The Value and Utility of Animals in Research

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SUMMARY PROCEEDINGS

THE VALUE AND UTILITY OF ANIMALS IN RESEARCH

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TUFTS CENTER FOR ANIMALS AND PUBLIC POLICY
1993
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>1</td>
</tr>
<tr>
<td>Welcome and introduction</td>
<td>2</td>
</tr>
<tr>
<td>Analysis of the arguments against animal research</td>
<td>3</td>
</tr>
<tr>
<td>Scientific problems with animal models</td>
<td>21</td>
</tr>
<tr>
<td>Public health prevention and other alternatives to animal research</td>
<td>32</td>
</tr>
<tr>
<td>Responses to the morning's presentations</td>
<td>35</td>
</tr>
<tr>
<td>The misrepresentation of evidence by the animal rights lobby</td>
<td>44</td>
</tr>
<tr>
<td>Concluding discussion</td>
<td>58</td>
</tr>
<tr>
<td>Summary statement</td>
<td>60</td>
</tr>
</tbody>
</table>
PREFACE

The Tufts University School of Veterinary Medicine, Center for Animals and Public Policy, sponsored an invitational seminar, *The Value and Utility of Animals in Research*, on October 14, 1993, at the Hyatt Regency Hotel in Baltimore, Maryland. This seminar was the second in a series of three organized by the Center for Animals and Public Policy and supported by The Pew Charitable Trusts to deal with issues relating to the use of animals in research. The first seminar, *Biology Education and Animals: Opportunities and Issues*, was held in the spring of 1993. The third meeting, at the National Press Club in Washington, D.C., on March 2, 1994, coincided with the Center's release of *The Animal Research Controversy, Protest, Process and Public Policy*, an in-depth report prepared by the Center on the status of research animals.

For this second seminar on the usefulness of animals in research, the Center brought together twenty representatives of animal protection organizations, animal welfare publications and universities as well as medical historians and defenders of animal research. The intent of this seminar was not to debate the moral questions involved, but to examine the technical arguments being put forth by animal activists and their opponents about the value (or lack of value) of animal use in research.

This publication is produced by the Tufts Center for Animals and Public Policy and the contents do not necessarily represent the views or opinions of all who attended the seminar. Speakers had the opportunity to review and correct presentations and comments attributed to them before completion of the final draft. A synopsis of each discussion period is included although the identities of the questioners and commentors are not necessarily provided.

Funding for the critique was provided in part by Working for Animals Used in Research, Drugs and Surgery (WARDS).
Dean Loew opened the morning sessions by welcoming everyone to the seminar. Following self-introductions by the participants, the Dean explained the history and purpose of the Center for Animals and Public Policy and reviewed the scope of its activities stressing that it was similar to a small "think tank" whose function is to conduct scholarly examinations and analyses of contemporary animal issues being debated by the general public by reviewing the existing literature, exploring the intellectual underpinnings, conducting independent research projects and reporting the results. He pointed out that the Center is unique in the U.S.

He then explained the role of The Pew Charitable Trusts who, for two and a half years, have generously supported Center projects.

Dean Loew noted that one turning point in regard to concern about the use of animals in research occurred with the publication of an article in Science in 1976 by Nicholas Wade. This represented the first time that a major science publication gave serious consideration to the arguments of the animal protection movement.

After briefly reviewing the April meeting on animals in education, the Dean explained the philosophy behind the seminar format design and the process for selecting participants. The goal was to develop an academic debate on arguments against animal research and testing. He stressed that even though many of those present were in the "advocacy business" and critical of animal research, all had been identified as intellectual leaders in this field and were capable of dealing with the ideas being presented in a constructive manner.
ANALYSIS OF THE ARGUMENTS AGAINST ANIMAL RESEARCH

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(Dr. Rowan's talk was based on the following text which was included in the preconference readings.)

Introduction

The use of animals in experimentation has a long history which, for the past few hundred years, has included a passionate debate over whether or not animal experimentation is moral. Despite the claimed productivity of animal research and our modern ability to take more or less effective steps to cure or ameliorate many diseases, the debate about the use of laboratory animals is today more heated than ever (Phillips and Sechzer, 1989). Opponents still challenge the morality and practice of animal research through the usual mechanisms of civic protest, and a small group of activists are even prepared to risk arrest and imprisonment by engaging in acts of theft and vandalism to publicize their beliefs and arguments.

Why has society been unable to develop appropriate mechanisms to defuse the passion and the polarization of this debate? Part of the problem has always been the emotive loading given to particular terms. Thus, opponents will talk of torturing animals in laboratories (implying some level of sadistic motivation among scientists) and scientists will refer to animal activists in similarly unflattering terms. Both sides also tend to take refuge in relatively absolute positions when they are confronted by the media, or under threat, or seeking public support. It is not easy to develop a reasonable dialogue that leads to practical policy solutions under such circumstances.

In addition to the unflattering attitude of each side for the other, there is no shortage of people on both sides who hold strong ethical positions. Views such as, "...it is meaningless to speak of their [animals'] rights to existence because they would not exist if man did not exist" (Jacobs, 1984, p. 1344-1345) and, "Whatever gains we might have harvested, for present or future generations of human beings, would have been ill-gotten" (Regan, 1989, p.28) are fairly common. Such views are also more likely to be publicized by the media because stark opposition is perceived to make for a better story in the age of the ten-second sound bite than subtle arguments and nuanced differences.

The current unproductive rhetoric over animal research comes at a time when it should be easier than ever to construct a reasoned dialogue around which to build a public policy consensus. According to most accounts, biomedical research (including research on animals) has produced tremendous advances in knowledge,
life expectancy and health care (but see McKeown, 1979, for a challenge to this view). At the same time, the biological sciences have made remarkable technological advances that have led to a relatively dramatic drop in laboratory animal use (30-50% over the past ten to twenty years) and a greater ability to promote laboratory animal well-being and alleviate animal distress than ever before. By contrast, at the end of the nineteenth century, when the animal research debate was almost as impassioned as it is today, very few therapeutic advances could be demonstrated to have emerged solely and specifically from animal research, and animal care in the laboratory was very crude by today's standards.

One problem in trying to address the policy issues is the lack of any detailed examination of the various arguments together with an assessment of their validity by a relatively independent group. The Tufts Center for Animals and Public Policy is currently engaged in such an exercise and in this paper, focuses on one subset of the arguments opposing the use of animals in research—the technical/scientific arguments.

In the last twenty years, the animal protection movement has recruited many professionals into its ranks, and they have produced a variety of different moral and technical challenges to animal research. There has been some attention to the moral arguments and their shortcomings and implications by relatively independent groups (e.g. Donnelly and Nolan, 1990; Smith and Boyd, 1991) but the technical arguments have tended to be ignored because the research establishment either did not wish to 'give credibility' to the opposition or because the arguments are perceived to be so ill-founded as to be worth no response. Nevertheless, these new technical arguments have sometimes garnered considerable respect from both movement members and the public, and it seems inappropriate that a community of scholars should deal with contrary or disagreeable arguments with little more than silence.

One of the first critiques was by Verhetsel (1986) who took on both moral and technical arguments against animal research. But his self-published monograph has largely been ignored. Charles Nicoll, a U.C. Berkeley scientist, has also critiqued some of the material and has a paper in press that criticizes Singer's chapter in Animal Liberation on animal research. The most detailed and compelling critiques are, however, those by Paton (1993) and Botting (1992 and 1993). We propose to extend their challenge in this paper. We start by categorizing these technical challenges to the animal research approach and then analyze two specific cases, the discovery of insulin and the development of the polio vaccine. Both of these have long been regarded as triumphs of animal research but these views have been strongly challenged by critics of animal research (e.g. Reines, undated; Sharpe, 1993).

### Criticisms of Animal Research: An Overview

The various technical criticisms of animal research may be classified into the following two broad themes: first, the practice is unnecessary, and, second, the practice produces too little benefit to balance the harm done to the animals.

#### A. Animal research is unnecessary

Some critics of animal research argue that animal research is not necessary because:

1. better use of preventive medicine will eliminate the need for animal research;
2. greater use of and reliance on public health measures will eliminate the need for animal research;
3. clinical approaches provide all the clues we need while animal research merely dramatizes clinical discoveries; and
4. the development of alternatives eliminates the need to use animals.

#### 1. and 2. Prevention and public health

Opponents of animal experimentation propose that the prevention of disease is the only truly effective way to insure universally good health. Sharpe (1988, p.49) states that since, "... treatment has little impact and often comes too late, real improvements can only come by preventing the disease in the first place." But a healthful diet, regular exercise, and avoidance of harmful substances is not always sufficient to keep people free of disease nor even alive in the modern world. Risk of injury and disease cannot be eliminated and life involves making constant compromises between conflicting risks.

The first two arguments tend to overlap and are vulnerable to the same general rebuttal—namely, that both preventive medicine and public health initiatives are heavily influenced by the development of new knowledge, a considerable amount of which is generated via the use of animals. Thus, it is true that the incidence of many of the major diseases was declining steadily before the advent of antibiotics, vaccines and other drugs (McKeown, 1979), but the development of clean water supplies, better hygiene, improved food supply and other measures that have been identified as contributing to the decline in infectious disease mortality occurred as the germ theory was being confirmed (including the adherence to Koch's postulates that required animal experimentation), as our knowledge of pathogenic organisms exploded and as other advances in biomedical knowledge were being made. It would be very surprising if one could isolate such advances from changing societal attitudes about hygiene and disease.

The history of medicine is full of examples of clever detective stories suggesting potentially important therapies that were not aggressively applied (or were even ignored or suppressed—e.g. the story of Semmelweiss and puerperal sepsis) until the
mechanism of the disease was more thoroughly understood. The connection between lung cancer and cigarettes is a more recent story of the linked role of epidemiology, pathology and laboratory research in supporting (all too little and too late) appropriate public health measures. (It is also an example of how powerful interests can manipulate the research enterprise to their own advantage.) One can legitimately argue that the animal and other laboratory research should not have been necessary, but, in the real world, the animal studies (and clinical investigations) played both a positive and negative role.

Even though diseases such as tuberculosis were in steady decline through the nineteenth and first half of the twentieth century, there is no question that the therapies developed, as a result of animal research, to treat sufferers were effective and important to those individuals who took advantage of them. When isoniazid and streptomycin became available to treat TB, there were still 50,000 people in the United Kingdom with the disease. As Paton (1993) shows, these two drugs produced a marked improvement of the outcomes of those with TB.

Also, the charts and statistics that are usually cited to support the idea that public health measures could have replaced much animal research are based on mortality figures rather than measures of morbidity and suffering (although McKeown, 1979, does begin to address this issue). If a family member came down with pneumonia prior to 1935, symptomatic treatment was all that was available. Many individuals survived their bout with pneumonia but they, and their loved ones, suffered through one to two weeks of uncertainty, high fever and considerable distress. The survivors then had lengthy weeks or months of recuperation ahead. After the sulphonamides and other antibiotics were discovered (involving a number of key studies on animals), pneumonia became a relatively minor inconvenience for most people. The sense of control over disease that modern advances in health care have provided may be very important in improving quality of life measures.

Thus, one can make some important arguments about the importance of prevention and public health initiatives in human health and even grant the argument that modern medical research has contributed only a small part directly to extending life expectancy. But one cannot imply either that these measures were not influenced by knowledge derived from animal research nor that prevention and public health benefits are responsible for the considerable ability we now have to control morbidity and suffering.

3. Clinical studies

The third claim in this category implies that animal research is unnecessary because we can achieve the same or better results by relying on clinical research. In the United States, a considerable proportion of federal biomedical research funding (around forty percent) does support clinical research while approximately one third supports animal research. Thus, the call to support clinical studies is already being met to some extent. The question is whether the clinic can completely supplant all animal studies. Brandon Reines, a veterinarian who now concentrates on medical history, has argued this issue most forcefully, drawing on a variety of case studies, including the discovery of some psychoactive drugs via clinical observation (Reines, 1990) and other case studies. In addition, Kaufman et al (1989) have produced a critique of animal models which argues that animal models are rarely cited in the clinical literature and are, therefore, not useful in terms of actual clinical medicine.

The case studies cited by Reines draw on instances where astute clinicians (following William Osler's advice) use interesting cases and clues from the clinic to make conceptual or therapeutic leaps into new areas. For example, important psychoactive drugs (e.g. chlorpromazine) were discovered in this way (Reines, 1990). However, this naturally led to a whole range of additional research questions about the mode of action of such drugs and the possibility of developing other drugs with different (improved?) properties. Thus, the initial observation or intriguing clue, whether clinical or experimental, is only part of the process of developing new knowledge and new therapies.*

In the critique of animal models, Kaufman et al (1989) analyze citations to ten randomly-chosen models from the animal model files at the Armed Forces Institute of Pathology. Of 693 citations to the 21 core papers describing the animal models, 78 (11.3%) were clinical with most of these citations (61) referring to only three of the models. The authors note that many of these citations appeared to be clinically unimportant and they conclude by questioning the usefulness of these models in understanding and treating human disease.

This study represented an interesting (and to this date the most sophisticated) attempt to undertake an objective analysis of the utility of animal models. However, it is not without problems. Citation analysis has developed into a complex science with many potential pitfalls. For example, it is well known that older papers rapidly disappear from the literature and become subsumed by more recent reviews. Thus, their simple citation analysis tracked the influence of the primordial papers that first described the animal model but not the influence of the model itself. In addition, errors in citation are fairly frequent, and one has to be careful to examine potential variants. Such variants can account for a significant proportion of the total citation record.

There are other problems aside from the technical difficulties of citation analysis. It is not clear how clinical "value" was judged nor how the citing literature was divided into clinical papers and other types of research. The scientific literature is also notoriously neutral in assigning value to prior literature, and it is likely to be very difficult to determine how much impact an earlier paper has had on an investigator merely by reading the journal report.

*It should be noted that Reines uses the term "discovery" in a non-colloquial way. As far as I can tell, "discovery" for Reines is the moment of insight or question formation which often comes from a clinical observation. The testing of the insight or question then is moved into a second phase of activity by Reines which he sometimes appears to describe by the term "dramatization."
The study also does not provide any control comparison, such as a citation analysis of the clinical studies of the same human diseases which the animals were supposed to be modeling. It may be that the clinical studies were similarly unimpressive in influencing the later literature.

Finally, this analysis sets out to assess the idea of the usefulness of animal models. However, much animal research only uses the animal as a model in the sense that the research animal is a mammal, as are humans. For example, in toxicity studies, mice and rats are used because they are small, relatively prolific mammals for which a great deal of background information is available.

4. Alternatives

The best available statistics indicate that the use of laboratory animals worldwide has fallen by 30-50% after peaking between 1975 and 1980. Several reasons have been put forward to explain this decline. First, it is argued that laboratory animals and their care have become increasingly expensive leading to an economic disincentive to use research animals. This is true but there is no data showing that animal research costs have risen any faster than general research costs. Second, it has been suggested that animal use has fallen because of economic uncertainty and recessions. During the last fifteen years there have been two recessions and one boom period but animal use fell steadily throughout. In addition, Hoffman-LaRoche reported that it cut its animal use from 1 million to around 300,000 per annum over ten years while maintaining the same number of Investigational New Drugs under study.

Third, it is argued that alternatives have played a major role. This is most likely true but it is not clear how much of the fall has been due to the specific search for and use of alternatives and how much has been due to the development of more efficient and powerful research techniques that also happen to reduce animal use. Thus, cell culture technology has improved considerably in the last fifteen years as has our knowledge of basic biological mechanisms. Partly as a result, the National Cancer Institute has replaced its use of the mouse cancer model for screening new chemotherapeutic agents with cultures of human cancer cells at a savings of around 3-4 million mice per annum (Rowan, 1989). The pharmaceutical industry has also made very good use of new techniques to reduce animal use in screening for potential new drugs.

Even given the progress made in reducing animal use (and in reducing animal distress in research) over the past fifteen years, it is difficult to see how animals could be eliminated now or in the foreseeable future from many research areas. By combining clinical, public health, cell culture and other approaches to research, it may well be possible to reduce animal use still further (perhaps substantially), but it is not realistic to expect to eliminate all animal use in the laboratories of the OECD countries and also argue that biological and medical research would be unaffected.

Finally, as indicated by the two papers on Nobel Prize Winners who used alternatives (Stephens, 1986) or animal models (Leader and Stark, 1987), there is room for disagreement on the role played by alternatives or animals in a particular discovery. A substantial proportion of the winners listed in the two papers are the same.

B. Animal research causes too much suffering for little/no benefit

Another argument used to criticize animal research addresses its utility for humankind. Some suggest that animal research produces a tremendous amount of suffering and little human benefit. For example, Singer (1990) states that he thinks that much animal research "... is of minimal or zero value" while it causes considerable suffering. Others suggest that no animal research is useful while it causes considerable harm to animals. For example, the Australian Association for Humane Research (1988, p.1) states, "We know of no animal experiments, as such, which ever led to a cure of a human disease."

Finally, others argue that animal experiments are not only useless, but are actually misleading. Sharpe (1988, p.200) states that, "... the real choice is not between dogs and children, it is between good science and bad science; between methods that directly relate to humans and those that do not. By its very nature vivisection is bad science: it tells us about animals, usually under artificial conditions, and not about people." All three approaches are found, sometimes together and sometimes not, but all depend on refuting the research argument that animal studies have proved to be very useful at a relatively small cost in animal suffering.

How much suffering is caused by animal research?

We have relatively little data on animal suffering in research and testing and what we do have depends heavily on what is perceived to constitute suffering. Thus, no establishment assessments consider that rats or mice suffer particularly while being housed in a research facility, or at least not when compared to a similar life in nature. The appropriateness of housing conditions for the larger laboratory animals have recently come under much greater scrutiny and animal care standards for them are changing quite rapidly. However, critics appear to consider even the new standards grossly inadequate. Interest in carnivore and primate housing is now spilling over to the other species and the housing standards for rodents and rabbits are also being examined and improvements are being suggested. Nonetheless, the available assessments of animal pain and distress in research do not consider the effect of care and housing practices.

The authorities in The Netherlands have collected data on the potential pain and suffering experienced by laboratory animals under study. The 1990 Annual Report on animal experimentation notes that 53% of the animals experience minor discomfort, 23% were likely to experience moderate discomfort and 24% were likely to experience severe discomfort. About one fifth of the animals in this last category
were given medication to alleviate pain. Examples of procedures that would place animals in the "severe" category are prolonged deprivation, some experimental infections, tumor induction, LD50 testing, and immunization in the foot pad or with complete Freund's adjuvant (The Alternatives Report, 1992). All of the animals are likely to be euthanized so they will also experience the harm of death.

In Great Britain, the only indication of pain control that is available is the recording of anesthesia use. In 1978, 3% of the 5.2 million procedures involved anesthesia for the whole procedure (they were terminal) and 14% involved anesthesia for only part of the procedure. In 1988, 19% of the 3.5 million procedures involved anesthesia for the whole procedure and 17% involved anesthesia for only part of the procedure. It is not clear why anesthesia use doubled from 1978 to 1988 although the 1986 Act that revised British controls over animal experimentation placed greater emphasis on the control of pain and distress (The Alternatives Report, 1990). However, it would appear that potential pain was being underassessed prior to 1986.

According to 1992 USDA statistics, 5.63% of the animals used in research in the USA experience pain or distress that is not alleviated by painkillers. However, USDA statistics on pain and distress are regarded with some suspicion by critics of animal research (and rightly so), especially in light of the tremendous variation in the way different institutions report their use of animals by pain category. There is also some direct evidence that actual use of post-operative pain relief is lower than stated (Phillips, 1993). States vary dramatically in the proportion of research animals that is reported to be painful and for which pain-relief is not provided. Kansas (45.5%), Washington (30.4%) and Colorado (26.0%) reported that more than a quarter of their animal research involved unrelieved pain while some relatively big users like Arkansas (0.03%), Delaware (0.65%), Florida(0.70%), Maryland(0.82%), Massachusetts(0.98%), Nebraska(0.13%) and Texas (0.70%) reported less than 1% of animal research in the unrelieved pain category. The USDA statistics cannot be used as a reliable assessment of research animal pain and distress.

Despite the problems of assessing animal pain and distress and the questionable reliability of some of the numbers, the available evidence does not indicate that all, or even a majority of research animals experience severe and unrelieved suffering. Of course, how one judges the total extent of animal suffering (and whether it is excessive) is going to be heavily influenced by one's personal values and interpretation of the data, and by one's assessment of the level of harm caused by the killing of animals.

**What are the benefits of animal research?**

Having attempted to address the cost side of the equation, what of the benefits? These are no easier to judge. Nonetheless, our knowledge of the natural world and human biology has expanded enormously in this century (although one may question changes in human wisdom over the same period). Our ability to develop vaccines, antibiotics, public health initiatives and reasonably good nutritional advice is much greater than it was even forty years ago. About forty percent of the research that has produced this knowledge used animals (at least according to NIH analyses of its funding allocations) and it seems reasonable to assume that, whatever value we place on our current store of knowledge, then 40% of the credit should go to studies using animals. However, it is not really possible to separate different research approaches to apportion credit. Research tends to be an endless circle with insights flowing from the clinic to the laboratory to the theoreticians and back again. If the flow is disrupted, then one will lose much more than the portion removed.

**Case Studies**

It is difficult to discuss these issues in the abstract which is why so many of the criticisms and defenses of animal research tell narratives about particular incidents or discoveries. Two case studies have been selected for more detailed discussion here—the discovery and development of insulin, and the development of the polio vaccine. Both have been put forward as examples of triumphs of modern medicine and have subsequently been criticized in animal protection literature. They thus serve as interesting examples of the claims and counter-claims in the animal research debate.

**A. The discovery of insulin**

The discovery of insulin as a treatment for diabetes mellitus has been described as "...one of the genuine miracles of modern medicine" (Bliss, 1982, p.11) and the role of animal experimentation in this discovery has received attention from both sides of the debate. A critic, Brandon Reines, claims, "...the animal experiments provided no clear direction, though ultimately the illusion was created that animal experimentation had led to the discovery of insulin" (Reines, undated, p.11) while Charles Best, co-discoverer of insulin, claims his work to be "...only one of the many, many thousand series of experiments which testify to the importance of dogs in medical research." (Best, 1974, p.439) Examining the arguments for and against animal research in the discovery of insulin should help us to judge their coherence and may help us assess what value we might place on at least some animal experimentation.

Diabetes is a disease which contradicts the claim that a high standard of living is all that is needed to remain healthy (assuming a well-fed state is one component of good health). "There tended to be more diabetics among people who were prosperous and well-nourished than among the poor and lean." (Bliss, 1982, p. 21) It is also a disease which contradicts Sharpe's claim that "...most disease is self-limiting..." (Sharpe, 1988, p.32) and the juvenile form of the disease cannot yet be prevented although it has been suggested that its incidence might be reduced by appropriate public health initiatives.

However, the case of diabetes does address the impact of new research knowledge on morbidity and distress (rather than the more absolute measure of mortality which hides many changes in human suffering since life is associated with inevitable
for example, Sharpe challenges the research paradigm with the statement, "... if vivisection were making such an enormous contribution we could confidently expect a massive improvement in health." (Sharpe, 1988, p.15) Did diabetics experience an improvement in health due to the discovery of insulin and was that discovery a triumph of animal experimentation?

Elizabeth Hughes's life is an excellent example of the life of a diabetic before the discovery of insulin. Elizabeth was diagnosed as diabetic in 1919 at the age of eleven or twelve and, in those days, "... the diagnosis was like knowing a sentence of death had been passed." (Bliss, 1982, p.43) The only available treatment at that time was a starvation diet developed by Frederick Allen. Dr. Allen developed this treatment after experiments on dogs which had been rendered mildly diabetic by partial pancreatectomy (thus mimicking human diabetes more closely than complete pancreatectomy). He discovered that undernourishment allowed the diabetic dogs to live symptom free. However, this form of treatment was never easy on the patient. Elizabeth Hughes is a single person but there have been countless others since then. It is difficult to dispute the value of insulin therapy in the face of similar stories of the alleviation of such suffering to produce decades of active and productive lives. However, McKeeon (1979) argues that the majority of diabetics (who experience the adult onset form of the disease) do not experience the type of miraculous change seen in the smaller group of juvenile diabetics. Nonetheless, insulin therapy has had a significant impact on patients and it now remains to assess what role animals played in the discovery. There are several potentially key discoveries and much spinning of wheels in the insulin story.

Early on diabetes was diagnosed by the sweet taste of the diabetics urine but knowledge about the etiology of the disease was scant. Reines (undated, p. 9) then suggests that the first link between diabetes and the pancreas was demonstrated by Thomas Crawley in 1788 when he discovered multiple calculi in the pancreas of a patient who had died of diabetes. Other autopsy studies on diabetics confirmed Crawley's observation and suggested that the pancreas was the most likely organ affected in this disease. Then, in 1869, Langerhans found two cell populations in the pancreas, one of which secreted the digestive juices but he did not know what the other cells did (these were the beta cells that secreted insulin).

According to Bliss (1982, p.25) (and contra Reines), evidence connecting the pancreas and diabetes was still tenuous in 1889 when Oskar Minkowski and Joseph von Mering made their discovery. They had removed the pancreas from a dog to see if the pancreatic digestive enzymes were vital to the digestion of fat. Minkowski noticed that the dog was urinating on the laboratory floor even though it was house-trained and tested the urine for sugar (he had been told by his supervisor to test for sugar whenever he saw polyuria). He discovered that the dog had become diabetic. This led the way for other researchers such as Hedon who, in 1893, proved in further experiments on dogs that the pancreas produced an internal secretion into the blood stream which controlled the metabolism of carbohydrates (Bliss, 1982).

This discovery unleashed a flurry of research aimed at producing a pancreatic extract that could be used to treat diabetes. This approach grew out of other work in the 1890s that had showed that several diseases (e.g. goiter and cretinism) could be treated by extracts of the thyroid. In the first few years of the twentieth century, the new field of endocrinology was blossoming and many investigators were searching for the pancreatic extract. However, the initial studies produced conflicting results and many red herrings and experienced researchers learned to be cautious of "pancreatic extract" effects. With the hindsight of history, Bliss (1982) identifies several researchers who might have been on the right track, but it is clear that the evidence did not point clearly in any one direction when Banting approached MacLeod in Toronto to do his dog experiments.

She died in 1981 from a heart attack after 43,000 insulin injections and a full life rescued from the "nightmare" years of starvation before insulin.

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Early on diabetes was diagnosed by the sweet taste of the diabetics urine but knowledge about the etiology of the disease was scant. Reines (undated, p. 9) then suggests that the first link between diabetes and the pancreas was demonstrated by Thomas Crawley in 1788 when he discovered multiple calculi in the pancreas of a patient who had died of diabetes. Other autopsy studies on diabetics confirmed Crawley's observation and suggested that the pancreas was the most likely organ affected in this disease. Then, in 1869, Langerhans found two cell populations in the pancreas, one of which secreted the digestive juices but he did not know what the other cells did (these were the beta cells that secreted insulin).

According to Bliss (1982, p.25) (and contra Reines), evidence connecting the pancreas and diabetes was still tenuous in 1889 when Oskar Minkowski and Joseph von Mering made their discovery. They had removed the pancreas from a dog to see if the pancreatic digestive enzymes were vital to the digestion of fat. Minkowski noticed that the dog was urinating on the laboratory floor even though it was house-trained and tested the urine for sugar (he had been told by his supervisor to test for sugar whenever he saw polyuria). He discovered that the dog had become diabetic. This led the way for other researchers such as Hedon who, in 1893, proved in further experiments on dogs that the pancreas produced an internal secretion into the blood stream which controlled the metabolism of carbohydrates (Bliss, 1982).

This discovery unleashed a flurry of research aimed at producing a pancreatic extract that could be used to treat diabetes. This approach grew out of other work in the 1890s that had showed that several diseases (e.g. goiter and cretinism) could be treated by extracts of the thyroid. In the first few years of the twentieth century, the new field of endocrinology was blossoming and many investigators were searching for the pancreatic extract. However, the initial studies produced conflicting results and many red herrings and experienced researchers learned to be cautious of "pancreatic extract" effects. With the hindsight of history, Bliss (1982) identifies several researchers who might have been on the right track, but it is clear that the evidence did not point clearly in any one direction when Banting approached MacLeod in Toronto to do his dog experiments.

She died in 1981 from a heart attack after 43,000 insulin injections and a full life rescued from the "nightmare" years of starvation before insulin.
Reines (undated, p.3) argues that "... it is clear from the factual evidence presented in Bliss' book that the animal experimentation which preceded the discovery of insulin was not part of the scientific process that led to the discovery of insulin" and he and others credit a clinical observation for stimulating his dog research. According to a booklet produced by the Australian Association for Human Research (1988, p.7), "... the real breakthrough came through the clinical work of an American pathologist, Dr. Moses Barron" who published a paper on a patient with a rare case of pancreatic lithiasis in which the stone blocked the main pancreatic duct. He reported that, while the acinar cells had atrophied, the islet cells appeared to prepare pancreatic extract by ligating the pancreatic duct and waiting for the acinar cells (that were proposed to contain a substance that destroyed the 'active principle' in the pancreas) to atrophy.

One breakthrough in diabetes research that occurred prior to the Toronto team's success, and certainly is part of what made their work successful, was the development of an easy and accurate way to measure sugar in the blood. Bliss (1982, p.40) states, "The single most important development in diabetes research, next to Allen's diets, was the rapid improvement between about 1910 and 1920 in techniques for measuring blood sugar." This development was so important because it permitted the measurement of blood sugar directly rather than the less accurate measure of a reduction of sugar in urine.

Another important ramification of the development of a better technique to measure blood sugar was that it quite possibly influenced Macleod's decision to encourage and assist Dr. Banting with his experimental ideas. Macleod certainly knew that other researchers had failed to isolate a useful pancreatic extract to treat diabetes, but also must have known that "... almost all experiments done in the past, with pancreatic extracts or by any other method, might show different results now that blood sugar could be tested easily and quickly" (Bliss, 1982, p.53). So, when Banting approached Macleod with his idea of how to isolate an anti-diabetic substance from the pancreas, Macleod agreed that the experiment was worth trying and agreed to provide Banting with laboratory space, some dogs, an assistant, and guidance.

Banting and Best's research on dogs during the summer of 1921 is well known but Bliss (1982) uses material from the original data books to point out the numerous errors in their research and their reporting of it. However, the results were sufficiently encouraging for Macleod to call on the services of Collip, a biochemist, who started working to purify the pancreatic extracts. One of Collip's key contributions at this stage was to demonstrate that the potency of the pancreatic extract could be readily tested by measuring its blood-sugar-lowering ability in normal rabbits. He was later responsible for describing the hypoglycemic shock reaction (and associated convulsions) and for showing that it could be reversed by the administration of glucose in his rabbit studies. When it came time to prepare insulin extracts from farm animal pancreases on a commercial basis, an animal

convulsion test became a critical part of ensuring that batches of relatively uniform potency were distributed.

One can question the role of the dog studies done by Banting and Best and it is clear from Bliss's (1982) analysis that insulin would have been discovered within a year or two even if Banting had not been given space by Macleod because of such technical developments as a better test for blood sugar. Nonetheless, animals, notably the rabbits used by Collip, played a critical role in the successful isolation of insulin. Reines's argument that animal research had not led to the discovery of insulin while also claiming that Banting and Best's (invalid) hypothesis stemmed from a clinical observation published by Barron is, to the say the least, paradoxical. If the animal research was unimportant, then the clinical observation that led Banting to his studies must also have been unimportant.

Ultimately, what the insulin discovery story demonstrates all too clearly is the difficulty of biomedical research, the sloppiness of some of the work, the frequent blind alleys followed by both clinical and experimental investigators, and the mixture of chance, technique availability, clinical observation and animal experimentation that all play a role in advancing knowledge.

B. The polio vaccine story

The history of the discovery of the polio vaccine shares many features with the discovery of insulin. Like the discovery of insulin, the discovery of the polio vaccine has been described in grand terms such as "... one of the greatest technical and humanistic triumphs of the age" (Paul, 1971, preface). Like diabetes, polio had no satisfactory treatment, could be fatal, and children were among those affected (polio primarily affected children). In addition, polio appeared in epidemic form in countries with high standards of hygiene and did not appear to be preventable by leading a healthful life.

Early attitudes toward polio were dominated by a feeling of hopelessness. As the disease grew into a national problem, parental concerns grew and mothers would keep their children away from communal places in the summer because of fear of the disease. It has also been suggested that some 'epidemics' might have been caused by mass hysteria, exacerbated by such treatment patterns as putting casts on any limb that appeared to show signs of weakness, rather than actual infection (Paul, 1971, p. 224). When the vaccine for polio virus was finally developed, the success due was to the efforts of many researchers over a long period of time building on knowledge gained through experiments involving animal and non-animal methods. The animal experiments have also become the focus of criticism from animal activists, probably because polio is often presented as a triumph of animal research.

The major criticism that appears to be leveled at animal research on polio is encapsulated in the statement that, "Tragically, animal experiments so dominated
research that prior to 1937 most scientists rejected the notion that polio is an intestinal disease" (Sharpe, 1993). This claim is usually bolstered by reference to Paul's (1971) magisterial history of the polio story that describes the wrong direction taken by Flexner at the Rockefeller Institute as a result of his reliance on monkey data. However, as Paul also documents, there were many other missteps in the search for a therapy for polio, many of which were advanced by clinical investigators.

Polio is unlike diabetes in that it occurred in epidemics that developed out of a previous endemic condition. The transition of the disease from endemic to epidemic occurred with, and was due to, the development of modern sanitation. With modern sanitation, children were not exposed to polio virus in infancy when the infection is usually silent. Without early exposure children were not naturally immunized against polio virus, and therefore large numbers of them could be infected at one time, leading to the appearance of the epidemics. In addition, older children are more likely to suffer the associated paralysis (Marten, 1981). Therefore, one cannot argue that polio would have been prevented by better public health measures.

With the advancement of scientific knowledge about the nature of contagion and infection, the etiology of polio slowly began to be puzzled out. With such knowledge came a growing hope that there could be a way to prevent or treat this dreaded and apparently spreading disease (Paul, 1971). Knowledge from many different scientific approaches, including epidemiology, clinical studies, animal experimentation and in vitro studies came together to build the knowledge base that allowed the development of the polio vaccine.

Both Pasteur's and Koch's theories of contagion and infection, and the birth of histology, were important steps in the path to a polio vaccine. Before the advent of histology, the site of the lesion of polio virus was not agreed upon, and so polio (a name based on the site of the lesion) was usually known as Infantile Paralysis. In 1870 Charcot discovered, through examinations of autopsy specimens (clinical work), that the anatomic location of the lesion was in the anterior horn of the gray matter of the spinal cord, rather than in the muscle or peripheral nerves. Later examinations of the spinal cords of monkeys sacrificed at different stages of the disease (animal research, and studies that could not be done with human polio patients) helped elucidate the degenerative nature of the lesion.

The pathologic organism of polio was also not agreed upon until 1908 when Landsteiner and Popper infected two primates with polio by injecting them with bacteriologically sterile spinal cord samples from a fatal human case of polio (Paul, 1971). The importance of this experiment in leading to an understanding of polio, and in helping explain why the monkey model was chosen time after time by researchers, is expressed by Paul (1971, p.100):

Seldom has the record spoken louder or in a more convincing

manner than it did when one of these monkeys "came down" with paralysis, and louder still when they were shown to have lesions within the spinal cord exactly like those seen in human poliomyelitis.

The monkey model convinced even skeptics that polio was caused by a virus.

Subsequent to Charcot's 1870 discovery of the site of the spinal cord lesion, Rissles, in 1888, pointed out the extra neural lesions of acute polio. His findings led him to the correct conclusion that polio is actually a systemic disease rather than exclusively neurologic. Many years later, in 1912, a team headed by Carl Kling in Stockholm, isolated polio virus (by infecting monkeys) from the throat and small intestine of both fatal and acutely ill polio victims. These findings indicated how polio virus might enter and exit the body, and therefore how it is transmitted. One member of Kling's team correctly concluded from epidemiological studies that immunity to polio could be naturally acquired through the process of sub-clinical infection. However, these data were soon forgotten or ignored as new studies (including both animal and clinical investigations) painted a different view of polio (Paul, 1971).

Paul (1971, p. 108) notes that Flexner was so impressed by how closely the primate neurological lesions resembled those in humans that he decided that one could study the disease in either monkeys or humans and he chose monkeys. Unfortunately, his studies on monkeys led him to determine that polio was a neurogenic infection and his stature in the field caused many to follow this idea. This led people away from the fact that polio might be a systemic infection but claims that this false step retarded the development of the vaccine can be disrupted. The technological advances in tissue culture that permitted the production of large quantities of virus occurred during and immediately after the war and not from 1910 to 1937 when Flexner's ideas held sway.

However, Flexner was not the only person to pursue false leads. A number of strange theories were proposed. One such was George Draper's 1917 theory of "constitutional susceptibility," which he formulated through his clinical investigations of children with polio. He concluded that "... large well-nourished children with widely spaced teeth..." (Paul, 1971, p. 162) were more susceptible to polio than other children. While this conclusion may now appear ridiculous, it was widely supported for the next twenty years and it was even suggested that, had a prophylactic measure been developed, it should be reserved for those children who qualified as susceptible by Draper's standards (Paul, 1971). These examples, one from clinical research and one from animal experimentation, demonstrate that neither approach was immune from error.

In 1931, Burnet and Macnamara made the important discovery that there were serologically different strains of the virus using monkeys (Paul, 1971). Their findings later inspired the 1946 virus-typing project using large numbers of monkeys that was very important in the development of a vaccine (Paul, 1971).
Monkeys were not the only animals used for polio research. In 1935, Maurice Brodie and his colleagues succeeded in adapting polio virus so that it could infect mice (Paul, 1971). In 1939 Charles Armstrong, and later Max Theiler, succeeded in experimentally infecting cotton rats and later mice, with the Lansing strain (Type II) of the polio virus. These findings were important because they facilitated an expansion of polio research, due to the much reduced cost of experiments on mice compared to monkeys. Another important insight from mouse studies was the finding that the virulence of polio virus could be attenuated without losing its ability to immunize (Paul, 1971). This pointed the way to the development of the live-attenuated Sabin polio vaccine.

Another major contribution to polio research came in 1948 with the successful growth of polio virus in cultures of human "non-nervous" tissue developed by Enders, Weller, and Robbins. The availability of reliable cell culture technology now made it possible to quantify the amount of virus in a tissue culture sample, and to replace monkey use with tissue culture for many purposes. This technique was critical in leading to the production of a polio vaccine from non-nervous tissue (a far safer alternative), containing an accurately measured amount of virus (Paul, 1971). The development of antibiotics to control bacterial overgrowth in tissue culture was a very important preliminary step leading up to the finding by Enders and his colleagues. So, while the final Nobel Prize winning "discovery" in the polio vaccine story was an "alternative," its development involved innovations derived from animal research.

The use of animals in polio research and production has declined dramatically since hundreds of thousands of monkeys were used every year in the 1950s at the height of the race to develop a vaccine. This decline can be attributed to improved technology and the implementation of alternatives. For example, further technical improvements led to dramatic reductions in the annual use of animals in polio vaccine (inactivated) production in The Netherlands from 4,500 in 1965 to 30 in 1984 (Hendriksen, 1988, p. 59). The debate about animal use in current methods of production and testing of poliovirus vaccine is described in detail in other books and articles on the subject of polio (see Hendriksen, 1988; LeCormu and Rowan, 1979; Marten, 1981; and Rowan, 1954). However, the polio vaccine story is another excellent illustration of the interlocking nature of different research approaches, the triumphs and missteps, and the way improved technology and changes in societal attitudes has led to dramatic reductions in animal use. Thus, the polio story can be used to bolster claims for both the utility of animal research and the potential of alternatives. It cannot be used as a good example of research error induced by reliance on animal models unless one is willing to accept that clinical research and other research approaches are equally susceptible to such errors.

References
Historian and philosopher of science Thomas Kuhn notes that every scientific age has its "paradigms," theories nearly universally regarded as true that form the framework for ongoing scientific investigations. Paradigms are rarely challenged until overwhelming contradictory evidence forces their revision or rejection. A currently dominant paradigm is that animal "models" are necessary for medical progress. However, critics of animal models argue that they are inherently flawed and point out the frequency with which animal models provide misleading information.

All species differ; animal-model conditions never exactly mimic human ones. Animal models are only analogues of human conditions because they share certain characteristics. Philosophers Hugh LaFollette and Niall Shanks observe that animal models are used primarily for two functions— to predict human responses to stimuli (such as infectious, traumatic, or toxic conditions and therapeutic drugs or devices) and to offer new ways of conceptualizing human anatomy, physiology, or pathology. Researchers who use animal models employ the following reasoning: a given animal model resembles an analogous human condition in some of its features (say, A, B, and C); therefore, it is reasonable to proceed as if an additional feature (D) found in the animal model—for example, a physiological function or a drug response—can be expected to be a feature of the human condition as well. As LaFollette and Shanks point out, this assertion is logical only if feature D is causally related to A, B, and C— in both the animal model and the human condition. That is, A, B, and C must be causal factors of feature D. The following reasoning illustrates a failure to recognize the importance of causal relationships:

Two dogs bark, love bones, and wag tails when their human companions arrive home; because the two dogs are similar in these respects, they can also be expected to be of the same breed. If we know the first dog's breed, we can reliably predict the second's.

Breed, however, is not causally related to the three features that the two dogs are already known to share. If we know a dog's breed and we also know that a second dog has the same parents as the first, then we can reliably predict the second dog's breed— even if the two dogs differ in many other respects, such as coat color or temperament.
LaFollette and Shanks distinguish between weak and strong models. Strong animal models are identical to the analogous human features in all causally relevant respects, and research using such models can be confidently applied to humans. Although many animal research advocates assert that animal models faithfully reproduce human conditions, LaFollette and Shanks argue that most animal models are weak models of little direct applicability to humans. Although they do not reject animal research's value, they do note that animal research advocates often assert that animal models faithfully reproduce human conditions, even though most animal researchers recognize that animal models tend to be weak analogues with limited utility. LaFollette and Shanks maintain that animal models, as actually used by researchers, may be helpful but are probably not necessary for medical progress.

In public, animal research proponents often suggest that weak causal models are in fact strong. For example, the Stanford Committee on Ethics states, "Cancer kills humans and animals alike." At any but the most simplistic level, the comparison immediately begins to break down. For example, in their causes malignancies that are experimentally induced in nonhuman animal and malignancies that occur spontaneously in humans differ significantly. Other important differences include the greater virulence of most experimental cancer strains and differing mechanisms of tumor growth and metastasis. Even nonhuman cancers that apparently share many characteristics with human cancers make unreliable research models, since human and nonhuman cancers inevitably differ in some relevant causal factors. Viewed in this light, an animal model such as the mouse-leukemia model is a poor means of attempting to identify potential anti-cancer drugs, and this model has, in fact, proved grossly inadequate.

Even if a disease's main causal factors were well understood—and were alike—in both humans and other animals, animal models would still be undermined by systemic differences between animal models and human conditions. Because of evolutionary divergence, species show differences in virtually every aspect of organ and tissue function. All organ subsystems interact, so every physiological difference between two species likely affects every given factor. Consequently, all tissues of an animal model will tend to react to an experimental manipulation differently than a supposedly analogous human condition. Animal models of human conditions tend to provide only the most obvious and general information, such as that cancers kill; in order for them to provide reliable and specific information, the model and the human condition must have identical causal factors and have no significant systemic differences that affect these causal factors. This is impossible, since there are always differences in causal factors between the model and the human condition and because systemic differences are an inevitable consequence of evolutionary divergence.

In theory, then, animal modeling is unreliable in predicting human responses to stimuli; and it has proved so in practice. Animal tests of acute lethal toxicity, eye irritation, skin irritation, teratogenesis (birth defects), and carcinogenesis have generally provided inconsistent results and failed to correspond to human experience. R. Heywood has estimated that only about 5-25% of toxic effects found in animal experiments occur in humans. Of course, animal models can serve as strong models when researchers attempt to predict gross toxicological effects, such as the ability of strong acids to burn the eye's surface; however, such effects could readily be predicted from the most rudimentary knowledge of chemistry. Most animal tests are supposedly intended to identify subtle effects, and they perform poorly in this regard.

Animal tests have also proved inadequate as a means of identifying potentially useful drugs. U.S. law requires that drugs be found effective and safe in animal testing before they are tested on humans. This law fails to reflect animal tests' poor predictive value: Ronald Hansen found that only about 12% of drugs that passed Phase I animal tests and entered human testing reached the market; earlier, Samuel Irwin had found that only 2.3% of drugs selected for clinical trial were eventually marketed. Most new drugs are similar to existing drugs, and so their clinical effect can be at least partially predicted based on structural analogy. Also, modern biochemical methods can help characterize specific drug-receptor interactions, and these interactions can suggest specific drug effects. Therefore, it is debatable whether animal tests help identify which drugs are most suitable for human clinical trials (the critical step in determining human safety and efficacy).

In addition to having failed to accurately predict drugs' efficacy and toxic side-effects, animal tests have, no doubt, prompted researchers to abandon numerous drugs and therapies that proved ineffective or toxic in nonhuman animals but would have benefited humans. It is impossible to determine how many valuable therapies were discarded on the basis of misleading animal studies.

Are animal models worthless, then? Although causal dissimilarities and systemic differences undermine animal models, they are not necessarily useless. For example, animal data need not accord perfectly with human data to be relevant. For example, animal data may be valuable in theory, but in practice they are generally inconsistent and misleading.

Although most animal models are weak models, strong ones are possible. As mentioned above, certain animal models can reliably predict gross toxicological effects. Canaries were once used to test for carbon monoxide in coal mines because canaries are much more sensitive to this toxic gas than humans. Animal models can also be useful in studying infectious agents. Although animal models cannot reliably elucidate mechanisms of disease induction and spread in humans, they have, in the past, afforded strong models for research on the organisms themselves. To illustrate, rats infected with the syphilis spirochete yield little insight into
human syphilis infection. Nevertheless, Erhlich discovered arsenobenzol as a treatment for syphilis by infecting rats with the spirochete and then trying different compounds for possible anti-syphilis effect. For Erhlich's studies, rats served primarily as reservoirs to harbor the organism, facilitating research on the organism itself. The many systemic differences between rats and humans did not significantly undermine his research. Today, in vitro cultures have replaced animals as mere reservoirs for almost all infectious agents.

Also, animal models may provide information about the species under investigation because there are generally few major differences in physiological parameters among individuals of the same species. Most animal experimenters, however, claim to address human health issues.

Many philosophers of science have distinguished between validating (or disproving) hypotheses and formulating them. An animal model cannot be used to test a hypothesis about humans because differences in causal factors between the animal model and the human condition render the animal model invalid as a predictor. The only way to support or disprove a hypothesis about human anatomy, physiology, or pathology is by studying human beings. Animal-model conditions are analogues, and it is impossible to validate or disprove any hypothesis by analogy. Therefore, logically animal models cannot directly contribute to medical discovery. Medical historian Brandon Reines maintains that animal models primarily "dramatize" hypotheses about humans without actually validating or disproving them.

Although animal models cannot validate or disprove hypotheses, they may function as heuristic devices that assist the process of discovery. That is, they may suggest different ways of conceptualizing problems and thereby help generate new hypotheses. In this regard weak models have potential value. An unexpected finding during animal experimentation (including experimentation that was poorly conducted or that failed to accomplish its original objectives) may lead to an insight.

Such insights, however, can also arise via other research approaches, such as observing human patients, conducting epidemiological studies, performing in vitro tests, or engaging in computer or mechanical modeling. Once again then, animal models do not appear to be necessary for medical progress. In fact, medical historian Brandon Reines and physician Paul Beeson consider the role of animal models as heuristic aids very limited.

In a review of hepatitis research, Beeson writes: "progress in the understanding and management of human disease must begin, and end, with studies of man." Although much hepatitis research has used animals, Beeson has found that hypotheses about hepatitis have derived from clinical observations, and that clinical studies have been necessary to test their validity.

Reines observes that nearly all hypotheses about human conditions derive from human clinical research. Animal experimenters, he contends, perform the superfluous and irrelevant function of experimenting with different animal models until they find one that accords with the clinical findings: typically they then claim that their model has "validated" the clinically derived hypothesis. Often, Reines observes, animal modelers highlight confirmatory animal data while discounting animal data that contradicts their findings.

Although Beeson doesn't share Reines's conclusion that animal experimentation is largely irrelevant to medical discovery, he agrees that most insights derive from human studies. Beeson writes,

- "The initial observations of manifestations and courses of human disease must be made in human beings. The important contributions of epidemiology depend on accurate clinical definitions. The occurrence of rare sequels or late manifestations is beyond any feasible approach through experiments on other species." Beeson cites progress in understanding hepatitis, appendicitis, rheumatic fever, typhoid fever, ulcerative colitis, and hyperparathyroidism as representative of most medical progress in having occurred almost exclusively through the study of humans. Nevertheless, like other researchers who have acknowledged the primary importance of clinical investigation yet remain lodged in the animal-model paradigm, Beeson continues to maintain the importance of animal experimentation.

The history of polio research illustrates many of animal experimentation's strengths and limitations. Proponents of animal research frequently claim that animal experiments were crucial in controlling polio. John R. Paul's review of polio research indicates that animal experimentation facilitated some insights but delayed others.

In the 1800s, polio's clinical presentation and natural history were deduced from bedside observation and post-mortem studies of human victims. Ivar Wickman's detailed epidemiological analyses of two Swedish epidemics in the early 1900s revealed that mild or even subclinical cases contributed to contagious spread of the disease. Most investigators, focusing on polio's life-threatening paralysis, considered polio a central nervous system disease. But Wickman found that polio affects the alimentary tract (throat, stomach, and intestines) and suggested that the gastrointestinal system may be the initial site of infection.

By contradicting Wickman's observations, animal data delayed understanding of polio's true pathogenesis and natural history. The first animal model of polio was developed by Simon Flexner, who induced polio-like paralysis in rhesus monkeys after placing infected human tissue into their noses. Convinced that his animal research was necessary to test their validity.
model precisely paralleled the human disease, he concluded that human polio was introduced to the brain via the nose and confined to the central nervous system. For decades, most scientists adhered to this erroneous theory, and this led to misguided therapeutic measures.47

While animal studies remained the principal focus of polio research in the United States, Swedish clinical investigators continued to make important contributions. They tested for the presence of polio in tissues of polio victims and family members by inoculating monkeys with test samples. If a test monkey contracted polio, the sample was determined to be infected. The investigators found that polio carriers could have polio virus present in their throats and intestines up to seven months after exposure.

Meanwhile, Flexner and other animal researchers continued to study rhesus monkeys infected with viruses obtained from other rhesus monkeys. This process selected for more virulent polio strains that tended to infect nervous tissue. Consequently, the animal model increasingly diverged from human polio in pathogenesis and natural history. Systemic differences between humans and rhesus monkeys undermined Flexner's animal model as a causal model of human polio.

In the 1940s researchers found that polio infection in chimpanzees accords more closely to the human disease. Like humans and unlike rhesus monkeys, chimpanzees were found to harbor the polio virus in their alimentary tracts. Researchers were now more willing to accept the clinically derived hypothesis that polio infects the human alimentary tract. But this response merely demonstrates the research establishment's reluctance to accept clinical findings in humans until parallel findings have been produced--however artificially--in the laboratory in another species.

Animal models of polio were not very helpful as causal models, and they significantly delayed development of an effective vaccine. After clinical studies showed that polio virus infects gastrointestinal tissue, decades of experimentation on rhesus monkeys suggested that the virus infects only neural tissue. Vaccine researchers mistakenly believed that polio would only grow in neural tissue, but vaccines derived from these cultures were too dangerous. In 1948, John Enders, Thomas Weller, and Frederick Robbins grew polio on human intestinal tissue, which led to a safe vaccine. Albert Sabin, who developed the Sabin oral polio vaccine, has written,

"The work on prevention was long delayed by an erroneous conception of the nature of the human disease based on misleading experimental models of the disease in monkeys."50

Nevertheless, animal experiments may have served heuristic functions by inspiring new ways of thinking about polio. For example, studies of other central nervous system diseases in animals suggested environmental roles in susceptibility to infection. Similarly, studies of TO virus encephalitis in mice revealed that animals infected early in life tend to have a more benign course: after initial exposure to virus, mice become immune.51 Researchers reasoned that, by analogy, early childhood exposure to the polio virus might protect most children from paralytic disease. This would explain why major epidemics tended to occur in remote areas, where populations were too sparse or isolated to permit an endemic state of polio infection. This insight, surely, did not require animal studies, but it is possible the TO virus research helped scientists conceive this theory. The TO virus model illustrates the limited utility of weak models.

Some strong models were also used in the fight against polio. Swedish investigators used monkeys to test for the presence of polio virus in tissue samples; later, researchers used the mouse neutralization test for similar purposes. In addition, monkeys were used in immunological studies that demonstrated multiple distinct viral strains. In these cases, however, researchers merely assessed whether or not the animals became infected under different conditions. Today the absence or presence of a virus in human tissue can be more reliably determined using in vitro methods.

In theory and practice, animal models generally fail to reliably predict human responses to stimuli. While some strong models exist, most are weak models of human responses to stimuli. Weak models may serve as heuristic devices and inspire new ways of conceptualizing clinically relevant issues, but this does not mean that animal models are indispensable analogues directly applicable to humans. As merely heuristic devices, animal models are not necessary for progress in human medicine.

**DISCUSSION**

Following Dr. Kaufman's talk, Dean Loew stated that it was hard to argue with much of what was said but asked Dr. Kaufman what he felt about the gamut of an understanding of human and animal diseases by looking at animals and their induced diseases. Dr. Kaufman replied that even observing naturally-occurring diseases can still be misleading for human medicine as the animal models are not the same physiologically as humans. Dean Loew then mentioned several examples where observation of one animal disease or abnormality has led to advances in knowledge for another animal disease.

At that time it was pointed out by one participant that there is an important logical distinction that must be made--it must be remembered that an animal model with a natural or induced disease is still merely a hypothesis for the same disease in humans. The animal is a heuristic device and the information gathered from the animal model must be tested in humans.
Another participant pointed out that not all induced animal models are the same—there is a spectrum of usefulness with some models being strong and some models being much weaker. Animal models of basic biochemical and physiological processes (like neurotransmitter action) are stronger models than those of disease processes. The comment was then made that it is usually just taken for granted that all animal models are useful. It was pointed out that animals generally prove to be strong models in toxicology testing.

The observation was made that some animal studies are simply used as a graphic illustration to dramatize rather than generate or test hypotheses. The use of primates in studies of violence was given as an example.

It was asked by a participant what would be used if one could not use animal models and pointed to multiple sclerosis as an example of a disease about which much was learned from animal studies. Another participant suggested the use of in vitro cultures or human tissues although it was admitted that animal tissues are more readily available. Then, based on the results of these studies, animal models and/or human studies could follow remembering that models may not always give correct information and can even undermine an experiment.

This discussion was concluded with the reminder that it is important where one starts and what are the personal values involved. Researchers can believe 1) that animal use as models is always good 2) that a variety of approaches is preferable or 3) models should not be used.

References


PUBLIC HEALTH PREVENTION AND OTHER ALTERNATIVES TO ANIMAL RESEARCH

Neal D. Barnard
Physicians Committee for Responsible Medicine

(The text is developed from the editors' notes. Dr. Barnard's talk was illustrated by a slide presentation using many graphs, charts, and lists.)

Dr. Barnard began his presentation by pointing out that one of the difficulties with the continuing animal research debate is that the protagonists not only have different viewpoints but are addressing different questions and issues. He feels that the central questions are not how to replace animal experiments but:

1) If animals do suffer, how do we end those experiments? (He stressed that, when determining the existence of suffering, the effects of confinement and stress should be considered as well as traditionally-defined pain.)

2) What are the best methods for improving public health?

The term "alternatives" is one that Dr. Barnard would like to retire as it implies that animal experimentation is the preferred method of research and anything else is less. In fact, animal use is itself often an alternative -- an alternative to using humans. He would also like to eliminate the term "biomedical" as it is often used when there is no true medical connection to biological research.

Dr. Barnard stated that in most cases human cures are not forthcoming from animal studies - animal research is not solving the problems. He feels it is not necessarily useful to define the mechanisms of diseases through animal experiments or other methods. The most helpful studies are human epidemiological studies that reveal the differences in the conditions of those who have a disease and those who don't, the risk factors involved, and recommended beneficial public policy changes. However, we, as a nation, have not yet decided to deal with public health problems. (In addition, "big" company money and lobbying often conflict with research, e.g. the tobacco companies and cancer research.) After citing several medical articles on tobacco written in the 1960s, Dr. Barnard pointed out that if researchers had not used animals in tests early on, but instead looked at the human condition, they would probably be much further ahead now. Animal experiments suggested that inhaled tobacco smoke is not a carcinogen, while epidemiologic studies showed that it is. On the other hand, animal tests have shown that dietary fat is linked to mammary tumors in agreement with human epidemiologic studies. In both cases, animal experiments were interpreted to maintain conservative views. Experiments suggesting tobacco is not carcinogenic carried political weight, while those indicating dietary fat have been largely ignored.
Dr. Barnard presented a series of slides dealing with human dietary studies, which showed the value of epidemiology to clinical studies. One visual, a graph, dealt with the relationship of cholesterol levels and risk for coronary heart disease and showed that a 1% increase in cholesterol leads to a 2% increase in the risk for heart attack. Other slides revealed the amount of cholesterol in specific foods and showed that blood cholesterol increases 5mg/dl, on average, for every 100 mg of cholesterol in the routine diet. Several slides supported Dr. Barnard's claim that a vegetarian diet reduces cholesterol. He stated that saturated fats cause the liver to produce more cholesterol so it is therefore not as helpful as some have thought to switch from beef to chicken, as skinless chicken has 23% fat content while the leanest beef has 29% fat. Ovolactovegetarians have lower cholesterol levels than omnivores, and vegans have the lowest levels of anyone.

In a discussion of heart disease, Dr. Barnard stated there are one and a half million heart attacks every year in the U.S. and the total health care costs for heart disease is 40.4 billion dollars a year. However, the diet promoted by the American Heart Association has shown little progress in lowering cholesterol levels while a vegetarian diet has often been shown to lower the level of cholesterol and to help, along with other steps, to reverse atherosclerosis. Dr. Barnard stated that researchers are at times distracted by looking at the microscopic aspects of this disease rather than the overall picture which would indicate a need for obvious changes such as diet.

Breast cancer also appears to be related to dietary intake of fats. A slide revealing data on breast cancer indicated a direct correlation between fat intake with death rates from breast cancer. The same appears to be true with prostate cancer. Another slide illustrated that both dietary fat and body fat result in increased estrogen production which is believed to increase the risk of breast cancer. It appears that factors that increase survival from breast cancer include low fat intake, low body weight, and high fiber, carbohydrate and beta-carotene intake.

Dr. Barnard's slides illustrated how cancer rates overall in the U.S. have gone up slightly between 1960 and 1985, with cancer death rates having risen dramatically for lung cancer, risen slightly for breast cancer, held roughly even for prostate cancer, and dropped for colon cancer. Every year in the U.S., 1,170,000 cases of cancer are diagnosed and 526,000 people die of cancer. Cancer treatment costs 35 billion dollars a year. However, while traditional diagnostic techniques such as mammography are highly publicized, the connection between diet and cancer is rarely discussed.

Hypertension treatment costs the U.S. 12.5 billion dollars annually and diabetes treatment costs 6.8 billion dollars annually with 10 to 14 million Americans suffering from diabetes.

Dr. Barnard does not suggest that changed life styles will help everyone but states it is incongruous that the U.S. government continues to promote the eating of meats and dairy products even though epidemiological and clinical studies suggest links between these products and disease. Cows' milk can encourage the onset of juvenile diabetes. He then explained the difficulties associated with gaining widespread acceptance for the new "four food groups" -- grains, legumes, vegetables and fruits.

Dr. Barnard concluded by restating that it is not useful to think of prevention as an alternative to animal use. However, animal studies distract us from vital research and lead us away from making important lifestyle decisions.

DISCUSSION

In the discussion following his talk, Dr. Barnard was asked what he feels is the better investment for the dollar. He replied that the wiser expenditure was for studies of life-styles and that animal experiments are a poor investment.

Dr. Barnard stated that there is new trend that concerns him -- the "dissecting" of diets in healthy cultures to find a "magic bullet" followed by the testing on animals of the suspected "bullet." These experiments are simplistic and unnecessary.

He was asked to comment on the lack of public reference to vegetarians and vegans. He replied that some members of the public are still resistant to vegetarian diets. A representative from Tufts Veterinary School pointed out that possibly there is a change on the horizon as, at the 1993 graduation dinner, 20% of the graduating veterinarians choose a vegetarian dinner compared to 2% in earlier years.

When asked if he would deny people other treatments, he replied that he would not. People who will not make lifestyle changes cannot be denied treatment and despite best efforts, people still get sick with non-preventable diseases. However, people are not doing enough to make even the simplest changes even though there are certain identifiable factors that can get people to change their diets. There is a definite need to study behaviors and encourage cultural changes. Animal experiments, he felt, are not the keys to prevention or to treatment.
Dr. Shapiro organized his response to the several papers under four headings: ethics, science, the concept of animal model, and costs/benefits analysis.

1. Dr. Shapiro began his response by observing that the title of the seminar, The Value and Utility of Animals in Research, presupposes a utilitarian viewpoint or ethic. However, this philosophy is only one of several competing philosophies in the current debate and one that is frequently criticized for failing to preserve the interests of the individual. Further, it is a philosophy which scientists, who do not like to think of themselves as talking about ethics, implicitly adopt. For utilitarianism allows them to apply ethical considerations using the familiar scientific language of measurements and results. However, despite the adoption of utilitarian talk about costs and benefits, in reality, scientists rarely actually do a cost/benefits analysis in anything approaching the rigor of scientific measurement. They also fail to recognize the complexities and problematics involved with applying such a calculus to evaluate animal research.

In any case, having invoked utilitarianism, the title leaves out the "costs" side of that ethic.

While realizing that the focus of this seminar is not the ethical but the scientific issues in the current debate, Dr. Shapiro presented his view that to achieve basic change, attitudes must change, and discussion of ethics is a primary vehicle for achieving it. More insidiously, "value and utility" talk can be an attempt to sidestep and downgrade the role of ethics by framing the issue as strictly a scientific question that must be answered by scientists in scientists' terms. However, many thinkers believe that the attitude or ethic regarding the value of nonhuman individual animals is of more consideration than any argument about utility and how to measure it. Garner says:

The debate then is ... not exclusively (or even mainly) about facts but is about the differing perception of what should be regarded as unnecessary suffering--which are inextricably linked to the moral status of animals.

A primary datum is that some people value animals and some do not.

2. The purpose of this remark is not to downgrade science but to restore it to its proper role. While science is incredibly resourceful, it is not what we thought it
The traditional view of science has been challenged in recent years by philosophers, sociologists, and historians of science.

The traditional view, referred to as positivism or modernism, featured a naive view of reality in which the scientist was a detached observer who could directly observe the facts and apply logic to them to arrive at the truth. By contrast, in the constructionist or postmodernist view, science is a socially-constructed enterprise. As much as it might espouse an ethos of logical empiricism, the scientific enterprise, like any other complex social institution, in practice is a competitive, conflictual, political and generally messy affair.

Incidentally, when applied to animals in the lab, this philosophy and sociology of science results in the view that the lab animal is itself a construct—that a distinct category of animal has been created—the animal not as individual or even member of a species, but as a receptacle for disease, an instrument, a preparation.

In the postmodernist view, science's insistence that there is just one way to reach the truth, that if we follow certain procedures we can be assured (positive) of the validity of our results, is displaced with the more pragmatic notion that the ways are inexhaustible and no one method has primacy. Science is a human project in which many approaches and alternatives are available.

This new view of science has ethical implications. Science is a human project in which there are choices and options. Science has no special status that somehow places it outside the present and changing values and needs of society. As with any other social practice, it is not within the purview of science to decide the ethical and policy issues that frame its own practice. In the final analysis, the public must decide the limits of any institutional practice, including the practice of science.

The thrust of the postmodernist view of science restores science to its proper role, recognizing it as a social enterprise that is a particular set of methods of trying to understand things. It has no special access to the truth and is subject to the same individual foibles and institutional faults as any other human enterprise.

In responding to Dr. Kaufman's presentation on scientific problems with animal models, Dr. Shapiro outlined four concepts of animal models—the animal as a host, as a causal analogue (strong analogy), as a heuristic analogue (weak analogy) and as a rhetorical device. His thesis was that contemporary animal models at best operate as heuristic devices and, at worst, as mere rhetorical devices. Notwithstanding this, various professional associations and individual scientists make the stronger claim that animal models provide causal analogues.

The idea that an animal model could provide a causal analogue of the target phenomenon—that is, an exact duplication of the mechanism producing it—originated in the late 19th century with Koch and others. The germ theory of disease in which the investigator infected an animal with a pathogenic bacterial organism led to the notion that the animal is simply a receptacle for the target phenomenon which is recreated identically in the animal site. TB is TB. The animal model, then, in this view of disease, duplicates the causal mechanisms of the human pathology. Both contemporary diseases, which are not primarily infectious or germ entities and contemporary theories such as systems theory and chaos theory show that the simple idea of the animal as host or receptacle for a phenomenon simply transported to a different species site is wrong-headed.

Animal models do not duplicate the causal relations of the original phenomenon—they are properly conceptualized as heuristic devices—ways of generating ideas and insights. These ideas must eventually be applied in the human context. This application is not so much a validation as a testing of whether the idea is useful. (For example, ideas that suggest differences between animal and human-based phenomena may be useful, although not "valid.") The claim that animal models provide a site in which the causal mechanism of interest can be duplicated and discovered is anachronistic, and needs to be understood in terms of political and public relations consideration.

There is misuse of even this proper heuristic function of animal models. For example, in psychological research, this misuse of the proper heuristic function of animal models is evident, as often a strong analogy is claimed, a "hypothesized parallelism of causal relations" emulating the natural science. However, on its face, when using animals to study such things as drug addiction, antisocial behavior, or eating disorders, causal relations cannot be exactly duplicated. Often animal models in psychological research do not even have the less stringent function of providing a heuristic device. Rather, their use is limited to a rhetorical device. The model provides something closer to a graphic image than a discovery of a causal mechanism. There are other problems with the use or misuse of animal models. Too often validation is ingrown as it is limited to comparing research on a model to other research using the same model. This criterion of internal consistency also applies within certain literatures: "cat people" do not cite "rat people" let alone "clinical people."

In addition to the use of animal models as simply relatively loose analogies, sometimes there is a reversal in the proper relation of the model and the targeted phenomenon. Researchers begin with an insight gained in a human clinical setting and then construct an analogy to it through an animal model. A backwards confirmation is then required. The status of animal models is such that facts are only facts if they are proven in the laboratory with animals. In this use, the model's heuristic function is limited.

Recognition of the limits of proper use of animal models places a considerable ethical burden on the researcher. For example, arguable, highly invasive is unacceptable given this limited function.
In regard to Dr. Rowan's comments on the problem of costs/benefits (C/B) analysis, Dr. Shapiro took the general position that researchers currently are not using the several available scientific measures of invasiveness. In any case, in his view, there are inherent limitations in a purely scientific assay of C/B. The limitations follow from the heuristic function of animal models. It is clearly a problem of historical interpretation whether any particular animal model and, as well, whether animal models as a general research strategy, have generated useful applications and understanding compared to other particular nonanimal studies and general strategies.

Dr. Shapiro disagreed with Dr. Rowan's data on animal use which show that less than a majority of animals experience severe suffering. For the data is limited by the amount of information provided, particularly in the U.S., and by the information's reliability.

Dr. Shapiro took issue with Dr. Rowan's suggestion that if 40% of studies use animals, then we ought to give such research 40% of the credit for benefits. He also challenged Dr. Rowan's view that the clinic and the animal laboratory are an endless circle of reciprocal influence and that the taking of any one portion of this circle results in losing more than the portion removed. Dr. Shapiro stated that the mutual influence is minimal as the two typically do not cite or even read each other, and, when they do, the influence of what the clinic takes from the laboratory is largely rhetorical and often misleading.

He elaborated on this point in the case of psychological research, and particularly an article by Neal Miller referred to by Leader and Stark. Miller makes a case for the value of psychological research. Dr. Shapiro pointed out that Miller, a behaviorist, and others in psychology, stress that the benefits of animal use are high while the costs are low. They employ such utilitarian language because it is sympathetic to science with its heavy emphasis on instrumentalism. Behaviorism itself places emphasis on utilitarian notions of reward, pleasure, reinforcement, etc. In fact, the doctrine of psychological hedonism as a driving motivational force is the child of Bentham.

But, Dr. Shapiro states, this is lip service utilitarianism only for Miller and others do not present any scientific data on C/B. In place of providing results of a measure of the costs of a given study or animal model, there is a global denial that pain is involved in psychological studies. However, there are available several rating scales which measure the "degree of invasiveness" and other components of the "ethical costs." In a recent study on attitudes toward and the use of analgesics in 23 biomedical laboratories, Phillips (1993) documents the denial of pain by laboratory investigators and shows that the data often used to argue the absence of pain, according to the USDA annual reports submitted by the primary investigator, are not reliable. Dr. Shapiro stressed that psychology can not claim, as it does, to have developed animal models for virtually every conceivable harmful, distressing and/or painful human condition and yet deny that animals are suffering.

The same lip service is employed in touting benefits. In his article, Miller simply lists animal models of human disorders and includes sweeping generalizations about beneficience. There is no application of rigorous case-by-case scientific or historical evaluation, and the generalized claim of benefits provided in such catalogues is paltry taken against the larger body of nonanimal psychology research with its relatively more direct application to human welfare.

Further, two sleights of hand are apparent. In place of a serious and rigorous assessment of the worth of a particular published or proposed study at the IACUC level, there is offered a global evaluation of the entire enterprise of animal-model research. A second sleight of hand is the disingenuous use of scientific findings beyond their proper purview. The simple presence of an animal model on a particular topic itself provides no scientific evidence of the benefits of that research. Although they provide no test of the null hypothesis of beneficence, they are presented as if they do. However, Kelly, in a citation analysis of the Journal of Consulting and Clinical Psychology and Behavior Therapy, found that animal models are not readily cited.

Dr. Shapiro stressed that historical considerations are critical, beyond any scientific assessment of C/B. A reading of the history of science is required to judge true costs and benefits. Many animal studies are incomplete or unpublished (publication rejection rates are 70% to 80% for psychology studies compared to 50% for other sciences). These are costs without benefits. In addition, of those animal studies published, few are cited in anything other than animal literature.

There is also the problem of historical evidence and historical interpretation. True assessment of the actual role of the model in any purported "benefit" is needed. Did the model suggest a new understanding or treatment or did it simply add a graphic image or legitimate stamp of approval? In psychology, animal model research rarely results in specific technical innovations or applications.

But this is not to say that animal research has not had an important influence on the directions taken by modern psychology. Which of those directions are beneficial, which are delays and which are misleads? For example, in the heyday of behaviorism (the 1940s and 50s), a significant proportion of a generation of research psychologists trained in and conducted animal-based research. If they had, instead, directly investigated human behavior, would behavior therapy have advanced more rapidly as Drewitt and Kani contend (in Sperling, 1981, p.197)? When psychologists learn sophisticated laboratory animal experimental techniques, their careers have a certain trajectory which usually precludes learning sophisticated human-based experimental techniques. Further, having learned surgery and other invasive techniques on animals, that is what they teach to the next generation of research psychologists. Those who invest in the strategy of developing animal models and those who would have taken their places in the research enterprise would have produced their own research. These roads not taken, these unrealized...
benefits, are then costs. Every time one project is chosen for funding, others, that also have associated costs and benefits, fail to be funded.

Science is determined by the philosophy of the science that frames it and the methods it employs as well as by the objects under investigation. The construction of the laboratory as the site and the laboratory animal as the object of study and the adoption of the animal model strategy strongly affected the kinds of questions investigators asked. In turn, these affected the kinds of answers and the kinds and power of applications derived. What is the limiting effect of framing research questions in terms of the construction of an animal model? What are the effects when that animal-model strategy is joined to a behavioristic approach which de-emphasizes the study of consciousness? Did this have an impact on the recognition, measurement and ethical consideration of pain and suffering of laboratory animals used as models or on the degree of suffering allowed to be imposed?

In his book, Man and Mouse, W. Paton confirms the need for a historical method in assessing the costs and benefits of animal research. He offers the test of deletion and applies it by a thought experiment in which we are to suppose that no animal experiments had taken place for the past 2000 years. Dr. Shapiro feels that he is being generous in taking this proposed method seriously. Paton’s historical method substitutes nothing for that which he deletes. Of those scientists who did invasive laboratory animal research, some would have studied humans directly and some would have studied nonhuman animals in noninvasive ways. Rather than leaving a gaping black hole in place of the deleted invasive laboratory animal research, Dr. Shapiro asked why it should not be replaced with 2000 years of more careful and respected clinical and epidemiological research, with 2000 years that led to the much earlier development of more sophisticated imaging technology that allows us to see human pathology. And on the animal side, with 2000 years of Jane Goodalls — Jane Goodall of the dog, the tree shrew, the Norwegian rat, the field mouse, the octopus, the starfish. What would have been the benefits of animal vivisection; what would have been the costs? This is the historical problem of interpretation.

Dr. Shapiro concluded his response with the appeal that if we are going to use utilitarianism, let’s do so genuinely and intelligently as we judge a particular study and the entire enterprise. Let’s recognize the limits of science in its own practice and as judge and evaluator of its own practice. Let’s get the help of professional historians. Ethics and attitudes, particularly attitudes toward the status and value of animals, is the critical criterion and engine of change. There are better ethics available than a utilitarian one, certainly a utilitarianism that forgets that it is an ethic and masquerades as a scientific question—one that only scientists can answer.

RESPONSE TO THE PRESENTATIONS

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(Text developed from editors’ and Dr. Stephens’ notes)

Dr. Stephens began his presentation by underscoring the importance of this workshop. He remarked that there is surprisingly little scholarly analysis of the value and utility of animals in research. The criticisms leveled by animal research critics have not been seriously addressed. The animal research controversy is sometimes called a debate, but there really is little debate. Instead, what we have is polarizing rhetoric and public-relations posturing. This creates an adversarial climate which, alas, dilutes the impact of well-intentioned ventures such as this meeting.

In this climate, some animal research proponents openly implore scientists to tout the importance of animal experiments to their work. Such propagandizing can skew later analyses of the contribution of animal experiments to modern research advancements.

While supporting the aim of the workshop, Dr. Stephens expressed his reluctance to engage in an analysis of the value of animal research that is divorced from ethical and humane considerations. Such compartmentalization of the issues, though valuable for purposes of today’s workshop, cuts against the grains of reformers, who typically argue that ethical and humane considerations should be at the forefront of discussions of animal research.

In Dr. Stephens’ view, determining the historical value of animal experiments in different fields of research is complicated. A full set of guiding principles is needed. Superficial approaches to the subject abound, with the most unhelpful and disingenuous, yet most common, being the mere listing of supposed advance that resulted from animal research.

Dr. Stephens distinguished two perspectives in historical analyses of scientific advances. The most common perspective traces the key studies/observations that led to the discovery in question. The other perspective adopts a more inclusive and long-term view by identifying the key methodological/technical innovations that enabled scientists to carry out the critical studies leading to the discovery (see Comroe and Dripps, 1981). Animal research proponents typically adopt the former perspective when touting the alleged contributions of animal research. However, they fall back on the latter approach when animal experiments played no obvious role in a major discovery but may have played some role in the development of the technology that facilitated the discovery.
Dr. Stephens agreed with Andrew Rowan that Dr. Rowan's paper and talk were provocative. Dr. Stephens had anticipated that Dr. Rowan would critique the establishment view of the overarching importance of animal research, a view in great need of closer scrutiny. Dr. Stephens accused Dr. Rowan of coming close to being guilty of some of the same sins as animal research proponents. Rowan's recounting of the Elizabeth Hughes story (detailed in the pre-conference readings) plays on public sympathy for the sick.

Dr. Rowan mentioned the scientific skepticism that greets human epidemiological findings, but there would be fewer skeptics if not for the irrational strangehold of Koch's postulates on scientific thinking. In his own work, Dr. Stephens has tried to demonstrate the historical importance of alternative methods (see Readings). More effort should be put into research and development of such alternatives. Given the capabilities of human-centered research, we now need to examine critically the role that remains for animal models.

Dr. Stephens agreed that the isolation of insulin (referred to in previous talks and pre-conference readings) was a great triumph, but called attention to Dr. Rowan's statement that non-animal methods probably would have led to the discovery of insulin a year or two after Banting and Best's work. This reveals the simplistic nature of Paton's test of deletion (see below).

Dr. Stephens agreed with much of Dr. Kaufman's presentation. He himself had reached many of the same conclusions in his own analyses, particularly with regard to the dramatizing function of animal modeling (Stephens, 1986). For the most part, animal research proponents have conveniently ignored the scholarly work of Dr. Kaufman and his colleagues and dismissed these individuals as antivivisectionists.

Dr. Stephens felt Dr. Barnard's presentation was important for calling attention to the "big picture" - the health benefits resulting from lifestyle changes and a preventive approach in health policy rather than the current emphasis on research directed at treatment after disease has already taken hold.

In Dr. Stephen's view, if Drs. Kaufman and Barnard's analyses are on target, the policy implications for public health in general and animal research in particular would be profound. The scope of animal research would be greatly diminished and much greater emphasis would be placed on human-centered work. Where such work would be limited by technological constraints, resources should be marshaled to expand the capabilities of these non-animal approaches.

Dr. Stephens described William Paton's analysis of the value of animal experimentation (in Man and Mouse, Animals in Medical Research) as surprisingly weak. Dr. Paton implies that studies of animals probe facts about humans, which is illogical. Paton's main principle, the "test of deletion," is superficial and guaranteed to inflate the importance of animal research. It ignores the historical issue of whether alternative methods could have achieved the same result as the animal experiments in question. The deletion test also ignores cases in which animal experiments were more harmful than helpful: i.e., Paton trumpets alleged successes of animal experiments but ignores their failures. Animal models of ischemic stroke, for example, have sent researchers scurrying after 25 false leads on treatment possibilities (Wiebers et al., 1990).

Dr. Stephens concluded by commenting on two of the workshop readings that came to different conclusions based on the same data: his own paper (The Significance of Alternative Techniques in Biomedical Research: An Analysis of Nobel Prize Winners) and one by R. Leader and D. Stark (The Importance of Animals in Biomedical Research). Dr. Stephens chided Leader and Stark for not citing his paper, much less addressing the apparent conflicts between the two papers. He explained that the aim of his paper was not to analyze the historical importance of animal research, but to devalue and demonstrate the importance of alternative techniques. He feels he accomplished this. One the other hand, Leader and Stark set out to demonstrate the importance of animal research. Dr. Stephens accused them of inflating the importance of animal research by defining such research overly broadly. In the animal research category, Leader and Stark included research using invertebrates, in vitro cultures, and tissue from slaughterhouse animals. The terms of reference of the animal research controversy indicate that such research falls into the alternatives category.

References
THE MISREPRESENTATION OF EVIDENCE BY THE ANIMAL RIGHTS LOBBY

Jack H. Botting
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(Dr. Botting provided the following text upon which his talk was based)

The contention between the protagonists of animal experimentation as a means of alleviating human and animal suffering and those that oppose such research has reached a totally sterile phase. The views of each group are polarized. From one side animal experimenters are held to be profit-driven bigots, adhering to old-fashioned methods of research. From the other, antivivisectionists are viewed as naive, scientifically ignorant individuals, upon whom no time should be wasted in attempting to explain the need for certain experiments since it would not be understood.

Of course, both views are incorrect. It must be acknowledged that there are some experimenters who manifest arrogance in considering themselves above the need to justify their work to the concerned laity. This is unacceptable—everyone in society must be held to public account and be made aware of public concern. Nevertheless, the opponents of experiments upon animals undoubtedly contribute to this hard line attitude of the experimenter, and this talk attempts to describe how, in the hope that it may play a part in producing an improvement in mutual understanding.

The problem stems from the rhetoric used by the animal rights (AR) lobby, and the fact it misinforms the lay public about the historical and current value of animal experiments. I would like to give some examples.

My interest in this issue was stimulated after reading the press release (in January, 1991) to mark the formation of a new organization with acronym LIMAV, which is from the French title of the International League of Doctors against Vivisection. The press release stated:

"The majority of doctors now accept that experiments involving animals are of no practical value: no lives have been saved, no new cures have been developed and no breakthroughs have been made by scientists using animals."

Additional statements in the press release claimed that LIMAV members include some of the world's leading doctors. Remarks such as this, apparently from an authoritative source, obviously encourage members of the lay public to challenge the contribution of animal experimentation to medical research. They believe what they want to believe. This is evidenced by the spate of letters to local newspapers in the UK which contain comments such as:
One hundred years of animal experiments have produced an endless stream of highly profitable drugs, countless human tragedies, but not a single cure." (Letter to Derby Evening Telegraph 8/27/93)

"Vivisection is, after all, a medical fraud. No animal experiment has ever had any human benefits, in fact it has hindered medical progress throughout history." (Leicester Mail 9/16/93)

The LIMAV statement is of course untrue. During the period in which I worked as an academic pharmacologist, I have seen some striking improvements in therapy that stemmed from animal experimentation.

**MALIGNANT HYPERTENSION**

As a student I remember being told that if one was diagnosed as having malignant hypertension, then one's life expectancy was less than one year. Death would certainly be preceded by devastating headaches and possibly blindness. Then, in 1950, William Paton and N. Zaimis (1), through animal experiments, demonstrated the interesting properties of the polymethylene-bistrimethylammonium salts. Some of these possessed muscle relaxant properties (which later Paton tested on himself and which were subsequently used in surgery and tetanus). Others of the series were ganglionic blocking drugs that were shown to be potent at lowering an elevated blood pressure. These drugs were very soon used in malignant hypertension and were life-saving. However they were not perfect drugs. They were poorly absorbed after oral administration, they caused constipation, blurred vision and in fact prevented all autonomic reflexes. But encouraged by the therapeutic success of the ganglionic blocking drugs, other drugs were produced; reserpine, diuretics, alpha-1 blockers beta blockers and ACE inhibitors that gradually rendered the treatment of malignant hypertension effective and relatively benign. Today I doubt if any pharmaceutical firm runs anti-hypertensive program since the present treatment is effective and mostly free of side effects. Drugs come off patent and treatment becomes cheap.

**TREATMENT OF PEPTIC ULCER**

A second, indisputable example of improvement in drug therapy has been in the treatment of peptic ulcer. Prior to the development of the histamine H2 receptor blockers, treatment of peptic ulcer was by diet, antacids, atropine-like drugs which, of course, had a myriad of unpleasant side effects. The H2 receptor antagonists "cured" the ulcer in that it disappeared but tended to return if drug treatment was discontinued. Proton pump inhibitors prevented acid secretion at a more distal mechanism and seemed to be as effective. Treatment of this condition appears to be set for a dramatic change however, with the apparent demonstration of the relationship between *Helicobacter pylori* infection and peptic ulcer. Removal of the *Helicobacter* apparently can cure the ulcer. A vaccine has now been developed that is effective in a mouse model and is at present undergoing trials in patients. If, as appears, it is effective, a simple one-off vaccination will obviate the need for continuous drug therapy.

These two examples of the development of effective drug treatment clearly disprove the statement by LIMAV.

**TREATMENT OF INFECTIOUS DISEASE**

Further refutation can be obtained from other fields. Arguably the most striking advance in medicine has been the treatment of infectious disease— to the serious medical historian an outstanding example of the value of animal experiments. Yet, in the UK, we see many, many letters to the local press that repudiate this, citing improvements in sewage disposal, purer water supplies and better nutrition as being responsible for the conquest of destructive epidemics. Is this true? In my infancy, the importance of purity of water supplies (and hence of proper sewage disposal) was well accepted, as was the need for aseptic technique during operations and the general cleanliness of wounds to prevent putrefaction. Yet three people within my own social circle died of septicaemia, including my first general practitioner.

Apart from anecdote, there are statistics which are familiar. Up until the 1930s, for every 100,000 live births, 200 women were dying of childbed fever (streptococcal infection), 60 in every 100,000 men between 45-60 were dying of lobar pneumonia. These deaths were dramatically reduced between 1935-40 because the German pharmacologist Domagk showed that a dye, prontosil, could protect mice against a lethal inoculum of streptococci (although it did not affect streptococci in culture). From this simple animal model the therapeutic use of prontosil was established, and consequently the sulphonamide drugs. Soon after came penicillin, the antibacterial value of which was also established using streptococcal-infected mice. It was the discovery of these antibacterial substances that reduced deaths from bacterial infections to low levels.

![Graph showing death rates from lobar pneumonia](https://example.com/graph.png)

**LEFT.** Maternal death rate per 100,000 births. England and Wales.

**ABOVE.** Death rate from lobar pneumonia in men aged 45-64 years. England and Wales.
Vaccination reduced deaths from tetanus and pertussis, animal experiments were necessary to establish the lack of virulence of the formalin or heat-treated toxin or whole cell preparation. Since it is readily preventable by appropriate immunization, tetanus should be a rare disease. It is thus a shameful situation that even today well over a million people die of tetanus per year, and the disease accounts for 50% of all neonatal deaths (2).

Diphtheria has also been conquered, firstly, through the production of an antitoxin, secondly, by immunization. The development of both depended on experimental work on guinea pigs. This achievement has also been challenged by the animal rights lobby who use statistics for the incidence of the disease in various countries to attempt to disprove the efficacy of vaccination. The statistics used however, were those of various European countries during and just after the 1939-45 war, when, because of mass troop and civilian movements across Europe, counts of percentages immunized were unreliable. The recent re-emergence of diphtheria in areas which have been clear of the disease for many years serves to emphasize the continuing need to immunize and maybe re-immunize.

Up to the middle of the nineteenth century, smallpox was a devastating disease killing 1 in 10 persons, affecting nearly everyone, leaving many scarred. Smallpox was eliminated from Europe and the USA in the early part of this century using vaccinia virus grown on the skin of calves. An aggressive smallpox surveillance and vaccination program has resulted in the eradication of the disease from all countries. The last case was recorded in Somalia in 1977. Now the discussion is simply when and if the stored virus should be destroyed.

At present every year in the UK 50 million prescriptions for antibiotics are filled, which would hardly suggest that infectious disease is a thing of the past, a phenomenon that disappeared with our increase in living standards. The point surely is made that social changes could not solely be responsible for the control of infections.

POLIOMYELITIS

Poliomyelitis is a particularly good example to illustrate both the value of animal experimentation in the dramatic reduction in mortality from an infectious disease and also to illustrate how scientific fact can be blatantly misrepresented to the anger and consternation of biomedical scientists.

One of the leading antivivisectionists in the UK is Vernon Coleman, a graduate in medicine and one-time general practitioner, but who, for the last 20 years or so, has made a living by writing popular books about medicine and simple articles on medical matters and antivivisection in what are called the "tabloid" newspapers in the UK (popular newspapers that have a large circulation). Thus one must acknowledge that Coleman has a considerable influence. He is also the present president of LIMA and he has written a book decrying animal experiments called Why Animal Experiments Must Stop (3). Here is a quotation from this book that refers to the story of poliomyelitis with regard to animal experimentation.

"As with other infectious diseases, the significance of poliomyelitis had dropped as better sanitation, better housing, cleaner water and better food had been introduced in the second half of the nineteenth century."

Coleman thus dismisses any contribution by animal experiments to the reduction of deaths from polio since he claims that polio was already beginning to wane at the turn of the century. This is the complete reverse of reality. Poliomyelitis was a rare and sporadic disease until the end of the 19th century, its occurrence until that time usually merited a write-up of the case as a rare example of paralytic disease. Then there was a series of devastating epidemics of infantile paralysis. Where did these epidemics occur? In underdeveloped countries? On the contrary, in those countries with the highest standard of living, Scandinavia and then the USA.

Relatively minor epidemics of between 14 to 44 cases occurred in parts of Norway and Sweden during 1868-1887. The disease became epidemic in the USA in 1893 when 23 cases occurred in Boston. The size of the epidemics began to increase with an outbreak of 132 cases in Vermont (1894). Then came the era of regular epidemics: 1031 cases in Stockholm (1905) and 750-1200 cases in New York City in 1907. From that time on there was a regular background incidence of the disease with periodic, dreadful epidemics (4).

The reason for this sudden transformation of polio from a sporadic disease is of course obvious. If contracted very early in life, polio is a relatively mild disease, like a mild influenza (presumably, due to the persistence of maternal antibodies). However, this mild attack stimulates an active immune response and one is thus protected against a further exposure. Therefore, children brought up in primitive conditions are likely to be exposed to the virus early in life and will be immune.

POLIOMYELITIS
As living standards are raised children are not exposed to the entero-virus and, should the virus then infect someone, the disease will spread very rapidly through a susceptible population. This point is very nicely shown by comparing the relationship between infant mortality (the best indicator of the standard of living) and incidence of poliomyelitis. Prior to 1950, countries with a high mortality had a low incidence of polio. Those like Sweden, with an infant mortality rate of less than 25 per 1000 births, had a high incidence of the disease. One contemporary epidemiologist observed that when a country reduced its infant mortality rate to less than 75 per 1000, it would endure a polio epidemic within five years (4).

Since the readily available data clearly shows that polio emerged as a widespread medical problem at the turn of the century, one must ask how is it that the president of LIMAV, Vernon Coleman, got the story so completely wrong in his book.

Did animal experiments contribute to the control of polio? From 1900 through 1950 everything we learned about the polio virus was derived from experiments on monkeys. In 1908, Landsteiner, later to receive the Nobel Prize for his work on blood grouping, showed that polio was caused by a virus by taking bacteria-free extracts from the spinal cord of a boy who had died of polio and injecting them into monkeys who subsequently succumbed to the disease. (Interestingly, Landsteiner gave up working on polio since his lab could not afford to maintain a monkey colony. It was for this reason he switched to working on blood groups.)

Similar techniques showed that the virus was harbored in the nasal, buccal and intestinal membranes. Of great significance was the demonstration that nasal washings taken during an epidemic from persons with no sign of the disease were able to produce paralysis in monkeys (thus showing that some people were immune). Monkeys continued to be necessary up until the time it was proven that the human diploid cell line could be used to grow the virus and hence prepare the vaccine.

The second piece of blatant misinformation in the book by Coleman was that vaccination was not a success, ostensibly backed up by statistics, for the incidence of polio in two states pre- and post- vaccination:

"Proof that the introduction of the vaccine was not the success it was made out to be comes from undeniable statistics. In Tennessee, USA, the number of poliomyelitis victims the year before vaccination became compulsory was 119, but the year after vaccination was introduced the number rose to 386. In North Carolina the number of cases before vaccination was introduced was 78, while the number after vaccination became compulsory rose to 313." (3, pp. 64, 65)

The biased selection of data, of course, is not scientific evidence. Certainly statistics for mortality shows a clear beneficial effect of vaccination for these two states.

At a national level, mortality statistics for polio show an indisputable fall consequent upon vaccination in both the USA and England and Wales. The World Health Organization (WHO) eradication program has now been underway for some years. South America has had the disease eradicated and the WHO program plans the worldwide eradication of the disease by the turn of the century.

Polio deaths dropped in USA:

The vaccine was originally prepared from virus grown on monkey kidney cells, and it was safe although one had to go to great pains to exclude simian viruses. In 1962, with the development of the human diploid cell (HDC) line, it became possible to grow the virus for the preparation of the vaccine in human cells. It might be claimed that there was excessive and unnecessary slaughter of monkeys to provide kidney cells to grow the virus, and I would have to agree. This was simply because the acceptance of HDC line as a medium for growing virus was slow in coming, particularly in the USA, where there were some fears that the HDC might cause leukemia and also the general attitude was that if something worked, one shouldn't change it. It wasn't until millions had been immunized with HDC vaccine in UK, Yugoslavia and USSR that a license was granted in the USA in 1972.

Thus we can now prepare the vaccine without the need to kill monkeys to obtain kidney cells although the live, attenuated vaccine must be tested for lack of virulence on monkeys. That is an example of modern developments gradually obviating the need to use animals, something which all experimenters would applaud.
SPECIES DIFFERENCES

The second example of misrepresentation by the animal rights lobby is its contention about species differences--"animals aren't like us," "they suffer from different diseases," etc. It is dangerous, it is maintained, to rely on animals since they cannot predict whether a drug will be toxic in humans.

This line of argument of course is based on a total misconception of the procedure followed, and indeed legally required, before a drug is marketed. The premarketing investigation of a drug actually involves humans to a greater extent than animals. Firstly, there is a detailed investigation of its effects in maybe 50-100 normal individuals (Phase 1 trials). During Phase 1 volunteers are closely monitored. A daily blood picture is examined and kidney and liver function are measured by appropriate tests. This is followed by an investigation, in a limited number of patients, to establish dose levels and to obtain a preliminary estimate of efficacy (Phase 2 trials). Finally, studies in some thousands of patients are undertaken to establish efficacy. It is an axiom among pharmacologists that one should get the drug into man as quickly as possible, but one must adhere to the pronouncement by the World Medical Association's Declaration of Helsinki that: "Biomedical research involving human subjects should be based on adequately performed laboratory and animal experimentation."

It is thus clear that the basic, premarketing establishment of the safety of a drug is carried out in man. Notwithstanding that, some of the examples put forward by the animal rights lobby are factually incorrect for more simple reasons.

CHLORAMPHENICOL

"Animal tests fail to predict the effects of drugs with tragic consequences ... Chloramphenicol ... passed as safe after animal tests - caused fatal blood disorders."

Bitter Pills, NAVS leaflet

The fatal blood disorder caused by chloramphenicol is aplastic anaemia. It is rare for the drug to cause this condition, lethality is reported as 1 in 76,000 (5). The rarity of the reaction indicates that is an idiosyncrasy due to a genetic predisposition. It is thus not surprising that the effect was not detected in the preclinical studies in humans. It is absurd to suggest it should have been detected in animal toxicity tests.

PRACTOLOL

"Eraldin (practolol)....Heart drug. Given to patients for four years before the horrific effects were identified, these include blindness, stomach troubles, joint pains and growths."

Bitter Pill, NAVS leaflet

Again, the reaction to practolol was idiosyncratic and was not detected until experience with the drug had amounted to 250,000 patient years (6). Obviously, premarketing studies in 5,000 to 10,000 patients would be unlikely to detect the toxic effects. The animal toxicity tests, which are carried out simply to ensure that a novel drug has no unexpected, acute toxic action, are irrelevant in this situation.

Thus these reactions are due to idiosyncrasy, and no amount of animal experimentation will ever ensure that people with an unusual genetic trait will not have an untoward reaction.

ENTEROVIOFORM (Clioquinol)

"All drugs are tested on animals and passed as safe for human use before they reach market. But many have injured or killed people, eg clioquinol."

NAVS leaflet advertising World Day for Laboratory Animals

This drug is a particularly bad example for the NAVS. It was synthesized at the turn of the century and soon used as a skin disinfectant to treat skin infection, then it was used a mouthwash to treat mouth infections. Clioquinol was thus never tested on animals before it was used in humans. When its use for diarrhea spread to Japan, it was shown to cause subacute myelo-optic neuropathy (SMON) (weakness paralysis, blurred visions, etc.). This prompted some animal studies which showed that clioquinol produced neurotoxicity in frogs, mice and rabbits (7). Moreover, there are two veterinary reports that show that clioquinol given to cats and dogs to treat diarrhea in veterinary practice produced nervous
disorders (8,9). Thus after the drug was shown to be toxic in humans, it was proved to be also toxic in various species.

OSMOSIN

"Osmosin passed as safe after animal tests... withdrawn 1983. Six hundred fifty had side effects, and 20 died."

Bitter Pills, NAVS leaflet

Osmosin was not a new substance. It was a new formulation, that is, a new method of preparation of indomethacin, a drug that had been in use since 1965. It was placed in a capsule, with a laser-drilled hole in the end, in the hope that the indomethacin would slowly leak out in the small intestine and not in the stomach and thus not cause ulcers. Unfortunately, they did not test the capsule for effectiveness. It became sticky in the gut, stuck to the side of the upper intestine and leaked its contents into a small area of tissue. The drug and the potassium ions in the capsule had a necrotic action on the mucosa (10).

Again, far from illustrating the invalidity of animal experimentation, these two examples provide justification for the effectiveness of animal experiments in safeguarding the welfare of the first human volunteers.

INSULIN

"Insulin produces (fetal) deformities in laboratory animals but not people."

Sharpe, R., Health With Humanity, ed. McIvor BUAV, 1990

The suggestion that the naturally-occurring hormone insulin is teratogenic in animals, but not in humans is so manifestly absurd that it is hard to reject that its promulgation is not a deliberate deception. How can one argue that a naturally-occurring hormone, variable concentrations of which are present in our blood at all times, is per se a teratogen? If one examines the literature one sees that enormous doses of insulin were given to animals, these doses sufficient to render them in a near convulsive state for hours daily (11). The severe hypoglycemia produced caused fetal abnormalities in the rabbits since the fetuses were starved of nutriment. The same effects would be seen in women if they were so treated.

ASPIRIN

"Aspirin causes birth defects in rats and mice but not humans."

NAVS

The doses used to produce the birth defects are not discussed. When the original papers are examined it can be seen that very large doses were used in the experimental studies. Rats were given 300 mg/kg per day throughout the period of organogenesis (12) or 250 mg/kg throughout pregnancy (13). This would be the equivalent to a 55kg woman taking 55 aspirin tablets per day for a least ten consecutive days during early pregnancy or 46 tablets per day throughout pregnancy—doses that would never be likely to be used in humans.

THALIDOMIDE

"Animal tests fail to predict the effects of drugs with tragic consequences: Thalidomide. Sedative, used for morning sickness. About 10,000 birth defects world-wide, and effects do not appear in most laboratory animals—so the human tragedy could probably still occur."

Bitter Pills, NAVS

Thalidomide was never administered to pregnant animals before being marketed. Five months after McBride's paper describing the alleged association between administration of thalidomide and fetal abnormalities, a paper was published, also in the Lancet, stating that thalidomide caused phocomelia in NZ white rabbits, the most common laboratory animal for the investigation of reproductive physiology (14). Subsequently, thalidomide was shown to be toxic to the embryo in rats, mice, hamsters, marmosets, baboons, macaques and rhesus monkeys.

The basic testing of thalidomide on animals was poorly performed. Orally-administered thalidomide was apparently non-toxic even when given in very large amounts. No studies were undertaken however, to establish that the drug was actually absorbed from the gut. In fact, it was not. The drug was simply being excreted with the feces. This possibility was noted by Dr. Kelsey, of the FDA, who was examining the application to market the drug in the USA. When responding to the potential marketers of thalidomide she stated:

"The animal studies were not reported in sufficient detail, and the study of the absorption of the drug in rats was not supported by evidence." (15, p.74)

Dr. Kelsey also stated that she would need evidence that thalidomide would be safe to take during pregnancy (15, p.79).

A new formulation of thalidomide was produced by the German manufacturers, a syrup suspension. The finely ground suspension of the thalidomide in this preparation was absorbed and, when tested on animals by pharmacologists from the British firm licensed to sell the drug, produced severe neurotoxicity. (At this time there were reports of thalidomide producing peripheral neuritis in patients.)

The ultimate proof, if required, that thalidomide was never tested on pregnant animals prior to marketing, comes from the defense raised by the firms marketing the drug. They stated that it was not customary to do such tests at that time. However, it is likely that if they had followed the best drug testing procedures of the time, the disaster may have been prevented.
In Britain, these statements about thalidomide perpetrated by the AV propagandists have been brought before the Advertising Standards Authority (ASA). The Council of the ASA have considered all the evidence and sought appropriate advice and have now decreed that leaflets and advertisements should no longer contain statements suggesting that the thalidomide tragedy was caused by mistaken reliance on animal experiments since the statement is "inaccurate and misleading."

I object to such statements of alleged "species differences" simply because they are factually incorrect. However, if asked whether there are species differences in reactions to drugs, it must be admitted that there are. But they are of no great significance for there are great differences between human beings. Japanese people are obviously particularly susceptible to clioquinol while 1 in 70,000 Caucasians suffer a serious reaction to chloramphenicol due to idiosyncrasy.

I cannot blame members of the lay public for the general promulgation of misstatements of fact. They wish to believe, and they take in good faith what they are told by self-professed experts. I do however, blame those that mislead the lay public, particularly if they assume a mantle of authority, such as being a scientific consultant for an AR group or being a medical expert. Since many of these statements peddled are easily exposed as incorrect after a desultory browse in a medical library, one can't help but suppose that such experts are deliberately misleading the public by being highly selective in the evidence they choose to produce.

This activity undoubtedly contributes to the hardening of the attitude of the experimenter. But it has a more malign effect, for it generates an unjustified sense of grievance in those that support animal experiments. This violence ranges from pouring super glue into the door locks of charity shops (such as those of the Imperial Cancer Research Fund), breaking such shop windows by catapulting large ball bearings, and harassing the staff of such shops with loud hailers, through attempted murder by the planting of bombs under the cars of scientists.

Whatever one's views on the moral question (which is certainly one that must be addressed by us all), the facts should be sacrosanct. Misrepresentation should be condemned.

**DISCUSSION**

Following Dr. Botting's presentation, he was asked if, in toxicity tests, it is not invalid to overwhelm an organism's protective mechanisms with huge doses such as the pumping of large amounts of aspirin into rats. The questioner added that these types of tests usually seem to be discredited in the end due to the large doses used, to the fact that animals respond differently, and to the fact that the same type of tests cannot be done on humans. Dr. Botting agreed that standardization levels are often faulty and that researchers can only do the best they can in adjusting for variables such as size and metabolism. At this point it was mentioned that there is a massive effort to overturn the Delaney Clause that states if a substance shows any carcinogenic effects in animals, it cannot be used in humans. (Congress mandated saccharine as an exception to this rule.)

One participant pointed out that in a General Accounting Office report on drugs marketed between 1976 and 1985, 102 of 198 drugs either had to be withdrawn or relabeled after full-scale use. It was pointed out the interpretation of data is influenced by values -- people holding different values can draw very different conclusions from the same information.

The issue of the releasing of misinformation was briefly discussed and the comment was made that it is wrong no matter which side does it. Often it is difficult to know who is right and who is wrong. For example, is the Leader and Stark article or the Stephens’ article on the use of animals and alternatives by Nobel Prize winners correct? Does it really matter if the articles draw different conclusions from the same data set?

A participant stated that the Physicians’ Desk Reference does not give a lot of comfort to doctors in regard to the use of drugs during pregnancy, and that since tests have "tightened up," some previously used drugs have been removed from the market even though they were subjected to animal and human trials. Thus, researchers must not be predicting toxicity very well. He went on to ask if we should not be questioning why some new drugs exist and if they should even be tested. Dr. Botting replied that every drug, given to some species, will show toxicity. Animal studies are only crude toxic screens. He added, in response to a criticism of the post-marketing animal tests of thalidomide, animal tests would have prevented the marketing of thalidomide if they had been done correctly. The comment was then made that if medicines affect even cats and dogs differently than humans, it seems that rats and mice must be very different than humans. Are we not making huge leaps from animals to humans? Another participant stated that the science community does admit that the extrapolations from animal tests are inadequate.

**References**

CONCLUDING DISCUSSION

Following the last presentation, the floor was opened for a general discussion with all participants invited to speak.

The first participant addressed the issue of drug discovery and testing. He stated that there is no doubt that pharmaceutical companies want to get their drugs into humans. This was countered by the argument that a lot of drugs, however, never reach the human stage because they either fail the toxicity study stage or fail the clinical study stage. The reply to this was that this is what the pre-clinical studies are designed to do—pick up the preliminary problems. The second speaker replied that animal tests, however, may indicate a toxicity level that humans do not share so "good" drugs may be kept out of the market while "bad" ones move on along the testing line. Therefore, animal test results may not protect the first humans to take the drug. A third participant observed that being the first human to take a drug would always be risky whether the drug had been successfully tested on animals or not.

It was observed that there is always a need to gather all possible information on a drug to protect the first human volunteers. However, in "selling" an experiment, there is often propaganda that implies that animal tests must be done and, if they are done, that the result is a safe drug. However, this is not always true and no one talks about the many drugs that fail the tests. Another participant added that, even if some animal tests are of some value, it does not mean that they are then necessary.

Referral was made to a new drug (FIAU), a viral-DNA inhibitor, that was given to humans suffering from the hepatitis B virus after being tested on rodents and rhesus monkeys. However, several of the human subjects suffered severe complications and several died. The speaker went on to tell of an article in the September, 1993, Journal of NIH Research, in which a Johns Hopkins clinician testing a similar drug for HIV-1 infection stated, "You never know how relevant an animal model is in predicting toxicity in humans." Another participant observed that it is impossible to get 100% assurance from any human or animal test, and it is difficult to figure out the acceptable levels of safety and ways to be sure that level is always achieved.

During the discussion, one of the participants commented that he felt there was a logical inconsistency to Dr. Rowan's "circular argument" (described in his talk). Dr. Rowan stated that as approximately 40% of the research that has produced vaccines, antibiotics, public health initiatives, etc. has used animals, it is reasonable to assume that 40% of the credit should go to studies using animals. He went on, however, to point out that it is not really possible to separate the various research approaches when assigning credit as research tends to be an endless circle with insights flowing from the clinic to the laboratory to the theoreticians and back again. If the flow is
disrupted, much more than just the portion removed is lost. The participant argued that 1) it is inconsistent to combine percentages with a circular analogy and 2) there is not much exchange between clinical psychologists and the animal laboratories and there has not been an enlarging of the knowledge base. He also felt that the years spent by many psychologists doing animal studies to investigate conditioning and other aspects of behaviorism have retarded the general knowledge base.

It was suggested that some of the psychology studies involving animal models have proven to be of unexpected benefit to animals, especially farm animals. Another participant replied that even in these studies there is most likely experimenter bias with the experimenter seeing what he/she wants to see. He expanded this thought adding that we are all taught our attitudes and that our degree of objectivity is based on our learned attitudes and values. He concluded by pointing out that just because something works doesn’t mean it is necessarily good—the ends do not always justify the means.

When Dr. Rowan was asked who is currently taking the lead in the debate, he replied that there are few leaders, that there is very little serious debate going on, and that the debate that exists is basically sterile and non-productive. He added that it is important for all participants to understand the language used in the debate and especially the assumptions and values behind the language.

Funding for research involving animals was briefly discussed. It was revealed that one third of NIH funds go to research involving humans, one third to research involving animals and one third to research using alternatives. In the United Kingdom, 97% of the money from the top 15 medical charities goes to supporting non-animal studies. One person questioned the amount of money spent on developing and validating alternatives — is it not unfair to demand the validation of alternatives when animal use is not validated? Another participant voiced the opinion that the NIH seems to be much more resistant to the use of alternatives than private corporations.

The debate over the utility of animal research is both factually complex and heavily influenced by values. Where one person might see animal testing of new drug entities as performing a useful function because the tests give some indication of potential side effects, another may view them as useless because such tests do not accurately predict all the likely problems with one hundred percent (or even ninety percent?) accuracy. These proceedings provide an overview of one attempt to focus the debate and to test one set of arguments - namely, those offering technical criticisms or challenges drawn from philosophy of science to the standard view that animal research has proved to be (very) important in the advancement of medical and biological knowledge. All participants were sent the critique (developed by myself) of the arguments opposing animal research prior to the workshop but it elicited relatively few comments during the course of the workshop.

Both Kaufman and Shapiro produced articulate arguments questioning the role imputed to animal models for both the epistemology of biomedical research and in the actual progress of biomedical knowledge. Despite the fact that those defending the use of animals sometimes do, or appear to, imply that animal models provide exact replicas of human biology and disease, it seems clear that this is an exaggeration (in some cases, by considerable degree). However, it should also be noted that differences between different animal species, and between animals and humans, have also proved to be very useful in helping biomedical science develop a plausible and coherent picture of the way living organisms work.

Barnard delivered his usual polished promotion of the benefits of preventive medicine and life-style changes. However, it was not possible to do more than provide a brief overview of his slide presentation in these proceedings together with the discussion. He did not address the issue that was raised in our critique of the current interpretations of clinical and epidemiological data to make recommendations about prevention and life-style options today.

Stephens was the only commentator who devoted much attention to the critique and to the other materials that were distributed to the participants prior to the workshop. He expressed surprise that the handouts should have focused so much criticism on the arguments of the animal activists rather than on the role and utility of animal models in biomedical research. However, the aim of the workshop was to examine the robustness of the arguments against animal research. Because of a relative lack of detailed criticisms of the writings of animal activists from the research community, the critique in these proceedings was developed to stimulate a criticism and debate. As for the use of the Elizabeth Hughes narrative in the example of the discovery of insulin (also criticized by Stephens), this was more than...
a simple appeal to emotions. The narrative provides important context to both the social influences that drove diabetes researchers and also the reason why the purification and distribution of insulin was perceived to be such a medical miracle at the time.

Botting's address concentrated on problems he has identified in the attacks on animal research presented in the animal protection literature. Botting is one of only a handful of animal research advocates (others include Karl Nicoll, William Paton and Ernest Verhetsel) who have begun to investigate carefully the claims made in animal protection criticisms of animal research. He has called into question some important claims in the animal research literature (e.g. if penicillin had been tested on guinea pigs it would never have reached the market). Although Botting's writings have been largely ignored by animal activists, they can only continue to do so at the risk of seeing their public support begin to erode. It may be unfair, but critics of the status quo usually have to keep themselves to a higher standard of factual accuracy and interpretative analysis than those defending it.

In general, this workshop was successful. Although the debate about the merits of the technical arguments against animal research was not really joined in the workshop, and has not been since, these proceedings still represent the most detailed look at the issue and provide a sampling of the more cogent and coherent challenges to the idea of animal models and the value of animal research.