reymond and Carl Ludwig, saw physiology as the key to a scientifically-based medical reform. Both men sought explanations of function in terms of physics and chemistry, de-emphasizing classical questions of morphology, development and adaptation. On the other hand, the "systematic" organicists, "old" physiologists represented by Karl Reichart, saw this approach as too narrow. They challenged the physicalists over the extent to which function required an account of form, organization and development.[9] For both camps, the goal was explanation via general law, but the terms

[7] See Kohler, 1982; Lenoir, 1982; Pauly, 1987b. In its early forms the approach is well illustrated in Lenoir's (1982, pp. 70–71) account of Dollinger's definition of physiology. Nyhart (1995) includes a discussion of the various meanings of physiology in her analysis of changes in the animal sciences in nineteenth-century Germany. Because both camps sought generality I avoid the phrase "general physiology" and instead refer to the teleologists and holists with the term "biological" physiology throughout. I use the term "physicalist" to refer to the narrower approach and greater specialization traditionally associated with du Bois, Ludwig, and Helmholtz and their strong advocacy of scientific medicine.

[8] Nyhart, 1995, quote from p. 98. Three distinct approaches to general physiology dominated, termed variously "biological physiology," "physiological morphology" and "general physiology" (see Geison, 1987a; Kohler, 1982; Maienschein, 1987; Nyhart, 1995; Pauly, 1987b).

[9] The terms are from Nyhart (1995, Chapter 3), who quotes physiologist Karl Reichart. Nyhart shows that by the late 1870s the physicalists dominated chairs of physiology while the opposition increasingly occupied chairs of anatomy and "scientific" zoology. Morphology and anatomy too, were splintered. The mechanical anatomists were more aligned with physicalist physiology and surgery, while the microscopic anatomists, and later, the scientific zoologists, sought holistic accounts of form and development. The institutional separation that placed

of those laws differed greatly, as did the breadth of their approaches and the methods required to establish them. For du Bois and Ludwig laws were mechanical, physical and reductionistic, while for the teleologists they were biological, holistic, and focused on the integration of organism with purpose.

Between 1870 and 1900, Holistic "biological" physiology was promoted in Germany by Eduard Pflüger and Max Verworn. Both recognized the value of the physicalist researches and the precise methods developed within that tradition. But both also emphasized its incompleteness, advocating a return to the comparative perspective of their great master, Johannes Müller. In his 1899 work, *General Physiology*, Verworn lamented the overspecialization on organ study that had dominated physiology in the preceding decades, stating that "practically nothing has been learned beyond the gross mechanical and chemical activities of the vertebrate body."[10] While valuable, he argued, these discoveries had missed the ultimate aim of physiology, which was "to put [vital phenomena] into causal relation with one another, to see whether their elementary causes are the same as those of the phenomena of inorganic nature." He advocated a renewed methodological pluralism and a more "philosophical conception of science," which Verworn saw clearly in Müller's earlier work. Pflüger shared this goal, but the two men differed sharply on the role of teleological explanation in scientific physiology. Pflüger saw teleology as central to understanding the purposeful adaptability apparent in physiology. In 1877, he stated his law of "teleological mechanics," which formalized the significance of end states in physiological research. Verworn, by contrast, advocated a monism that explicitly denounced teleology. He saw purposefulness and goal orientation as constructions of the human mind. He stated that "[n]ature itself has no goal to strive for."[11]

Despite their differences, however, by 1885, both "biological" camps shared one emphasis whose importance had grown enormously since the time of Müller. That was the value of experimentation, which in physiology increasingly depended on vivisection. Both Pflüger and Verworn advocated

"biological" physiologists in the faculties of zoology, comparative anatomy and morphology but medical physiologists in the medical faculties deepened the divide, as did the tension between comparative and experimental approaches.

[10] Verworn, 1899, quote from p. 29.

[11] Pflüger, 1877; Verworn, 1899, quote from p. 319. Verworn elevated psychology to a position that was logically prior to physiology. He cited Müller's famous doctrine of specific nerve energies to argue that the senses could not provide an accurate account of the world. This law of scientific physiology required that general physiology anchor itself in philosophy and psychology. Verworn argued that the two types of research that must be resumed to complete a modern integration of physiology and philosophy were psychology and comparative physiology. He believed that both had been ignored or trivialized by the mechanists. See Harrington (1996, Chapter 1) for a summary of the significance of holism and teleology in German biology after 1890.

the value of comparative research, but they did so as more and more live animals were being used in experimentation. How did these test animals alter their quest for generality? To explore the impact of test animals on assumptions about diversity, I compared the contents of two physiology journals that best voice the competing views of the physicalists versus the biologists. They are *Archiv für die gesammte Physiologie des Menschen und der Tiere* (hereafter *Pflügers Archiv)* and *Archiv für Anatomie und Physiologie*, *physiologische Abteilung*, (hereafter *du Bois Archiv*). They are arguably the two most prominent general physiology journals of the period. Neither is primarily an expressly zoologically-oriented journal, and each represents the distinct approach of its editor, Eduard Pflüger and Emil du Bois-Reymond, respectively. Both men sought generality in natural law. But, the character of those laws was radically different. [12] Their differences reflect the divided state of physiology in the late nineteenth century, and they suggest that one might expect a greater range of diversity in the more holistic biological orientation of *Pflügers Archiv* and less diversity associated with the physicalistic emphasis of *du Bois Archiv*.

A Comment on Methods

In this flux, three issues must be addressed, not by way of solution, but by way of caution. The first deals with the difficult notion of disciplines. In physiology from 1885–1900, disciplines were forming at a rapid at rate, national styles of science were emerging and the boundaries among today's familiar subdisciplines were either rather indistinct or non-existent. Individuals readily crossed lines that only later would define clear disciplinary boundaries. The development of disciplinary boundaries no doubt both contributed to and was influenced by the ways in which animals came to be used.[13] So, while I do not address the development of subdisciplines, I recognize that the changing relationship between generality and diversity may have occurred in different ways, as test animals helped to shape boundaries between what eventually became distinct disciplines.

A second problem is a practical one that concerns selecting a countable unit of diversity. In this period scientists performed experiments on a

[12] Maienschein, 1991; Nyhart, 1995; Pauly, 1987a, see Chapter 1; Schlich, 1993; Simmer, 1977. Schlich explains that Pflüger's teleological approach was justified in part by his quest for generality. Lohff (1981) by contrast, summarizes the mechanical idealism that underlay du Bois' quest for generality. He sought functional relationships that revealed the hidden truths of physical law through mathematics. Robert Kohler (1987, p. 29) quotes du Bois on the importance of a general physiology.

[13] See Clarke, 1991; Fujimura, 1996b; Kohler, 1994.

wide variety of animals, but there was not yet a standard form for reporting either the source or the level of test animals used. As a result, no consistent characterization of "organism" was presented in published work. Sometimes a scientist might experiment on himself, and the individual scientist was the measurement unit. Other investigators named particular species, using the taxonomic level of species to describe their research subjects. Quite often, however, either several breeds of domesticated animals or a vague grouping (e.g. frogs) was named, with no mention of a biological species. In the following tabulation of animals, where possible I have chosen the taxonomic unit "species" as the smallest and most unambiguous unit to quantify the different types of test subjects. When no species was named, I tabulated more inclusive units (e.g. frogs) as one animal. However, I used no grouping smaller than species. So in cases in which lower order descriptions were provided, as with different breeds of domestic dogs, I counted the test organism as one species.

Finally, my analysis deals exclusively with German-language journals. In the late 19th century Germany and Austria stimulated enormous growth in experimental physiology, which then flourished in several other scientific communities, including those in America, Japan and Russia, as well as in Europe.[14] Important cultural differences very likely shaped research traditions in the ways in which animals were used. I discuss below the impact of trends in Germany on the development of American physiology, emphasizing the impact of the development in America of test animals selectively bred for research in physiology.

The Range and Types of Test Animals

I reviewed all volumes published in the two periodicals from 1885–1900.[15] Most contained from 25–35 articles. However, I did not include all papers in each volume. Because the choice of organism was either absent or less relevant to their contents, I excluded the following types of papers from the analysis.

1. Papers dealing with chemical or physical interactions that involved no organs or organisms and concentrated on, for example, chemical properties such as the solubility in water of iodine, gelatin, or acid, or physical properties, such as the refraction or transmission of light. I have also excluded

[14] Geison, 1987b; Maienschein, 1991.

[15] This included 45 volumes of *Pflügers* and 16 volumes of *du Bois Archiv*. Because their content overlapped with that of the published reports, I did not use reports from the proceedings of the meetings of the Berlin Physiological Society, which were usually included in *du Bois Archiv*.

papers that used a physical apparatus to generate data that in theory modeled organic processes.[16]

2. Papers dealing only with plants or organic substances far removed from the animals that produced them. One such paper, for example, examined the fermentation of cheese.

3. Methodological papers introducing a new apparatus or technique that concentrated only on the details of the apparatus. However, if a paper introduced an apparatus with examples of how it was used to collect original data, I included it.

4. I also excluded theoretical articles or comments, historical reports, obituaries, and review articles that included no new data. The latter often referred to a wide range of species in research conducted by others, but if they reported no original data, the animals mentioned were not included.

In a few instances empirical data were presented, but I was unable to discern what organism generated them. I counted these instances as undetermined; but they constitute less than 1% of the papers examined. The average percentage of papers included in the analysis was 74.3% of the total for *Pflügers Archiv* and 80.1% of the total for *du Bois Archiv*. This method of exclusion, therefore, retained roughly three-fourths of the contents of each periodical.

Pflügers Archiv. The 45 volumes of *Pflügers Archiv* included 931 papers whose content I examined. Of those reporting data on a single species, four organisms dominated. These were dogs, rabbits, frogs and humans. Humans were the most common test organism, accounting for 24.4% of the total;[17] dogs followed, used in 13% of the studies; frogs were used in 12% and rabbits in 5.2%. Approximately 10% of the remaining papers presented data on a single species that was not one of these four. In only five of 45 volumes were single species papers restricted to the four dominant types.

Many papers reported original data on more than one species. Because the above estimate excludes multispecies papers, it underestimates the range of diversity present. Over 14% of the papers presented data on two species. Roughly 18% reported findings on three or more species. Therefore, almost one-third of the papers presented original data on two or more species.

[16] The research itself either used artificially produced materials or generic biological materials, such as albumin, with no mention of the source of the substance. For an example of research using only physical models, see Bernstein, 1886.

[17] Data on humans came from several sources. Often the experimenter served as his own subject. Clinical patients were also used, as were Italian farmers, soldiers, mountain climbers, suicide victims, collaborators and students. Much research with humans was made possible by technical advances in instrumentation that analyzed or recorded human reactions or expanded the human senses (see, for example, Herman, 1890).

These might include one of the four most common species along with a less common one, e.g. pigeons and humans. Sometimes, however, they reported on two or more species that were not among the four dominant groups. These included relatively common animals, such as cats, chickens, pigs, horses and guinea pigs; but they also included wild or exotic species such as eels, elk, monkeys, monotremes, lions and various mollusks. Papers on unicellular organisms or invertebrates often reported data on as many as eight species, and studies labeled "comparative" often included from 8–30 species.[18]

Therefore, each volume incorporated a surprising array of diversity. Excluding studies that reported data on several species, the range of different animals that occurred in each volume was from 3 to 10, with the mode equaling six. This means that with an average of approximately 20 empirical papers per volume, the reader typically encountered data on a different single species every 3.5 papers. Including the multispecies papers as well, the range of diversity is considerably greater. In fact, single species papers often concealed greater diversity. Though a paper might present data on only one species, authors occasionally reported that several other species had been examined, though only one set of data was included. For example, examining cell types in the small intestine, Julius Steinhaus stated that his main subject was *Salamandra maculosa*. Data had also been collected on frogs, marine mollusks, dogs and rabbits. But, he preferred salamanders, so data were included only on them, in effect obscuring the multispecies approach to the problem.[19] Therefore, through great by the relatively conservative methods used above, the range of diversity in *Plügers Archiv* could be so high that almost every other paper included data on a different animal.

du Bois Archiv. The 16 volumes of *du Bois Archiv* included 402 papers whose content I examined. Interestingly, the same four organisms dominated single species papers, though the frequency of papers just on humans decreased to 15.4% and the frequency of papers just on frogs increased to 15.2% of the total. Dogs were the most common, occurring in 19.1% of the total, and rabbits were least common of the four (6% of the total). An additional 8% of the papers were on single species not among the four dominant types, and in *du Bois Archiv* as well, many studies reported original data on more than one species. The number of papers including data on two species was somewhat higher (17.2%) and that on three or more species was somewhat lower than in *Pflügers* (16.4%). Here too, however, about one-third of all papers were multispecies papers. Using only studies on single animals, the number different animals used ranged from 4 to 9, with, as in *Pflügers*, the

[18] See, for example, Steinach, 1890.
[19] Steinhaus, 1888, quote from p. 312.

mode equaling six. With an average of approximately 25 empirical papers per volume, the reader typically encountered data on different single species every 4.5 papers. Again, this underestimates diversity because papers with two or three species often included those not mentioned in the four dominant groups. Studies on vision and the function of the semicircular canals in the ear, for example, often involved several species of birds (usually doves, hens, geese and raptors), and studies focusing on blood often used both horses and cows. Though somewhat less frequently, *du Bois Archiv* also contained several articles on invertebrates and, in these, the number of species was high, usually above four.[20] Therefore, despite substantial differences in the philosophical approaches of their editors, both periodicals included a surprising array of diversity.

Grounds for the Choice of Test Animals

In both journals, many authors explicitly stated the reasons for their selection of test organism(s). Several occurred repeatedly. For example, choice of organism was often made as a result of convenience and availability. Due to size, hardiness or the integrity of a system in the face of experimental intervention, often a procedure could be more effectively done on one animal, but not on another. Analyses of blood, for example, often used horses or cows, probably because blood could be taken from them in large quantities. Several studies compared different breeds of dog, or a mix of rabbits and dogs, both using forms that were simply readily available. Sometimes authors noted a preference for one animal and used it predominantly, but then also included data on a few other species. This suggests that practical constraints, e.g. money or access, sometimes prevented them from completing the research on one species, when in fact they might have preferred to do so.

J. Athanasiu, from the physiological laboratory at Bonn, offered an explicit rationale for the choice of organism based in practicality. Studying the influence of phosphorous on the production of fat,[21] he explained both the advantages and disadvantages of the two species of frogs he used in contrast to either mammals or birds. Cold-blooded animals provided the best test, he argued, because the conditions of nourishment were difficult to control in warm-blooded animals. Test animals that received phosphorus refused nourishment, making them different in important ways from controls. Depriving the controls of meals was not a good solution, because it left them in unnatural circumstances. However, cold-blooded animals like the frogs

[20] Not surprisingly, given du Bois-Reymond's own interests in electrical polarity, *du Bois Archiv* contained many studies on the electric organs of fish.

[21] Athanasiu, 1899.

could normally sustain long periods without eating. He believed that this produced a better comparison between test animals (with phosphorus) and controls (without) because neither had eaten and for both the long period without nourishment was natural. He also noted that the smaller body size of frogs made it feasible to use larger numbers of animals, thus permitting him to balance the effects of individual differences between groups. But Athanasiu also pointed out that there were disadvantages associated with using frogs. One was that he could test only males because males and females differed so in mass of body fat. The concern shown for differences between warm and cold-blooded animals, for disadvantages as well as advantages, and for sex differences was typical of the serious analysis of the choice of test organism voiced by many authors.

Some studies employed a true "August Krogh" emphasis on diversity justified by convenient access to a process. This might or might not be associated with an interest in the evolution of that process. For example, du Bois-Reymond completed many studies on electric fish to measure electrical activity and polarization in nervous tissue. Torpedos, electric fish in the ray family, had been central to the study of animal electricity since the eighteenth century. The strong discharges of their electric organs rendered them an excellent species with which to address issues of electrical polarity in animal tissue, and du Bois and his students published many papers on them. Even du Bois' research program, however, was not restricted to one "model" fish species. In 1886, Gustav Fritsch reported comparative data on the electric organs of 23 species of Torpedos.[22] A preference for annelid worms in studies of the anatomy and physiology of smooth muscles also was based on the Krogh principle. Several species had been used, but W. Biedermann recommended *Arenicola piscatorum* (a marine worm) as more suitable than *Lumbricus* (earthworms) or *Hirudo* (leeches) because in *Arenicola*, the thinness of the skin and the width of the segments made observation of the reactions of smooth muscles to curare very easy.[23]

The rise of statistics coupled with the growing expense of research introduced practical considerations that gradually produced a tradeoff between animal size and animal numbers. For example, expressing concern that accident or chance might influence experiments done on only a few beasts, W. Hall selected mice for studies of the impact of iron on physiological processes. He noted that mice could be tested inexpensively and in very large

[22] See Fritsch, 1886. Much of du Bois' research on electric fish was completed at the Zoological Station in Napels, Italy. However, in 1885, du Bois reported with great excitement that he had completed research on living Torpedoes housed in Berlin. See chapter 5, Clarke and Jacyna, 1987, and Dierig, 2000, for discussions of the importance of electric fish and the significance of their institutional context in the history of the neurosciences.

[23] Biedermann, 1889–1890.

numbers. However, Hall also provided a comparative rationale for his choice of mice: he argued that because they are omnivores, mice would yield results that would be more useful for humans than those obtained on birds, frogs or rabbits.[24]

Theoretical comparisons that used different organisms to compare differences in the mechanics of the system under study also led to the use of several species. Here choice of test animal was a part of the independent variable, but comparisons were linked less to biological diversity, and more to comparisons of a process that for physical reasons should manifest itself differently in different animals. For example, any process thought to be affected by temperature, e.g. muscle contraction, might work differently in warm-blooded versus cold-blooded animals, and in both periodicals the comparison of temperature effects in, for example, frogs versus rabbits was common. The logic however was based in assumptions about the mechanical impact of heat or cold on processes in warm- versus cold-blooded species.

A particular animal also might be chosen to settle empirical disputes about conflicting data that, perhaps as matters of convenience, had been collected on several different animals. The goal was simply to determine whether the differences were the result of different techniques or the different animals used. A similar rationale involved continuing a program of research on one species because earlier studies had been completed on that animal.[25]

Sometimes applied considerations dictated the use of several species. Donkey milk, for example was thought to have special healing powers, and to determine why, Ellenberger compared it to cow, horse and dog milk.[26] Particular animals were also sometimes viewed as the best exemplars of a disease process of interest for clinical reasons related to human health. Here application to humans often dictated which study species was used, and the choice was based on both practical and on evolutionary grounds. The "best" model varied, depending on the nature of the disease and its relation to a number of physiological processes, sometimes as a function simply of whether an animal contracted the disease. Scientists at Heinrich Obersteiner's neurological institute, for example, used the induction of experimental epilepsy in guinea pigs as a medical model of epilepsy in humans.[27] Similarly, curare had been used to induce the symptoms of diabetes. But early attempts to model diabetes using curare on dogs or rabbits had produced inconclusive results. Langendorff argued that frogs would work better. They readily exhibited the symptoms, and because respiration depended on dermal as well

24 Hall, 1896, see p. 52.
25 See, for example, the series of studies by K. Hällstén, 1885, 1886, 1887.
26 Ellenberger, 1899.
27 Seitelberger, 1963. See, for example, Gutnikow, 1891.

as lung processes, in them, unlike in mammals, the results of injections would not be confounded by the effects of apnea.[28] For some, the apparently still controversial question of whether experiments on animals would yield information applicable to humans turned on the choice of organism and on the value of studying many types. E. Impens explicitly refuted those who argued that animal experimentation could not be the basis for conclusions about humanity. But he also maintained that valid conclusions about humans would depend on the intelligent choice (*verständige Wahl*) of test animal. And, because of diversity, only some would do. In examining the effect of morphine on breathing he stated that neither cats nor dogs would yield data applicable to humans. He claimed instead that rabbits offered a better analogy.[29]

Though practical reasons abounded, several authors also sought phylogenetic or evolutionary comparisons in the use of diverse species.[30] These took several forms. Some were truly phylogenetic, others referred to vague evolutionary constructs. The former involved comparisons among several members of a taxon thought to share common descent. For example, Theodor Ziehen used dogs, rabbits, hedgehogs, sheep and humans to examine differences in localization of function in the motor areas of the cerebral cortex. His interest was in whether within the mammalian class homologous brain regions performed the same functions.[31] Also illustrating strongly phylogenetic research was P. Schultz' analysis of the structure of smooth muscles in vertebrates.[32] Schultz compared differences in the smooth muscle layers of the stomach in eighteen species including reptiles, amphibians, birds and mammals. He noted that because of their great length, the fine structure of the muscles might be more accessible in *Salamandra maculosa*, but a notable difference distinguished carnivores and herbivores as well. Though he clearly aimed to sample much of the vertebrate series, in subsequent studies he explored the physiology of different smooth muscle layers primarily in frogs.

28 Langendorf, 1891. Christoph Gradmann (2001) states that Robert Koch's use of guinea pigs was related to the ease with which they could be infected by the tuberculin bacillis. Koch first tested both dogs and his daughter's pet mice. But because of their hearty immune systems, these animals did not die of the infection. This made them less suitable for research that depended on the death of the subject as the most unambiguous outcome. Guinea pigs died quickly.

29 Impens, 1899.

30 In 1899, Verworn stressed the importance of comparative research and called for even greater attention to diversity. Naming three of the four most common animals reported in the two journals, he stated "The comparative method has not been employed in physiology since Johannes Müller's time, unless the few researches that have been conducted upon other animals than the usual dogs, rabbits and frogs are to be considered as comparative (p. 26)."

31 Ziehen, 1899.

32 Schultz, 1895, 1897.

Along with the frog work, however, he also included data on dogs in an effort to compare the processes in warm and cold-blooded animals.

Some studies involved either explicit or unintentional ecological comparisons, though these were rarer. Ecological comparisons, those among animals exploiting very different conditions of life, i.e. between plant eaters and flesh eaters, were common in studies of digestive physiology or musculature. Here cats or dogs were often compared to rabbits. Lüderitz, for example, stated that it would be difficult to draw an accurate conclusion about digestion without exact knowledge of the musculature of the intestines in both herbivores and carnivores.[33] Interestingly, many ecological comparisons involved frogs. Frogs are considered to have become one of the most established test organisms by the 1880s, and Holmes has documented the unusual advantages that frogs offered, especially for studies of nerve-muscle preparations.[34] To be sure many investigators identified their test animals simply as "frogs" (many, only the frog gastrocnemnius). But, the use of frogs often involved more attention to diversity than is apparent from the label "frog." For example, many studies included not one, but two species of frogs, both of which were relatively common and which shared the advantages discussed by Holmes. The two most frequently used were the grass frog, *Rana esculenta*, and the water frog, *Rana temporaria* (also called *Rana fusca*). Their habitats and distributions differed across much of Europe, and differences between them were often stressed. Some research explicitly compared the impact of their differing ecologies. For example, A. J. Ploetz examined testicular processes in both species during different seasons.[35] He stated that despite their similarities there were surprising differences in the size and function of the testes. Average testis volume per body mass was four times lower in *R. esculenta*, and fluctuations in volume from season to season were much less than in *R. temporaria*. He explained differences in anatomy and physiology in terms of differences in their cycles of sperm production (continuous versus phasic) and the lengths of their breeding seasons. These were in turn explained by differences in geographic distribution. Similarly, in research on the physiology of fat buildup and glycogenesis, Athanasiu compared *R. temporaria*, which

33 Lüderitz, 1891.

34 Holmes, 1993. Historians that focus on "frogs" are following the lead of science. A 1959 textbook entitled *Animal Form and Function* (W. Breneman, Ginn & Co.) presented the frog as an "average vertebrate." Several reasons were given. One was that there were seven classes of vertebrates and the amphibians are "the middle class (p. 324)."

35 Ploetz, 1890. This and other research less concerned with time of year paid close attention to the season in which the frogs were obtained (e.g. Greife, H. 1896). This too, apparently introduced diversity, as did the condition of the animals. Most of the frogs used were freshly caught, and authors often noted that freshly caught animals generated better data than frogs that were housed for extended periods.

hibernates, with *R. esculenta*, which does not.[36] Some studies reported data on basic processes in both species, noting correlations between differences in process and differences in ecology, but offering no ecological explanation. In others, both frog species were included with several other types of organisms apparently in a simple and unstated effort to include data on as many animals as possible.[37] These examples indicate that "the frog" may have sometimes implied much more diversity than the label suggests.

Among the more vague evolutionary constructs were frequent comparisons between "higher" and "lower" organisms and the comparison of warm-blooded with cold-blooded species. Higher versus lower animal comparisons often involved quite different taxonomic levels. Higher vertebrates (usually mammals), for example, were regularly compared with lower vertebrates (usually amphibians), and within class comparisons of higher versus lower mammals were also common. The goal of the latter was often to obtain findings that would be most applicable to humans. In the rare instances in which apes or monkeys were used, this was made explicit. For example, in studies of the innervation of muscles of the back, M. Sternberg chose macaque monkeys because in them anatomical relationships were presumed most similar (*am nächsten stehen*) to humans.[38] But because primates were expensive and difficult to obtain, dogs often represented "higher" mammals, while rabbits or, less often, rodents, might represent "lower" mammals. In comparisons between warm- and cold-blooded animals, frogs or toads usually represented cold-blooded animals and cats, rabbits or dogs represented warm-blooded animals.[39] Finally, even when comparisons were not included in the data presented, authors using what were considered lower organisms often reminded readers that additional data were needed on higher organisms. For example, Adolf Bickel stated that his investigations of spinal cord physiology in amphibians and reptiles must also be carried out on higher species.[40]

Interestingly, the comparison of "lower" to "higher" animals did not always entail the assumption that processes or structures seen in the "higher" animal would be more complicated versions of simpler ones apparent at the "lower" level. This was an empirical question, and scientists often examined

36 Athanasiu, 1898.

37 Steinach (1898), for example, measured differences the inhibitory functions of nerve roots in the medulla oblongata in both species. See also De Zaayer, 1887; Kunkel, 1885.

38 Sternberg, 1898. Dogs were regularly used as "higher" animals in a mammalian "series" of three in studies comparing humans, dogs and rabbits.

39 See Aronson, 1885.

40 Bickel, 1898. Higher versus lower mammal comparisons seemed especially prominent in brain research, perhaps because the bias of human superiority rested largely with that organ. Bekterev, 1899, for example, compared rabbits and guinea pigs (described as lower mammals) with several species of monkeys in examining the effects of stimulation of the frontal lobes.

both just to complete the picture. J. Bernheim, for example, studied neural innervation of the bladder in frogs and salamanders. Similar research had already been completed on dogs and cats, but no data were available on frogs. He assumed that because the anatomy and physiology of amphibians and mammals were so different, innervation of the bladder in frogs would also be idiosyncratic (*eigenartig*);[41] it therefore, deserved examination. Such statements indicate that for many, generality depended on evidence from a broad spectrum of types.

Comparative approaches were also regularly brought to the analysis of clinical problems. Ewald Hering, for example, aimed to explain the occurrence of motor ataxia in syphilis. His goal was primarily clinical. But he chose a comparative approach ("*der vergleichend physiologische Weg*") using experimental analyses of frogs and dogs to show that the phenomenon should be understood physiologically and not "psychologically." The comparison of "simpler" animals (frogs) with "higher" ones (dogs) was useful for practical reasons. Many animals were needed, and more frogs were available. Moreover, certain details could be examined more easily in frogs. He believed that frogs had enabled him to isolate the most fundamental form of the problem, revealing underlying principles of ataxia that applied both to dogs and to humans. He stated that had he not repeatedly gone back to frogs, interspersing research on dogs with that on frogs, he would not have been able to confirm that similar processes operated in both. He concluded that, despite species differences in locomotion and in the way the motor disturbance revealed itself, the cause of ataxia was the same in both groups.[42] His account illustrates well the assertion that in this period generality was based in empirical demonstration of similar processes or outcomes in different species. Conclusions of generality, and the continued use of a test animal (in this case, frogs) followed on empirical demonstrations of similarity.

Many historians locate the tension between medical physiology and "biological" physiology in the former's quest for utility in understanding human disease and the latter's focus on a broader understanding of the general laws of life. Yet several of these examples indicate that despite their philosophical differences and the strong association between the Berlin school and the move to scientific medicine, medical concerns were often expressed in *Pflügers Archiv*, and "biological" concerns were often expressed in *du Bois Archiv*. In the examples above, both Impens and Hering argued in *Pflügers* for the application of experimental physiology to medicine, though with careful attention to the choice of test animal. Similarly, biological considerations

41 Bernheim, 1892.

42 Hering, 1897. See also Obersteiner (1894) for a late nineteenth century account of the value of comparative analyses in clinical neurology.

including both the ecological (e.g. omnivore versus herbivore) and the phylogenetic were not uncommon in *du Bois*. Ploetz' strongly ecological analysis of the comparative physiology of testes function in male frogs (p. 17) was published in *du Bois*, as was Ziehen's analysis of differences of function in homologous brain regions in mammals (p. 16).[43] Philosophical differences between the two almost certainly continued to influence the interpretations placed on data generated by diverse organisms, but both camps appear to be using test animals in much the same kinds of ways.

It is important to note that the use in one study of only a single species did not necessarily reflect a disregard for diversity. Practical considerations sometimes explicitly disrupted an attempt to incorporate diversity. This often resulted from the simple need to keep the animal or system alive. When a complicated procedure that had sustained viability and worked well on one animal proved impractical on others, scientists were restricted to fewer types. For example, Cohnstein and Zuntz attempted to extend a method for examining the physiology of the mammalian fetus to a wider range of animals.[44] Their earlier work had been done on sheep, and to achieve empirical generality they tried to examine rabbits, guinea pigs and dogs as well. But the partial detachment of the placenta disrupted nutrient and gas exchange in these species. This had not been a problem in sheep, so rather than using four species, they restricted their experiments just to sheep. In some cases authors of single species papers spoke directly to the issue of generality, occasionally expressing regret that they could not examine other species, but had been restricted to only a few. Langendorff, for example, regretted that so few species were included in his study of automatic activity in the breathing centers of mammals: "Because it is very doubtful that questions of so far reaching significance . . . can be answered with experiments on a single species, studies on dogs and cats would have been desirable. Unfortunately up to this point we have not been able to comply with this requirement."[45] In a study on fluctuations in arterial blood pressure, S. De Jager was concerned about whether results already completed on other animals could be applied to humans. Most prior work had been done on dogs. But he cautioned that to determine their applicability to humans, such experiments could not be limited to a few species; they must be carried out on different animals that clearly deviated from one another in their living conditions (*Lebensver-*

[43] See also P. Schultz' (1895, 1897), phylogeny of smooth muscles, which was published in *du Bois*. The presence of comparative studies need not entail one view or another of evolution. Du Bois was a strong Darwinian, and the forms of evolutionary arguments might, therefore take quite different shapes in the two periodicals.

[44] Cohnstein and Zuntz, 1888.

[45] Langendorff, 1888, quote from p. 290. His experiments were done on rabbits and frogs and included a promise to add more mammals later.

hältnissen). To add to the diversity he chose rabbits, and his paper included data only on rabbits.[46]

These and other observations suggest that beyond true evolutionary comparisons and the limitations imposed by practical considerations, many authors attempted to include as many animals as possible. The value of diversity appears to have been simply assumed. Generality was the goal for both camps, and to reach it investigators publishing in both periodicals seemed obliged to at least consider including as many animals as possible. Several observations support this interpretation. As indicated above, when only one animal was employed, the authors often apologized for that fact. They also regularly expressed intentions to examine more. For practical reasons Jegorow completed research on the innervation of blood vessels only on frogs; but he promised that as soon as conditions permitted, he would extend the experiments to "higher" animals. Similarly, after stating that he used only dogs in work on bronchial muscles, W. Einthoven wrote: "... and it would certainly be desirable to extend these experiments to other animals such as rabbits, cats, and guinea pigs. We hope later to have the opportunity to do this."[47] Without stating why, other authors simply stressed the value of more experiments on other animals. In studies on the fat content of blood during conditions of hunger, N. Schultz stated: "Following these observations on rabbits it is valuable to undertake experiments on still other species."[48] Similarly, though other work had already been done on rabbits, dogs and guinea pigs, F. Tangle added research on the heat centers in horses, only because nothing was yet known about them.[49] Often the range of animals used in a single study showed no rhyme or reason. A case in point is T. Beer's work on vagus nerve stimulation of the lung. The research was done on rabbits, nine different breeds of domestic dogs and a hamadryas baboon. Reasons for inclusion of so many types was barely mentioned, and no attention was given to species differences.[50] Most likely, this was simply the range of animals available in the author's attempt to include several.

The above example illustrates that even when many different test organisms were used, the rationale was not necessarily anchored in an obvious interest in ecology or evolution. Rather some comparisons were "incidental." But the "incidental" inclusion of diverse groups still occasioned the opportunity to measure differences. When investigators then inadvertently obtained

[46] De Jager, 1886.

[47] Jegorow, 1892; Einthoven, 1892, quote from p. 368.

[48] Schultz, 1897, quote from p. 304. Without providing any reason for which species would be preferable, he chose doves.

[49] Tangle, 1895.

[50] Beer, 1892.

different results on different animals, they addressed those differences. The result was that even "incidental" comparisons became part of an analysis of the problem. Whether or not comparison had been explicitly sought, therefore, the outcome was similar to that seen in comparative studies: processes were measured in many species. A quote from a study on the percentage of urea in the blood versus the serum of horses nicely captures an attitude expressed regularly in both journals: "although it can probably be assumed with certainty that the facts ... described for horse blood are not limited to them, it would be desirable to confirm them on other species."[51] The issue of generality was too important to be left to presumption.

Teleology in the Age of Experimentation

Three pervasive influences from within science altered the development of physiology in the late nineteenth century. They were the Darwinian revolution, the unprecedented growth of the experimental method, and the growth of scientific medicine. The popular and scientific receptions of Darwin's theory were intense in Germany. But they were not uniformly positive. From early in 1860, German scientists debated the plausibility of natural selection, and they did so in the context of renewed discussion of the dominant problem of the century – the philosophical grounding of the biological sciences in mechanism versus teleology. Darwin had, for the Germans, once again raised the issue of teleology. So though the physicalists had claimed the final demise of the *Lebenskraft* in the 1850s, from 1880–1900, these influences exerted their effects in the context of new debates between teleologists, holists, and physicalists.[52] By the 1890s, the anti-Darwinian challenge of Weismann, and the rise of neo-Lamarckism and orthogenesis had given an advantage to the

[51] Schondorff, 1896, quote from p. 196. Changes in laboratory practice in the 1880s gradually began to influence education, and recommendations for greater laboratory involvement in education were accompanied by mention of the species to be used in laboratory exercises. These are an important indication of the diversity of species used because they reflect not avant garde research practices, but those so common that they had begun to enter traditionally conservative educational structures. Hensen, 1889, published a report in *du Bois Archiv* on the "physiological practicum" he offered at Kiel. He described 15 topics for student research, which included neural, sensory, cardiac physiology and mental chronometry. The report illustrates the range of animals to which students might be exposed. Exercises are described for eight test species; all are vertebrates. Along with frogs, rabbits and humans, were doves, rays, sharks, ox eyes and calf heads.

[52] Issues were also fed by misunderstandings that resulted from questionable translations of key concepts in *The Origin*. But for both advocates and detractors the validity of natural selection required a reexamination of these philosophies of nature (see Engels, 2000; Junker, 1995). Zoologist Rudolph Wagner, for example, welcomed controversies over natural selection because they renewed interest in philosophical questions that for too long

teleologists. But in physiology the new "biological" approaches grew along side an increasing reliance on two somewhat contradictory traditions: an emphasis on holism, teleology, form and adaptation, and the growing requirement for analysis, external control, standardization and replicability implied by the experimental method. Because it was in physiology that the use of live animals in experimentation flourished, the use of test animals must be understood amid the convergence of these two trends.

For the "biological" physiologists, the tension between these two trends intensified as laboratory procedures involving experimental vivisection became firmly established as biology's benchmark methodology. Eduard Pflüger's controversy with Oscar Minkowski over duodenal diabetes illustrates the conflict posed for strong proponents of teleology by the growth of experimentation. In 1890, Minkowski and Joseph von Mering reported experimental evidence indicating that the absence of internal secretions produced by the pancreas was key to the cause of diabetes.[53] Criticizing Minkowski's methods, Pflüger initially used results from experiments on frogs to argue instead that pancreatic function was controlled by antagonistic nervous impulses originating in the duodenum. But his attempt to extend his theory to mammals using dogs failed. Instead, J. Forschbach's experiments with parabiotic dogs (those whose circulatory systems had been joined) showed that neither of the joined animals became diabetic when the pancreas of one had been removed, severing neural input. This demonstration of the impact of secretions in the absence of neural input led Pflüger to concede that

had been "hidden behind mere detailed studies [*hinter bloßen Detailstudien zurückstehen*]" (Engels, 2000, p. 26). It is significant that evolutionary debates between Darwinism and competing teleological perspectives on evolution regularly involved physiology. For example, in the immediately post Darwinian period mechanism-teleology debates were central to Carl Ludwig's criticism of Rudolph Wagner's theory of spinal reflex transmission (Nyhart, 1995, see Chapter 3). Later, a hypothetical wave-based neurophysiology of memory was the prime candidate mechanism for the inheritance of acquired characteristics in the environmentalist variations of Lamarckism. Gould (1977) cites physiologist Ewald Hering as the source of the theory, which was accepted by both Edward Drinker Cope in America and by Ernst Haeckel in Germany.

53 Thomas Schlich (1993) recounts the terms, philosophies and personalities that influenced Pflüger's five year rejection of evidence supporting the theory. Daniel Todes' (1997) analysis of Ivan Pavlov provides another example of the conflict between changing experimental criteria and purposive *Weltanschauungen*. Pavlov's "scientific vision" reflected the influence of Claude Bernard's "biological" physiology. Pavlov's "managerial vision," however, carried out that work in a fashion that was stimulated by Russia's demand for and the resources made available by scientific medicine. The dual role of Pavlov's dogs reflects the blending of these two goals. Todes decribes how Pavlov's dogs were modified to become mechanisms of data production, at one and the same time organisms *and* industrial "products." See Coleman (1985) for a description of the earlier tension associated with Claude Bernard's strong advocacy of experimental vivisection in France.

the neural processes that he had described in frogs were specific to them, and to accept Minkowski's theory of the causal effect of pancreatic secretions.

Thomas Schlich discusses the extent to which experimental vivisection provided *common ground* that guided both Pflüger's shifting objections and the final resolution of the dispute. Animal experimentation had so altered the differences between medical and "biological" physiology that Eduard Pflüger himself was faced with the dilemma of either disputing the logic of results generated by "the common ground of vivisectional physiology"[54] or acknowledging the validity of Minkowski's theory. He opted for the latter, because by 1908, medical physiology and Pflüger were playing much the same methodological game. The experimental culture had changed since Johannes Müller's day. Mathematics, precise analysis, and mechanical aids had been (according to du Bois-Reymond[55]) foreign to Müller. But philosophical issues and teleology aside, by 1900, they could not be foreign to Müller's descendants. Modern teleomechanists, like Pflüger, were obliged to reconcile their philosophical bent toward holism and purpose with the precise, analytical standards of modern experimentation. Though strong philosophical differences still persisted, precise mechanically contrived, controlled experiments on operated animals had become the primary adjudicator of disputed empirical findings.

Standards, Generality and Test Animals as "Things"

Experimentation also brought new scientific materials to laboratory practice in physiology.[56] Among the most significant were the automated machines that were first developed in the 1850s–1860s for the precise measurement of life processes. Soraya de Chadarevian has shown that these devices too changed the game. She argues that by the 1890s, two central trends had emerged with the mechanization of methods in physiology. First was the attempt to "objectify" life using ever more exact measurements taken by automatic recording devices (such as the kymograph), which produced graphic portrayals of life. The goal of this effort was to develop a precise language

[54] Schlich, 1993, quoted from p. 423.

[55] Lohff (1981) compares the approach to experimentation advocated in the 1850s by du Bois and the physicalists with the quite different attitude expressed by their teacher, Johannes Müller.

[56] Several historians have stressed the direct influence on explanation and theory of "epistemic cultures," that include the technical and social features of the laboratory. For discussions of the role of materials in shaping conceptual change in science, see Hacking, 1992; Knorr-Cetina, 1999; Latour and Woolgar, 1986; Pickering, 1992; Rheinberger and Hagner, 1993.

with which to describe physiological processes. Second, and related, was an explicit move toward standardization.[57] These devices had permitted much more exact measurements of dynamic and fleeting physiological phenomena. To assure reliable accounts, several investigators had to obtain similar results under comparable conditions. But differences between apparatuses frequently led to different graphic displays of the "same" phenomenon. The mid-century promise of precision through mechanized apparatuses and quantitative language had, by 1898, given way to a crisis of replicability. This, in turn, required standardization. That year the French physiologist Etienne Marey called attention to the crisis and recommended internationally agreed upon procedures for the standardization of the devices.[58] This ensured that mechanical *methodologies* were separated from mechanical *philosophies*, as acceptance of methodological and even mechanical standards became essential both to the "biological" physiologists and to the physicalists.

But what of the organisms whose physiology those machines registered? Standard machines and parts of animals had been intertwined from the start, and by the 1890s the boundaries between animals and the machines that measured them had become even more obscured (see Figure 1).[59] That distinction all but disappeared in America after the turn of the twentieth century, as American biologists began the selective breeding of commercially available laboratory animals. Rodents led the way. Between 1905 and 1930, rats and mice were selectively bred for science in an explicit attempt to stand-

[57] De Chadarevian, 1993. De Chadarevian quotes T. Beer in a 1895 memorial to Ludwig in which he stated that graphic methods stimulated by the invention of the kymograph and its successors had raised the "moral level of physiology" (*moralische Niveau der Physiologie*, p. 32). The linguistic goal was especially important for those associated with the physicalist school. Lohff (1981) describes the philosophical power of these apparatuses for du Bois, whose "mechanical idealism" made them the key to anchoring illusory perceptions in the hidden truths of physics and mathematics. See also Daston and Galison, 1992.

[58] He proposed the establishment of an international commission to set standards and normalize the quantitative language applied to their output. Standardization of machine results would occur through pre-arranged agreement in which, for example, scientists concurred on what constituted a "normal" pulse rate. The universality of the phenomena was a result of "the negotiated standardization of a common experimental practice and the associated norming of [the scientists'] experience" (de Chadarevian, 1993, p. 45). Later, at about the time that selectively bred animals were developed for research in life science, other influences reinforced an emphasis on standardization in laboratory practice. See Clarke, 1987; Gossel, 1992; Kimmelman, 1992.

[59] Physical objects often replaced or extended parts of animals. For example, de Chadarevian (1993) describes Helmholtz' myograph preparation as follows: "In Helmholtz' myograph [*Froschzeichenmaschine*] a feather could be hung instead of a frog muscle, and the contractions of opposing muscles could be compared to the behavior of a fluid in an elastic tube" (p. 41). See also Brain and Wise, 1994.

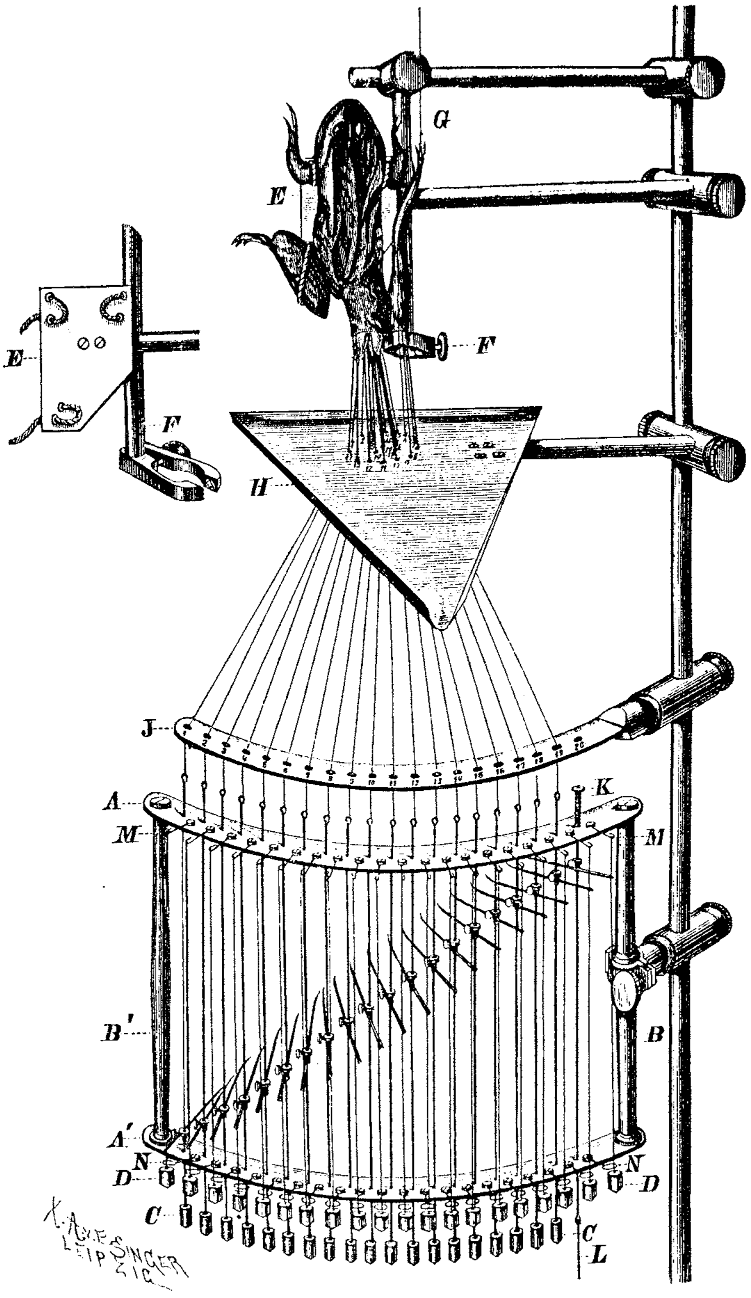

Figure 1. Frogs provide an excellent example of the fusion of animal and machine. From Lombard, W. 1885. "Die räumliche und zeitliche Aufeinanderfolge reflectorisch contrahirter Muskeln." *du Bois Archiv*: 408–489. p. 423.

ardize the entire animal as a critical element of the experimental program.[60] In America, therefore, both of the trends identified by de Chadarevian were applied not just to machines and parts of animals, but to entire organisms.

How well do the trends described for German physiology prior 1900 apply to American physiology? I suggest quite well. In the 1880s and 1890s Germany led the world in research in physiology, and America took its cue primarily from Germany. In the 1870s and 1880s, most of the American pioneers in physiology studied in Germany, and many reformed American universities explicitly modeled themselves on the example of research established in Germany. Geison argues that it was not until the out break of World War I that American physiology assumed independence from its European, primarily German, origins.[61] Though it followed less directly on the mechanical rejections of classical teleology developed in Germany in the middle of the century, America too, promoted specialized branches of scientific medicine anchored in experimental physiology. And in America in the 1890s, the growth of medical physiology produced a similar conflict between medically-oriented and "biological" physiology. Pauly even suggests that in this period "biological" perspectives were more strongly institutionalized in American universities than in German ones. This probably strengthened the conflict with scientific medicine.[62] Finally, in America, as in Germany, by 1900, the teleological approaches of neo-Lamarckism and orthogenesis dominated evolutionary thought. Though perhaps not as deeply anchored in philosophy as in Germany, in America too, the renewed emphasis on teleology prominent in these approaches clashed with the rapidly growing emphasis on experimentation.

The tension produced by these converging trends in America is reflected in the lingering doubts expressed by some of the first American biologists to pioneer the selective breeding of laboratory animals. Many were trained

60 Clarke, 1987; Clause, 1993; Fujimura, 1996a; Logan 1999, 2001; Rader, 1998.

61 Geison, 1987b; Frank, 1987. Geison also notes that the early issues of the *America Journal of Physiology* (founded in 1898) included both physiological chemistry and "biological" physiology. Later, more specialized journals reflecting a less integrated biological emphasis were gradually founded. Harwood (1993) compares the American to the German response to the "crisis of biology" after 1900.

62 Pauly, 1984, 1987a, Chapter 3. Pauly (1984) has shown that biological physiology grew in America first at universities, such as Johns Hopkins and the University of Chicago in which strong traditions in medicine were very late to develop. See also Pauly (1987b) and Kohler (1982) for comparisons among American versions of "biological" physiology and medical physiology and for a discussion of the various meanings of general physiology in America. C. O. Whitman's debates with Jacques Loeb at the University of Chicago is an excellent example (Pauly, 1987a, b; see Maienschein, 1988, for a description of Whitman's biological approach). Fye (1987) recounts the impact of scientific medicine on the growth of American physiology. The development of evolutionary thinking in America is discussed in Bowler, 1983.

in Germany before 1900, and many shared a regard for diversity similar to that apparent in German physiology. So though they spearheaded the animal breeding programs, they voiced a tension over the standardization increasingly linked to the use of the animals in experimentation. Between 1906 and 1915, for example, neurologist/physiologist Henry Donaldson inspired the Wistar Institute's breeding of the Wistar rat, one of the first mammals bred for science in America. The effort was extremely successful. But by 1924, Donaldson expressed serious reservations that the by then widely-used rat standard could work in quite the way he originally imagined. The difficulty of replicating findings from time to time with standard rats led him to conclude that the accuracy of the physical sciences might be unattainable in biology because animals are always in flux.[63] Donaldson was a proponent of the "biological" approach, and the doubts he voiced reflect a conflict similar to that faced by Eduard Pflüger. Because in America the breeding programs were already well underway, however, the conflict extended to doubts about the promise of these new standardized animals.

The emphasis on standardization coupled with the selective breeding of test animals for science had two consequences for the relationship between animal and experiment in America. The first was that as procedures and instruments became more standard, the objects they measured had to be just as standard. So the standardization of the whole animal quickly followed the use of standardized machines. This in turn affected assumptions about the generality of empirical results. Albino rats again provide an example. The Wistar Institute's explicit efforts to breed a "standard rat" had disseminated thousands of selectively-bred rats to American laboratories. By 1930, these animals had transformed scientists' assumptions about generality. Many factors contributed to the change; but, once underway, lab rats fed scientists' *a priori* assumption that there were widespread commonalities across vertebrate organisms.[64] Joan Fujimura has described a similar later trend in genetics and cancer research. In these fields, selectively-bred strains of mice not only became the standard method for generating data, but they themselves were "purified." That is, genetically pure strains were bred in an explicit

[63] Logan, 1999. Donaldson was aligned with the "biological" perspective established by Whitman at the University of Chicago in the 1890s (Pauly, 1987a). Breeding programs in America were begun at almost the same time as ties between European and American physiology were severed by World War I (see Geison, 1987b). For this reason, I do not assume that the trends apparent in America following the breeding of animals for physiology reflect German patterns as well.

[64] Logan, 1999; Logan, 2001. Other work has also shown the impact of standardized test animals on the laboratory process. See Kimmelman, 1992; Kohler, 1994; Fujimura, 1996a, b; and Clarke (1987), for descriptions of laboratory contexts in genetics, cancer research and physiology, in which study organisms led to the standardization of laboratory findings.

attempt to create similar results, and to actively eliminate diversity. Methods that were originally designed to guarantee reliability (the standardization of methodologies) fused with those designed to eliminate diversity as a factor. The influence of the experimental method is clear here. Fujimura states that with such inbred animals, cancer researchers "could *control for* genetic 'factors' ... [The mice] were novel phenomena constructed by scientists in their efforts to study a 'controlled' 'nature' in the laboratory."[65] With these animals scientists could view diversity as a confound and take it out of the experimental picture altogether. As such, they did not just explore generality; they created it.

The standardization of the whole animal eventually came full circle, as standard animals became basis for standardizing other phenomena. Fausto-Sterling describes the development of animal-defined standards in reproductive endocrinology in the 1930s. Endocrinologists were troubled by data indicating that the presumed female sex hormone, estrogen, occurred in large quantities in males as well. This "dilemma" was resolved by standardizing the impact of estrogen using albino rats. In 1932, participants in the First Congress on Standardization of Sex Hormones established the Rat Unit (RU) as the standard measure of estrogen action. The albino rat had itself become an instrument to restrict the range of diversity of acknowledged hormone actions.[66]

The second consequence of the convergence of standardization and selective breeding was that as increasingly more standard animals were used, organisms gradually became more like things and less like natural objects of study. Several historians have emphasized the transition of test animals from "organisms" to "things."[67] Amann, for example, describes the role of model systems in research in molecular biology and genetics to illustrate the different roles of animals as natural entities (*vorgegebenen Einheiten der Natur*) versus things constructed as research materials (*epistemische Dinge*). Like the machines of early physiology, modern model systems are designed to accomplish specified laboratory tasks. Amann suggests that these entities have replaced organisms as the reference objects of the scientific process. As such, animal models, like lab mice, are no longer a modification of nature adapted to laboratory practice. Rather, coupled with other lab procedures, they become the basis for new scientific knowledge, new technofacts (*Technofakte*) that may have no "objective" counterparts in nature. They are "a second

65 Fujimura, 1996, pp. 11, 13. See also Fujimura, 1996b.

66 Fausto-Sterling, 2000, see Chapter 7. The RU was defined as the amount of estrogen needed to produce a standard change in the cells of the vaginal secretions of female albino rats.

67 Logan, 2001; Lynch, 1988; Todes, 1997.

nature [*eine zweite Natur*]" (p. 271), a "Bio-Logie," quite distinct from the house mouse that inhabits the cellar. That creature has become irrelevant both to the acquisition of scientific knowledge and as an object of the explanatory process. The reconfigured second nature of the lab mouse and the procedures that guarantee its stability, not the living house mouse, direct knowledge generation in the modern laboratory.[68]

I suggest that this perception of organisms as "things" or "materials" eventually influenced not merely the standardization of data collection procedures, but also scientists' implicit assumptions about scientific generality. The emphasis on organisms as things enabled laboratory animals, as constructions, to hasten the shift from the presumption of diversity to the presumption of generality. It made standardization less at variance with biologists' notions of animal. Things, after all, can be made as similar as one needs them to be. Organisms, on the other hand, are diverse. Beasts that initially were standardized simply to ensure that scientists could produce comparable findings under similarly controlled experimental conditions, that is to achieve reliability, instead became sources of generality. The situatedness of these controlled conditions was lost, and standard animals assured *a priori* that empirical findings that were gathered under one restricted set of circumstances would apply broadly to other *quite different* settings and to other species. To be sure, the observation of fewer and fewer types contributed. But the increasingly Taylorized use of a few in-bred animals and the accompanying standardization of experimental procedures altered the presumption brought to the measurement situation. Before 1900, scientists attempted to conclude generality from similar data collected on diverse organisms, dealing with differences wherever they found them. They expected differences to be present. But the requirement for standardization and the increasing availability of standard animals rendered that diversity invisible.

Many other factors almost certainly helped produce the shift in America. Among them are the growth of statistics, the unification of science movement, the enormous practical successes of industrialization in the early twentieth century, and economic realities of the institutionalization of science. Philip Pauly, for example, has described the growth of the engineering ideal in physiology, a view in which controlling life and replicating outcomes became

[68] Amann, 1994. Like several other authors, Amann has invoked American Taylorism to describe this process. See also Clause, 1993, and Todes, 1997. From a different perspective, Michael Lynch (1988) has also examined the rat as a mechanical object that, when transformed by laboratory procedures became a "bearer of a generalized knowledge (p. 266). . . . viewed as standardized time points." (p. 272)

more important than explaining it.[69] But another, less often acknowledged influence may have been the need to simplify in the face of complexity. A huge proliferation of biological knowledge began at the turn of the twentieth century. It may have gradually become clear that life processes were *so* complex that they might challenge the ascendancy of the experimental method. Controlled experimentation, after all, imposes artificial simplicity in an attempt to harness complexity. It must simplify things. How could scientists harness the complexity of life without sacrificing the obvious advantage of simplification that experimentation brought to it?

Thomas Hughes' analysis of the cognitive role of models in the solution of complex problems of scale in engineering may provide a key. Standard animals were first bred for the commercial use of scientists in America beginning around 1910. At the same time, America was in the midst of what Hughes calls the second American revolution. He suggests that beginning after 1870 America defined itself as a "technological nation . . . imbued with a drive for order, system and control."[70] By 1900, the early period of independent inventions was ending, and scientists and inventors were faced with extending those inventions to the solution of large scale and very complex problems. To do this, the inventors employed model builders who developed small scale applications of the inventive principle, which was itself often based on a simple application of pure physics. Hughes describes Elmer Sperry's extension of the invention of the gyrostabilizer in this way: "Sperry turned to the model builder, who could preliminarily test ideas in simple ways on a small scale."[71] In extending the concept of the gyrostabilizer to ships at sea, Sperry first used the period of a pendulum to simulate the roll of a ship. That smaller scale test provided a stepping stone to address the more complex problem, as successively honed models addressed increasing degrees of complexity, whose solution permitted the final application. Models permitted successive approximations by which the original concept was extended to large scale complexity. In an age in which American industrialization and engineering offered successful exemplars for research in the life sciences, developing animal models as approximations to the complexities of life would have been a likely step. And animal models may have emerged in experimental biology for the same reason. But the logic of scale models too, rested on generality: the fundamental principle behind the original invention

69 Pauly, 1987b. The growth of private research institutes also played a role. The Wistar Institute established the breeding of the standardized Wistar rat as a goal on which the success of the institution depended. See Clause, 1993; Logan, 2001.

70 Hughes, 1989, p. 1.

71 Ibid., p. 44.

must apply in the more complex context. With "animal" models, handling complexity paradoxically may have required eliminating diversity.

Conclusion

I conclude that the relationship between diversity and generality did indeed change in America after the turn of the twentieth century. Early German physiologists and their American students assumed diversity; they were quite aware of the impact of biological diversity on conclusions based on a limited number of test animals. What distinguished *du Bois Archiv* from *Pflügers Archiv* was neither the application of physiology to medicine, nor the desire for a general physiology. The rise of experimentation guaranteed that their differences were more philosophical than methodological. In both, authors regarded generality as an empirical conclusion that required data from many species. By contrast, in America the twentieth century's standard animals "carried" the presumption that nature might not be so diverse after all; or, if it was, the presumed essential commonalities would be retained in extensions from the standards to more complex systems. The decline in the number of animals used, the selective breeding of an increasingly few convenient and uniform strains serving ever greater experimental reliability, and the industrialization of the life sciences which portrayed animals as "things" fed the marginalization of natural diversity and the *a priori* expectation of generality.

August Krogh first voiced his warnings about the choice of organism in 1929. But the principle that carries his name was emphasized and formalized by Krebs much later, in 1975. Why did it take almost fifty years for the Krogh Principle to be stated as a valuable rule for the choice of organism in experimental biology? One possibility is that in the absence of modern precise controls over the conditions of life and the forces of nature, the unstated Krogh Principle quietly dominated the choice of organism in late nineteenth century physiology. Just *because* they lacked the technology needed to pull almost any process out of almost any organism, scientists were forced to examine a problem wherever it presented itself naturally, and in diverse but accessible forms. Only later, after it was assumed that common experimental animals represented important processes of life without essential variation, was it necessary to formalize a principle emphasizing the importance of attention to diversity.

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