Animal Experimentation: the legacy of Claude Bernard

Hugh LaFollette & Niall Shanks

Abstract *Claude Bernard, the father of scientific physiology, believed that if medicine was to become truly scientific, it would have to be based on rigorous and controlled animal experiments. Bernard instituted a paradigm which has shaped physiological practice for most of the twentieth century. In this paper we examine how Bernard's commitment to hypothetico-deductivism and determinism led to (a) his rejection of the theory of evolution; (b) his minimalization of the role of clinical medicine and epidemiological studies; and (c) his conclusion that experiments on non-human animals were, "entirely conclusive for the toxicology and hygiene of man". We examine some negative consequences of Bernardianism for twentieth century medicine, and argue that physiology's continued adherence to Bernardianism has caused it to diverge from the other biological sciences which have become increasingly infused with evolutionary theory.*

> But when we reach the limits of vivisection we have other means of going deeper and dealing with the elementary parts of organisms where the elementary properties of vital phenomena have their seat. We may introduce poisons into the circulation, which carry their specific action to one or another histological unit . . . Poisons are veritable reagents of life, extremely delicate instruments which dissect vital units. (Claude Bernard, 1949)[1]

Introduction

In 1988 the American Medical Association (AMA) issued a White Paper defending biomedical experimentation on animals.[2] Although they trace the history of animal experimentation to the ancient world, it was the nineteenth century physiologist Claude Bernard who set out the principles of experimental medicine. Claude Bernard continues to be cited by bench scientists who wish to provide a scientific justification of animal experimentation. Nobel Prize winner Sir Peter Medawar lauds Bernard for having offered, "The wisest judgements on scientific method ever made by a working scientist . . . ."[3]

The defenders of animal experimentation are correct: Bernard is the father of

modern experimental medicine. More than a century after his death, his basic methodological assumptions are central to the theory and practice of biomedicine. Since Bernard was a thoughtful and theoretically sophisticated scientist who was trying to lay the foundations of scientific physiology using intuitions based on the best science of his day (more so, we think, than many current scientific defenders of animal experimentation), the reliance on Bernard seems reasonable. Expect for one thing. Current scientific defenders of animal experimentation forget that the best science of Bernard's day is not the best science of our day. His methodological commitments reflect a now outdated understanding of science in general and biology in particular.

1. Bernard's vision of physiology

In defending biomedical research on animals, the AMA says:

> In fact, virtually every advance in medical science in the 20th century, from antibiotics and vaccines to antidepressant drugs and organ transplants, has been achieved either directly or indirectly through the use of animals in laboratory experiments.[4]

This assertion reflects two Bernardian beliefs: (1) all biomedical advances come from the laboratory, and (2) all legitimate biomedical laboratory experiments are experiments on animals. Bernard asserts the primacy of laboratory science and denigrates clinical medicine. Moreover, he asserts not only that experiments on animals will yield significant biomedical truths about humans, but that there is, in principle, no other method (save immoral and illegal human experimentation) which could yield the same results.

The Primacy of Lab Science

Bernard praised laboratory science and denigrated clinical medicine. Why? Partly it was a matter of historical circumstance. The clinical medicine of his day was little more than alchemy. But to attribute his views merely to the sad state of mid-nineteenth century clinical medicine would be a mistake. Bernard wanted to place physiology on as firm a scientific footing as chemistry or physics. So he tried to import their methodological assumptions into physiology. For instance, his views on the centrality of laboratory medicine were framed by the 19th century debate between inductivists and hypothetico-deductivists.

Inductivists claimed that a hypothesis that merely explains or predicts the phenomena may be an artifact of the investigator's fancy or an idea imported from tradition or systematic theory. (Hence Newton's claim: "*hypotheses non fingo*"). Inductivists want an independent warrant for their hypotheses, an inferential connection (one that is not merely explanatory or predictive) between the phenomenon and the hypothesis.[5]

On the other hand, hypothetico-deductivists claim that a hypothesis is confirmed—or at least made probable—if it explains and predicts a variety of scientifically significant phenomena. By the mid-nineteenth century hypothetico-deductivism was part of the theoretical vanguard in physics and chemistry. Following their lead, Bernard acknowledged the legitimate role of testable hypotheses:

> People who condemn the use of hypotheses and of preconceived ideas in the experimental method make the mistake of confusing invention of an experi-

> ment with noting its results. We may truly say that the results of an experiment must be noted by a mind stripped of hypotheses and preconceived ideas. But we must beware of proscribing the use of hypotheses and of ideas when devising experiments or imagining means of observation. On the contrary . . . we must give free rein to our imagination; the idea is the essence of all reasoning and all invention. All progress depends on that. It cannot be smothered or driven away on the pretense that it may do harm . . . [6]

Although Bernard recognized that hypotheses had a legitimate scientific role, he was also aware of their limitations. Bernard was sensitive to the distinction between the context of discovery and the context of justification. He acknowledged that in the context of discovery hypotheses arise from observation and creative imagination. But when the consequences of an hypothesis are to be tested, the investigator must exclude his imagination and preconceived ideas. The hypothesis must be rigorously tested in the laboratory. If it is not testable, it is useless.

> The experimental hypothesis . . . must always be based on prior observation. Another essential of any hypothesis is that it must be as probable as may be and must be experimentally verifiable. Indeed, if we made an hypothesis which experiment could not verify, in that very act we should leave the experimental method to fall into the errors of the scholastics and makers of systems.[7]

Bernard's claims, in this regard, portend the Hempelian analysis offered nearly 100 years later:

> In his endeavour to find a solution to his problem, the scientist may give free rein to his imagination, and the course of his creative thinking may be influenced even by scientifically questionable notions . . . Yet, scientific objectivity is safeguarded by the principle that while hypotheses and theories may be freely invented and *proposed* in science, they can be *accepted* into the body of scientific knowledge only if they pass critical scrutiny, which includes in particular the checking of suitable test implications by careful observation or experiment.[8]

Bernard's views on the testing of hypotheses still guide the theory and practice of biomedical research. Bernard firmly believed that scientific medicine could occur only in a laboratory—not in the hospital.

> We cannot imagine a physicist or a chemist without his laboratory. But as for the physician, we are not yet in the habit of believing that he needs a laboratory; we think that hospitals and books should suffice. This is a mistake; clinical information no more suffices for physicians than knowledge of minerals suffices for chemists and physicists.[9]

By emphasizing the significance of the laboratory Claude Bernard " . . . put scientific medicine on a new foundation. His philosophy *worked*."[10]

Bernard's principles "worked" because he incorporated the principles of physics and chemistry into the physiology laboratory. Physicists and chemists observe the properties and behavior of matter in the laboratory and extend their results, by induction, to matter outside the laboratory.[11] Bernard claimed physiologists should act similarly. They should frame their hypotheses by clinical observation, imagination, and

previous experimentation. They should then test hypotheses in the laboratory and extend the results, by induction, to patients in hospitals. As Bernard explains:

> In a word, I consider hospitals only as the entrance to scientific medicine; they are the first field of observation which a physician enters; but the true sanctuary of medical science is a laboratory . . . In leaving the hospital, a physician . . . must go into his laboratory . . . [12]

Of course, Bernard rightly thought it was immoral to conduct laboratory experiments on humans. However if physiology was to be a genuine laboratory science, there must be subjects on which physiologists could conduct their tests. Non-human animals would be their subjects. "[T]here in the laboratory by experiments on animals, he [the physiologist] will seek to account for what he has observed in his patients, whether about the action of drugs or about the origin of morbid lesions in organs or tissues."[13] Exactly why he though tests on animals would be directly applicable to man will be explained in the next section of the paper.

What is crucial for the moment is to recognize that Bernard thought clinical medicine, based on observation and comparison, could never be a science, it could at most be physiology's handmaiden. It could help frame hypotheses; it could provide an arena for applying its findings. But it could not in principle be a science. To see why, consider Bernard's distinction between observers and experimenters:

> . . . we give the name observer to a man who applies methods of investigation . . . to the study of phenomena which he does not vary and which he therefore gathers as nature offers them. We give the name experimenter to the man who applies methods of investigation . . . so as to make natural phenomena vary . . . and to make them present themselves in circumstances or conditions in which nature does not show them.[14]

Bernard had a particular horror of so-called "observing physicians" who limited themselves to the mere observation of biomedical phenomena. For medicine so conceived:

> . . . normal and pathological anatomy, vivisection applied to physiology, pathology and therapeutics—all would become completely useless. Medicine so conceived can lead only to prognosis and to hygienic prescriptions of doubtful utility; it is the negation of active medicine, i.e., of real and scientific therapeutics.[15]

Morally unable to vary biomedical phenomena in human subjects in order to test biomedical hypotheses, Bernard determines that these hypotheses must be tested in the vivisectionist's laboratory. This distrust of clinical medicine still lives. So powerful is this Bernardian paradigm, that it has led many researchers to downplay the contribution of clinicians to the advancement of medicine. As medical historian Brandon Reines put it:

> . . . the net effect of Bernard's publications on the pancreas was to begin to canonize the vivisectional element of his experimental medicine at the expense of clinical analysis. His later pedagogic works led to further diminution in the rhetorical impact of clinical studies, and corresponding augmentation of the drama of already alluring animal experiments.[16]

2. The Primacy of animal experimentation

Laboratory experimentation on animals is not merely relevant to the study of human biomedical phenomena, it is scientifically essential for it:

> Experiments on animals, with deleterious substances or in harmful circumstances, are very useful and entirely conclusive for the toxicology and hygiene of man. Investigations of medicinal or of toxic substances also are wholly applicable to man from the therapeutic point of view; for as I have shown, the effects of these substances are the same on man as on animals, save for differences in degree.[17]

Bernard's belief that findings in animal experiments are straightforwardly applicable to humans stems from his commitment to one side of another great scientific debate—the debate over determinism. Bernard was a causal determinist. Indeed he argued vociferously that if the living world was not deterministic, no science of life—and physiology in particular—would be possible.[18] He was especially repulsed by the suggestion that medicine is an inherently statistical science:

> This false idea leads certain physicians to believe that medicine cannot but be conjectural; and from this, they infer that physicians are artists who must make up for the indeterminism of particular cases by medical tact. Against these anti-scientific ideas we must protest with all our power, because they help to hold medicine back in the lowly state in which it has been so long.[19]

And again,

> . . . if based on statistics, medicine can never be anything but a conjectural science; only by basing itself on experimental determinism can it become a true science . . . I think of this idea as the pivot of experimental medicine, and in this respect experimental physicians take a wholly different point of view from so-called observing physicians.[20]

Bernard accepted the then current statement of determinism: [1] all events have causes (*principle of causality*), and [2] for numerically distinct but qualitatively identical systems, same cause, same effect (*principle of uniformity*). The application of these principles to physiology was direct:

> [I}f a phenomenon appears just once in a certain aspect, we are justified in holding that, in the same conditions, it must always appear in the same way. If, then, it differs in behavior, the conditions must be different. But indeterminism knows no laws; laws exist only in experimental determinism, and without laws there can be no science.[21]

Conversely, if seemingly identical systems behaved differently, there must be a difference to account for the difference. A mature science should be able to account for these differences. Bernard believed experimental medicine would find laws akin to those of Newton—or since the honor of French science is at stake—Laplace. He believed living systems were like the planets: although they may appear differently and their masses may vary, they nevertheless obey the same "universal" physiological laws. Using Bernard's words:

> Physiologists . . . deal with just one thing, the properties of living matter and the mechanism of life, in whatever form it shows itself. For them genus, species

> and class no longer exist. There are only living beings; and if they choose one of them for study, that is usually for convenience in experimentation.[22]

At first glance it seems that physiology could never have laws akin to those of physics. After all, there are significant physiological differences between species. But Bernard was under the sway of the governing physics paradigm. That paradigm suggested that all laws were deterministic and uniform across nature; it specifically rejected the very idea of species differences and statistical laws. As Newton himself said: "Therefore to the same natural effects we must, as far as possible, assign the same causes. *As to respiration in a man and in a beast*; the descent of stones in Europe and in America; the light of our culinary fire and of the sun; the reflection of light in the earth and in the planets." (emphasis ours)[23]

It is not surprising that Bernard assumed the same would be true of physiology. He thought species differences were not ultimately qualitative (resulting from evolutionary differences in complexity and organization) but quantitative. Once we make suitable mathematical adjustments for quantitative differences (e.g., body weight), we can apply experimental findings from one species to problems of interest in another. Bernard illustrates this reasoning in his discussion of a case that had initially puzzled him. Doses of toad venom which speedily stop the hearts of frogs, do not stop the hearts of toads. At first glance this is an example of same cause, different effect. But Bernard thought there was a better explanation:

> Now, in logic, we should necessarily have to admit that the muscular fibers of a toad's heart have a different nature from those of a frogs heart, since the poison which acts on the former does not act on the latter. That was impossible: for admitting that organic units identical in structure and in physiological characteristics are no longer identical in the presence of a toxic action identically the same would prove that phenomena have no necessary causation; and thus science would be denied. Pursuant to these ideas, I rejected the above mentioned fact as irrational, and decided to repeat the experiments . . . I then saw that toad's venom easily kills frogs with a dose that is wholly insufficient for a toad, but that the latter is nevertheless poisoned if we increase the dose enough. So that the difference described was reduced to a question of quantity and did not have the contradictory meaning that might be ascribed to it.[24]

Bernard, who had studied the physiological effects of poisons in great detail, lays down here one of the main principles of contemporary toxicology. Once purely quantitative differences have been allowed for (say, differences in body weight, metabolic rate, surface area, etc.), we may infer same effect from same cause, even when the test subjects belong to different species. Or, as it is stated in *Casserett and Doull's Toxicology*, "The first [principle] is that the effects produced by the compound in laboratory animals, when properly qualified, are applicable to humans. This premise underlies all of experimental biology and medicine."[25] This is a central element of Bernard's legacy.

3. Bernard's legacy

The previous discussion shows that the Bernardian principles are alive and well and living in biomedical science. Bernard's importation of the methods of chemistry and physics was historically understandable. The problem was not Bernard's decision

to duplicate the methodological prescriptions of physics and chemistry—he did exactly what we would expect any theoretically sophisticated scientist of his day to do. The problem is the decision of contemporary animal researchers to continue using those methodological prescriptions despite dramatic changes in our understanding of science—especially biology. To illuminate this claim, let's look more carefully at the methodology Bernard advocates. Later we will show how that methodology clashes with our best understanding of the biological sciences.

When a chemist does laboratory experiments to determine the properties of potassium, she reasonably assumes that her findings can be extended by induction to potassium outside the laboratory. She can predict that if potassium reacts to sulfur one way in the lab, then it will react to sulfur similarly outside the laboratory (assuming, of course, that the other conditions remain constant).

Bernard concluded the same must be true of physiological experiments. Therefore, he downplayed (non-experimental) clinical medicine. He claimed that since all living matter obeys the same physiological laws, then experiments on animals can yield significant biomedical truths about humans. The consequences of biomedicine's continued acceptance of this belief is far from positive.

Denigration of clinical medicine

Bernard's particular understanding of hypothetico-deductivism, coupled with his rejection of all statistical laws, led him to assume that clinical medicine (including epidemiological studies) could never be a genuine science. Perhaps, though, he would have given more consideration to clinical medicine had he not believed he had a rigorous science ready to hand in the animal laboratory. However, Bernard believed in the interchangeability of species; he thus had reason to assume clinical hypotheses could be tested by laboratory experiments on animals.

Why exactly did Bernard assume the interchangeability of species? Perhaps it was merely an understandable desire to make physiology a science and he simply did not know any other way to do it. Moreover, as the earlier quotation indicated, Newton himself believed physiological laws were not species specific—and Newton's views were doubtless much in the scientific air.

Moreover, certain types of creationism may involve a commitment to the interchangeability of species. Those who think that all creatures are products of a designer would likely assume—on grounds of ontological simplicity—that the designer took the same basic stock of parts and re-arranged them to produce different species. Certainly this was one response to the discovery of homologous structures by 19th century comparative anatomists: what Darwin would see as evidence of descent with modification, creationists were apt to see as evidence of a designer's variations on a basic common blueprint. According to creationists, the main difference between men and animals was merely that the designer added an extra ingredient—a soul. But the basic body parts remained constant. Under these assumptions, if we knew how a rat's liver functioned, we would likewise know how a human liver functioned (once we had adjusted for differences in size and weight).

We should not tar Bernard with creationism. But certainly he was no evolutionist. His narrow view of experimental methodology led him not only to downplay the role of clinical studies, but also to reject Darwin's theory of evolution. He thought the theory of evolution, like the clinician's uncontrolled observations and case studies, did not have consequences that could be subjected to controlled experimental tests. Evolutionary

hypotheses were not directly testable in the laboratory, and hence were speculative and not properly scientific. As medical historian Paul Elliot puts it:

> Leading French biologists, such as Bernard himself . . . were resistent to the Darwinian theory of evolution . . . .[he] resisted these ideas because he saw them as the results of speculation unsupported by proper experimental evidence. The emergence of experimental physiology based on vivisection was therefore an integral part of a general trend in French science away from anything that could be interpreted as speculation towards a science based rigidly, too rigidly perhaps, on laboratory work and experiment.[26]

Given Bernard's rejection of evolution it is perhaps unsurprising that he assumed continuity of physiological function across species lines.

Species differences are merely quantitative

Belief in inter-species similarity and determinism lead Bernard to the conclusion that animals were interchangeable in laboratory experiments.[27] Nonetheless, Bernard was well aware many people thought species differences were biomedically significant. "Even to-day, many people choose dogs for experiments, not only because it is easier to procure this animal, but also because they think that experiments performed on dogs can be more properly applied to man than those performed on frogs."[28]

Such claims, Bernard believed, mistook quantitative differences in initial conditions for fundamental qualitative differences between species. He thought the fundamental properties of vital units were the same for all species. Livers may come in different sizes, but they all respond to stimuli in basically the same way. In so far as there are species differences, these seem to consist in slightly different arrangements of essentially similar building blocks. This was simply one more implication of the then current understanding of determinism:

> Now the vital units, being of like nature in all living beings, are subject to the same organic laws. They develop, live, become diseased and die under influences necessarily of like nature, though manifested by infinitely varying mechanisms. A poison or a morbid condition, acting on a definite histological unit, should attack it in like circumstances in all animals furnished with it; otherwise these units would cease to be of like nature; and if we went on considering as of like nature units reacting in different or opposite ways under the influence of normal or pathological vital reagents, we should not only deny science in general, but also bring into zoology confusion and darkness . . . [29].

Bernard recognized that members of different species behave differently to qualitatively identical stimuli. These "diversities" and "idiosyncracies" should not be ignored; they should be studied and eventually brought under universal deterministic physiological laws. "Only experimental studies of these diversities can furnish an explanation of the individual differences observed in man, either in different races or in different individuals of the same race . . . "[30]

The following analogy—of which Bernard himself was probably aware—may illuminate his proposal for dealing with idiosyncracies. In 1846, the French astronomer Leverrier, aware of some seemingly anomalous and idiosyncratic motions of the planet Uranus, predicted the existence of a hitherto unobserved planet Neptune. Neptune was

subsequently found within a degree of its predicted location, and order was once again restored to the Laplacian universe.

Whether he was aware of this particular case or not, Bernard evidently thought we could find physiological "Neptunes" which would explain observed idiosyncracies. Differences were to be explained by more fundamental similarities; they were not physiologically irreducible.

Some practical consequences of Bernardianism

Bernard shaped the mechanistic physiological paradigm that has reigned for most of the twentieth century. It has had some unfortunate consequences. For instance, the negative results of downplaying clinical studies and overemphasizing laboratory investigation can be seen vividly in the history of the battle against polio.

The Rockefeller Institute was the main center for polio research in the U.S. By 1912, Simon Flexner—one of the institute's most influential researchers—had established the governing paradigm for the pathogenesis of polio. Flexner had discovered that Rhesus monkeys could contract polio through the nose. He subsequently asserted that Polio viruses entered the body through the nose, moved from the olfactory nerves to the brain and eventually to the spinal cord—where they might cause paralytic lesions.

Although Flexner's paradigm remained dominant until the late thirties, as early as 1916 there was substantial clinical evidence that the nasal hypothesis was inappropriate for humans. Swedish investigators found the virus in the intestines and feces of infected persons. Flexner's followers dismissed these clinical findings as the results of back-swallowing nasal secretions. Still other clinicians had noted the involvement of the lymphatic system and the spleen in early stages of human infection. These findings were likewise dismissed by laboratory investigators. Commenting on Flexner's influence, medical historian J.R. Paul—himself a distinguished polio researcher—notes:

> The experimental path he had elected to follow in later years only led him further and further away from the human disease and deeper into the woods. He had convinced himself that the virus was a strictly neurotropic one that entered the body via the nasal route and proceeded directly to the central nervous system . . . He steadfastly held out against the alimentary tract as the portal of entry. Remarkably enough he was resistant to the idea that polioviruses are actually a family composed of several types with different antigenicity. But more than that he held out doggedly against methods of clinical investigation which included clinical virology—approaches that eventually made possible the unravelling of the whole story.[31]

Not only did the nasal hypothesis give researchers a mistaken understanding of the virus's pathogenesis, it also promoted fruitless therapeutic strategies—such as the Schultz-Peet prophylactic nasal spray, which was used to no good effect in Toronto during the 1937 epidemic.

The break in polio research came from clinical studies. In 1948 Enders and his colleagues discovered that polio virus was an enterovirus. (They later won the Nobel Prize for this finding.) Prompted by clinical studies, Enders grew the virus in human embryonic intestinal tissue. Ultimately this led to the development of live attenuated Polio vaccines.[32] The case of polio, though dramatic, is not unique.

Bernard's ignorance of the biomedical significance of species differences continues to infuse biomedicine. In the 1960s Thalidomide was marketed without animal tests to

detect possible birth defects. The AMA White Paper says that the resulting disaster shows the importance of animal trials. Hardly. Let's look at what subsequent trials have shown.

> [I]n approximately 10 strains of rats, 15 strains of mice, eleven breeds of rabbits, 2 breeds of dogs, 3 strains of hamsters, 8 species of primates, and in other varied species as cats, armadillos, guinea pigs, swine, and ferrets in which thalidomide has been tested, teratogenic effects have been induced only occasionally.[33]

Moreover, as Manson and Wise note of multi-species/multi-strain thalidomide tests:

> An unexpected finding was that the mouse and rat were resistant, the rabbit and hamster variably responsive, and certain strains of primates were sensitive to thalidomide developmental toxicity. Different strains of the same species of animals were also found to have highly variable sensitivity to thalidomide. Factors such as differences in absorption, distribution, biotransformation, and placental transfer have been ruled out as causes of the variability in species and strain sensitivity.[34]

In other words, the usual quantitative differences between species have been ruled out as the source of the variable responses.[35]

Moreover, this tendency to conceptualize animal experimentation as the centerpiece of biomedicine has lead researchers to downplay the significance of species differences, and to assume that if a phenomenon cannot be reproduced in animals in controlled laboratory experiments, then it cannot be a genuine human biomedical phenomenon. For instance, by 1957 there was abundant epidemiological evidence that smoking causes lung cancer. Nonetheless,

> The failure of investigators . . . to induce experimental cancers, except in a handful of cases, during 50 years of trying, casts serious doubt on the validity of the cigarette-lung cancer theory.[36]

The rejection of evolution

Bernard's influence on physiological methodology and practice has led to a tension between modern physiology and the other biological sciences. In Bernard's time, physiology established the governing paradigm guiding all biological investigations. But of all the contemporary biological sciences, only physiology has remained wedded to the deterministic "bottom-up" paradigm of the 19th century physical sciences. Although physiology's commitment to 19th century determinism was, according to Mayr, " . . . productive, . . . it left a vast number of phenomena in the living world totally unexplained."[37] As biologists confronted unexplained phenomena and entered the biological world of Darwin, it became increasingly clear that deterministic physiology was not a fruitful paradigm.

As Mayr notes:

> Physiology lost its position as the exclusive paradigm of biology in 1859 when Darwin established evolutionary biology. When behavioral biology, ecology, population biology, and other branches of modern biology developed, it became even more evident how unsuitable mechanics was as the paradigm of biological science. . . more and more biologists recognized that all processes in

> living organisms are consistent with the laws of physics and chemistry, and that the differences which do exist between inanimate matter and living organisms are not due to a difference in substrate but rather to a different organization of matter in living beings.[38]

By moving away from the deterministic bottom-up paradigm, biologists have come to recognize emergent properties consequent upon hierarchical organization, and even the possibility of "downward" causation.[39]

Evolved species differences are frequently acknowledged by bench scientists in their professional communications. Such differences form the basis of much modern biological thought. For as Mayr points out:

> Modern biologists are almost unanimously agreed that there are real discontinuities in organic nature, which delimit natural entities that are designated as species. Therefore the species is one of the basic foundations of almost all biological disciplines. Each species has different biological characteristics, and the analysis and comparison of these differences is a prerequisite for all other research in ecology, behavioral biology, comparative morphology and physiology, molecular biology, and indeed all branches of biology.[40]

There is thus a tension between physiological theory and the other biological sciences. In one way this is highly surprising. One would have expected comparative physiology to be the branch of physiology most sensitive to evolved species differences. Not so:

> Unfortunately, comparative physiology traditionally has been, and continues to be, outside the framework of contemporary evolutionary biology, often embracing theories, positions or approaches that contemporary morphologists, evolutionary biologists, and geneticists have abandoned.[41]

Specifically, contemporary physiologists are inclined to follow the Bernardian analysis (discussed above) of the effects of toad venom on toads and frogs. They are inclined to reduce all interspecific differences to differences in quantity. There is likewise a tendency to downplay the significance of intraspecific variation. Mice, for example, may have widely varying heart rates, yet at the level of gross anatomy there may be no discernible differences between the hearts. As Burggren and Bemis note:

> While comparative physiologists have made an art of avoiding the study of variation, such heritable variation nonetheless is the source for evolutionary changes in physiology as well as for all other types of characters.[42]

By ignoring inter- and intraspecific differences the comparative physiologist focuses on paradigm "model" species. But these usually have two significant deficiencies: (1) they do not reflect intraspecific variation; (2) they are frequently "atypical" species. Burggren and Bemis remark:

> Yet, the use of "cockroach as insect", "frog as amphibian", or "the turtle as reptile" persists, in spite of clear evidence of the dangers of this approach. Not surprisingly, this type of comparative physiology has neither contributed much to evolutionary theories nor drawn upon them to formulate and test hypotheses in evolutionary physiology.[43]

Contemporary physiologists are also inclined to hold Bernard's belief that test

animals should be chosen primarily because for their convenience as test subjects. The physiologist need not choose test subjects because of any special biological resemblance to humans. While there is no non-human animal—no panacea species—on which all human biomedical phenomena can be conveniently studied, the Krogh principle[44] states that for each problem of interest there is an animal upon which it can be most conveniently studied. This ignores the significance of evolved differences between the species. Consequently,

> . . . animals are usually chosen for comparative physiological experimentation either on the basis of extreme physiological characters or because the animal is conducive to a certain physiological technique (i.e., squid axons 1mm in diameter can be punctured relatively easily by microelectrodes). This manner of choosing animals, known as the Krogh principle, is not concerned with whether a species occupies a key position (or any position!) within a putative evolutionary sequence.[45]

Even when physiological investigators refer to species differences in their publications of experimental results, they do so not to discuss their significance, but to exhort other researchers to find a better species (one where the problem in question might be more conveniently studied). Thus Nishimura and Shiota comment:

> Finally, it can be concluded from the above review that good animal models are not uniformly useful with all kinds of teratogens; in other words, an animal species or strain which is known to be an appropriate model for a certain teratogen does not necessarily serve as the good animal model for another teratogen. Therefore, the proper approach to the selection of the best animal species or strain would seem to be extensive experimentation with a variety of animal types.[46]

Moreover, test species are almost invariably selected for non-scientific reasons:

> Species are rarely chosen for scientific reasons but are used because they are available, economical and easy to manage . . . These practical considerations often legitimately outweigh more theoretical ones . . . [47]

This is a theme which recurs frequently in the experimental literature.[48]

In short, even when many physiologists recognize species differences, they rarely conceptualize these from within the theory of evolution. Rather they conceptualize these differences as mere quantitative disanalogies which do not undermine extrapolations from animals to humans. These differences can simply be explained by appropriate scaling formulae:

> Scaling factors are a means for correcting species differences in cross-species comparisons . . . In practice, scaling factors . . . use dose adjustments across species based on some normalizing factor such as body weight or surface area. The most common form of scaling factor is body weight.[49]

Consequently, physiology has not merely diverged from the other biological sciences, its position of dominance in the field has been reduced. In contrast, clinical medicine—based on observation and comparison (as opposed to the determinists' controlled experiments)—is emerging as a genuine science, and epidemiological studies, while irredeemably statistical in nature, have provided much valuable information about human pathology. Indeed, late 20th century medicine has begun to incorporate

probabilistic causality in its discussions of the incidence of diseases in human populations.

4. Conclusion

The continued acceptance of Bernardian methodology has serious consequences for the practice of biomedicine and for the current public policy debate over the use of animals in biomedical research, both from the standpoint of animal welfare and the distribution of increasingly scarce healthcare resources. Most lay people may not see the disparity between physiology and the other biological sciences; nor may they comprehend the limitations of animal research. This makes them susceptible to the self-assured proclamations of some researchers. As one prominent animal researcher explains it:

> Judges and juries may not be able to evaluate the scientific implications of primate studies, but they are favorably impressed when a manufacturer appears to have done more that the required minimum by testing his product on pregnant primates.[50]

But the same researcher also notes that:

> Animal tests, however extensively or carefully done, can never establish human safety regarding teratogenic risks from some new chemical or physical agents. The numbers of potential human exposures will usually far exceed the numbers of animals used in such tests, quite apart from the impossibility of precise extrapolation of data from species to another.[51]

Thus, Claude Bernard's pioneering work in physiology—and especially his methodological prescriptions—strongly influenced the institution of a paradigm governing biomedical research using animals. This paradigm, uncontaminated by the appearance of evolutionary theory, has guided the practice of biomedical research for most of the twentieth century. The costs of researchers continued acceptance of the Bernardian paradigm are substantial. Physiology's continued insensitivity to evolution has led it further and further away from the other biological sciences. And it has likely hindered medical advance by insisting on a single-minded methodology which assumes all significant advances come from laboratory experiments on non-human animals, and which downplays the significance of clinical and epidemiological studies.

Notes

1. Bernard (1949), p. 104. Originally published in 1865.

2. American Medical Association (1988).

3. Medawar (1987), p. 73.

4. AMA (1988), p. 16.

5. In the first half of the 19th century there was some considerable opposition to the use of hypotheses in the English scientific community. As pointed out by Medawar (1988), pp. 123-4:

> Dugald Stewart said that an `indiscriminate zeal against hypotheses' had been `much encouraged by the strong and decided terms in which, on various occasions, they had been reprobated by Newton'. `Newton appears to have had a horrour of the term *hypothesis*,' said William Whewell. Sir John Herschel spoke up in favour of hypotheses. Samuel Neil in 1851 deplored the `widely prevalent prejudice in the present age against hypotheses', and Thomas Henry Huxley had felt obliged to say, `Do not allow yourselves to be misled by the common notion that a hypothesis is untrustworthy merely because it is a hypothesis' . . .

6. Bernard (1949), p. 24.

7. Bernard (1949), p. 33.

8. Hempel (1966), p. 16.

9. Bernard (1949), p. 148.

10. Medawar (1988), p. 134.

11. As Newton put it in his third rule: "The qualities of bodies, which admit neither intensification nor remission of degrees, and which are found to belong to all bodies within the reach of experiments, are to be esteemed the universal qualities of all bodies whatsoever". (1962), p. 398.

12. Bernard (1949), pp. 146-147.

13. Bernard (1949), pp. 146-147.

14. Bernard (1949), p. 15.

15. Bernard (1949), p. 19. Bernard's prophecy about "hygienic prescriptions of doubtful utility" has not been borne out. There is considerable evidence that interventionist medicine has played only a relatively small role in lengthening life and improving human health. As *Lancet* summarizes the evidence (August 1978), pp. 354-355: " . . . public health legislation and related measures have probably done more than all the advances of scientific medicine to promote the well-being of the community in Britain and in most other countries." Or, as medical historians J.B. McKinlay and S. McKinlay explain it (1977, 425):

> In general medical measures (both chemotherapeutic and prophylactic) appear to have contributed little to the overall decline in mortality in the United States since 1900—having in many instances been introduced several decades after a marked decline has already set in and having no detectable influence in most instances. More specifically, with reference to these five conditions (influenza, pneumonia, diphtheria, whopping cough and poliomyelitis) for which the decline in mortality appears substantially after the point of intervention—and on the unlikely assumption that all this decline is attributable to intervention—it is estimated that at most 3.5 per cent of the total decline in mortality since 1900 could be ascribed to medical measures introduced for the diseases mentioned here.

16. Reines (1991), p. 191.

17. Bernard (1949), p. 125.

18. Biologist Ernst Mayr also notes the connection between determinism and experimental methodology (1988), p.9:

> Such deterministic laws allowed a strict prediction of future events, once the present conditions were understood. The role of chance in natural processes was completely ignored. Consequently, the controlled experiment was considered the only respectable scientific method, whereas observation and comparison were viewed as considerably less scientific.

19. Bernard (1949), p. 138-9.

20. Bernard (1949), p. 139.

21. Bernard (1949), p. 139.

22. Bernard (1949), p. 111.

23. Newton, (1962), p. 398.

24. Bernard (1949), p. 180.

25. Klaassen and Eaton (1993), pp. 31.

26. Elliot, (1987), p. 73.

27. Of course, differences in the physiological condition of two animals of the same species may vary the experimental outcome. For example, Bernard observed acidic urine in starving rabbits. Feeding them grass rendered the urine alkaline. But this just shows the need to ensure that all extraneous conditions are controlled in a properly designed physiological experiment.

28. Bernard (1949), p. 123.

29. Bernard (1949), p. 124.

30. Bernard (1949), pp. 125-126.

31. Paul (1971), pp. 117-118.

32. It is interesting to note that one of vivisection's leading apologists—Sir William Patton—has a discussion of the contributions of animal experiments to the war against Polio. Patton's account begins in 1949, conveniently ignoring the period from 1912 until the late forties—the time where animal experiments on rhesus monkeys radically misled researchers (1993), p. 73.

33. Hawkins (1983)

34. Manson and Wise (1993), p. 228.

35. For some further documentation of misleading animal experiments, consult LaFollette and Shanks: (1993a), (1993b) and (1993c).

36. Northrup, (1957), p. 133.

37. Mayr, (1988), p. 9.

38. Mayr, (1988), p. 12.

39. Mayr, (1988), p. 15. Similar points are also made by Gould (1982), p. 132:

> The general alternative to such reductionism is the concept of hierarchy —a world constructed not as a smooth and seamless continuum, permitting simple extrapolation from the lowest level to the highest, but as a series of ascending levels, each bound to the one below it in some ways and independent in others. Discontinuities and seams characterize the transitions; `emergent' features not implicit in the operation of the processes at lower levels, may control events at higher levels. The basic processes—mutation, selection, etc.—may enter into explanations at all scales . . . but they work in different ways on the characteristic material of divers levels.

40. Mayr (1988), p. 331.

41. Burggren and Bemis (1990), p. 193.

42. Burggren and Bemis (1990), p. 202.

43. Burggren and Bemis (1990), p. 206.

44. This principle is named after Danish physiologist August Krogh, but is highly reminiscent of Bernardian remarks on the choice of experimental subjects.

45. Burggren and Bemis (1990), p. 205.

46. Nishimura and Shiota (1978), p. 143, 146.

47. Palmer (1978), pp. 219-220.

48. For example, consider the following discussion of species selection criteria suggested by Hood (1990) pp. 184-185:

> In practice, such selection seems to be dominated by factors based on practicality. Animal models are selected on the basis of how many criteria they possess, such as: ready availability, low cost, ease of handling, high fertility, ease of breeding, large litters, short gestation length, ease of mating time determination, low rates of spontaneous deaths and developmental abnormalities, ease with which their fetuses can be examined, and the amount of information available on their reproduction, development, and response to developmental toxicants . . . The rationale for using such criteria is that none of the animal models tested is an obvious counterpart of humans in response to developmental toxicants. This leaves the issue of practicality foremost in the selection process.

49. Klaassen and Eaton (1993), p. 43.

50. Wilson (1978), p. 261.

51. Wilson (1978), p. 260.

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