1986

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Recommended Citation

Will, J.A. (1986). The case for the use of animals in science. In M.W. Fox & L.D. Mickley (Eds.), Advances in animal welfare science 1986/87 (pp. 205-213). Washington, DC: The Humane Society of the United States.

THE CASE FOR THE USE OF ANIMALS IN SCIENCE[1]

James A. Will[2]

Animals are now used extensively in research and teaching, and the appropriateness of their use appears to be questioned. Some people believe that we are in a new era where the animal activists have become much more influential, and that the antagonism between the scientists and these groups is worse than it ever has been. This does not appear to be the case. The preeminence of various influences seems rather cyclic, even perhaps influenced by such things as economic conditions or wars. At present, the question is often asked, "Should we continue to use animals in science?" The real question should be, "How do we use animals in research and teaching responsibly?" Anyone asking the first question begs credibility, while the second question implies that the questioner is realistic and responsible, with a concern for humanity as a whole.

By way of presenting the arguments for the continued use of animals in research and teaching, I will discuss responsibility of developed society as a whole, the responsibility of individuals, societal and individual priorities, the process of discovery in science, the safeguards for animals in science, and so-called alternative methods.

The European, some Asian, and the American societies (and especially the latter), are very privileged societies that constitute a small minority of the world's population. At present, this small minority controls the destiny of most of the world; rightly or wrongly. Thus, in many ways we must be held accountable not only for our own destiny, but also for the destiny of the world as a whole. We are privileged in that most of us know full well where our next meal is coming from, we have shelter available even though it may be our choice not to use it, and we have the opportunity to be instructed or even educated. It is in this state of being that we can enjoy the luxury of thinking about our responsibility toward other human beings, and other creatures in the world that may be as sentient as we but unable to control their own destinies.

We have a responsibility to these thousands of millions of people that is as demanding as any priority we establish. A look at the statistics in figure 1 proves the magnitude of some of these disease entities. Figure 2 shows that the distribution area of malaria is not small, and that in the past or in the future much more of the world has been or may yet be threatened.

Diseases like AIDS have seemingly mutated in man from a nonpathogenic and therefore non-threatening organism in non-human primates, to a very virulent killer. Only prior research on this class of virus has allowed us to move as quickly as we have to identify the virus and develop a rationale for intervention.

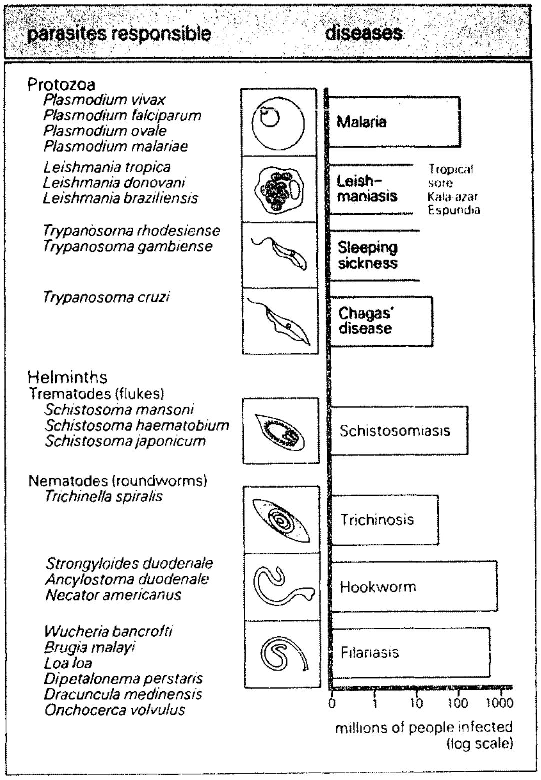

Figure 1. The most important parasitic infections of man and the numbers of people affected. The precise figures for leishmaniasis and sleeping sickness are not known. (Figure used with permission from *Immunology*, 1985, by Roitt, Brostoff and Male. Glower Medical Publishing, London.)

If we are to concede that there is some societal value in the use of animals in science, how do we assign responsibility for the appropriateness of animal use? In our present society, it is easy to put the blame for inappropriate use of animals on someone else. There is no escape from the fundamental responsibility for our own actions. It is the responsibility of each person involved in the sciences which use animals to assume responsibility for their own actions. There can be no shifting of this responsibility to the unaccountable "they."

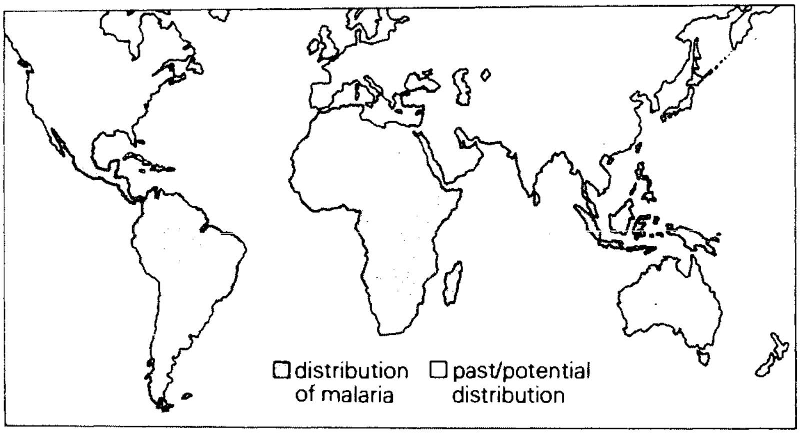

Figure 2. The geographical distribution of malaria is shown for 1981. The potential distribution is also shown and this represents a "time bomb" we live with. Diligence and enormous research efforts are the only protection society has today. (Figure used with permission from *Immunology*, 1985, by Roitt, Brostoff and Male.Glower Medical Publishing, London.)

To my way of thinking, each person must decide for him- or herself what their decision will be regarding this whole question. The decision to eat meat, to hunt, or to use the products of research which required animals are all fractions of a central question concerning our relationship with animals. Because these are personal decisions, there is no reason why we should not develop a pattern that is consistent. Furthermore, since these are personal decisions, we should respect the right of each person to live by the decisions they make. I believe it is also consistent that we put priorities on our concerns about how animals are cared for and used because at any given time the resources of humanity cannot mitigate, much less satisfy, all of the needs perceived as being necessary and good for the world. I believe that these priorities should be exercised in the most responsible way to alleviate the suffering of all animals, including man, as equitably as possible. With our present state of knowledge, we cannot accomplish the task of improving or even maintaining the health of humans and animals without the use of experimental animals in research and teaching.

As a practical person who knows little, if anything, about theoretical philosophy, it seems unimaginable to me that we could exercise our responsibility toward other peoples and higher animals in this world without the use of animals in research and teaching. Whether we like it or not, we live in an evolutionary era characterized by the necessity for animals in science. This era may pass, but not in our lifetimes and most likely not during the lifetimes of our children and grandchildren. How then shall we conduct ourselves in this era? Responsibly. There is no room in good science for any other standard. This does not mean that there will not be waste in the use of animals, nor will we abolish abuse. People are not infallible, and no plethora of regulations or laws will govern man's moral sense; society cannot afford one policeman per animal experiment, nor can society afford one policeman for any single situation where there is potential for abuse. Appreciation and understanding of the relationship between the quality and responsibilities of life will only change through example and instruction.

How then have we arrived at where we are today, how does science really work, and what does the future portend? Science has arrived where it is today through the dedicated lives and intelligence of people with a more-than-average level of curiosity and the persistence to pursue this curiosity. Without them, it is safe to say that probably half of us would not be on the earth today. We are still fighting age-old problems and seem to find new challenges each day. The knowledge that a better diet and exercise seem to be elements that help us to be healthier and perhaps to live longer is not something that suddenly arose from nowhere; nor is it knowledge based on evidence from a single experiment. The truth behind information such as this is the result of hundreds, and more likely, thousands or millions of experiments testing many hypotheses. One might wonder about the relevance of many of these hypotheses at the time they are tested by experimentation. Sometimes these experiments were very basic in nature and seemingly totally unconnected to the problem they are used to solve even generations later. Because of the ethical considerations, the problem of establishing the "need" to do an experiment "at this time" is not one that is easily solved. Many instances can be demonstrated in which an observation made in an experiment 10 or even 70 years earlier provided the key or clue to a mechanism that now explains how something works, and, knowing how this system works allows therapy or preventive treatment to be developed and implemented (Comroe 1977). It is easy to look through our retrospectroscope and proclaim that this mechanism was very obvious and that the animal experiments done were unneeded. An example that is frequently cited is the recent remarkable decrease in heart disease attributable to community education programs. The community programs were important and even essential to effect this great change in the incidence of heart disease, but no one should forget that the knowledge allowing us to develop these programs came from very basic research, much of it in animal models. The world continues to be challenged with new threats to a healthful existence, with Legionnaires' disease, with AIDS, and with the major causes of morbidity and mortality (which are not such civilized diseases of affluence like heart disease or cancer), as well as the parasitic diseases such as malaria. These parasitic diseases have an obligate requirement for a whole animal host to complete their cycle. Epidemiological evaluation of these diseases in affected populations has provided valuable insight into the disease syndromes, but such evaluation is ineffective in answering critical and basic questions. Tissue culture is widely used to study portions of the cycle and to examine particular mechanisms, but in the end, only the whole animal can confirm or reject the hypotheses proposed.

How does science work in the typical situation? Usually this process begins with an observation that something occurs in a specific situation. Questions begin to proliferate. Someone comes up with a theory as to how the phenomenon might be explained and possible mechanisms for the explanation. From these discussions, a theory develops and then the hypothesis or hypotheses to test are formalized. At this point it is most appropriate to do some pilot studies to decide if there is a chance that the hypothesis might be plausible and go further, or to reexamine the problem and develop new hypotheses. Up to this stage of the process, the numbers of animals used are very small. We assume that before using any animals, the investigator has searched the literature to find clues that either support or dispute the hypothesis. At this point, the investigator reviews the literature, critically asking such questions as was the animal model appropriate and will age make a difference? The investigator also considers the implications of the genetic strain used, looks for clues in the articles that would indicate that the animals used were not disease free (a factor which might influence the results), evaluates the analytical techniques used to determine if they are adequate in light of today's technology (and therefore if the conclusions would likely be the same), and finally, determines if the statistics used were adequate to discriminate between possible type one and type two errors. These are just general questions that the investigator must ask; for each specific area of science the questions are more specific and appropriate to the particular hypothesis to be tested.

I hope from this example to have demonstrated that the problems of duplication in research are not simple. Most so-called "duplication" is research that is taking place almost simultaneously at several places in the world, and this type of duplication is virtually impossible to prevent. This is just as much a facet of progress as the competition between two manufacturers of automobiles or household appliances.

This is where we are today—in an era of fantastic growth in knowledge and yet as naive as newborns about the mysteries of life and how biology works. Although we have made great strides, it seems that each answer we get is accompanied by a hundred additional questions, each a little more difficult to answer. What are the prospects for the future? We will never be a disease-free society; new challenges to our intellect and resources will come as fast or faster than our solutions to the existing problems. If we slacken our efforts to meet these challenges, we will be worse off as a society than we are today or were perhaps even decades ago. The plagues we are presently experiencing are just new names added to the lists of the old.

There are safeguards already in place for the animals used in research and teaching. The radical groups of animal activists are not satisfied that these safeguards are sufficient because the stated goal of these groups is to abolish the use of animals in research and teaching. I do not believe that this is a reasonable stance, nor do I believe that the present system of regulations is cost effective. By this I mean that the pendulum has swung too far in the direction of over-regulation of animal protection for very little increase in abuse prevention and is therefore not a good use of the world's finite financial and natural resources. I would make the point that a large majority of investigators are very concerned and compassionate individuals who abhor animal abuse as much or more than the most concerned animal activist. Guidelines for the responsible use of animals such as the ones we all adhere to now are not new either. Dr. H. Newell Martin, the pioneer physiologist who became the first head of biology at Johns Hopkins University in 1876, drew up guidelines for animal experimentation in March 1885 (Fye 1985). The Animal Welfare Act is certainly not the first national or state effort to protect animals from abuse, nor will it be the last.

The institution I represent has undergone a change in the last years, not in the level of responsibility, but in awareness of what this responsibility means and the public expression of this responsibility. This change probably occurred as a result of the efforts of the animal activist movement. Although I firmly believe that there was, in fact, little abuse of animals in teaching and research, there have been changes within science itself that have tended to improve the care and use of animals. One of the greatest influences has been the progress in cellular and subcellular research that allows us to do more definitive experiments capable of elucidating mechanisms at this level.

Another reason for change is, purely and simply, money. As research becomes more sophisticated, the cost of doing each experiment becomes greater. This means that investigators can no longer afford to use animals that are not best suited to test an hypothesis. Special strains and animals that are disease free are much more in demand than they were 10 years ago. This does not mean that animals of random breeding are no longer useful. It is by using such animals that idiosyncratic responses were uncovered. This makes sense if you think about it. We know that there is a great deal of genetic variation in man many times manifested in overt syndromes resulting in an easily visible deformity. Many more genetically different characters in man are not apparent through casual observation; they are not expressed as phenotypic but as genotypic characteristics. It seems logical then to suppose that this same degree of genetic variation occurs in the random populations of other animals. This is the way things happen in nature. The most important finding of an experiment using random source animals may be that one animal responds much differently than the majority. An inquisitive investigator will ask "why?" and this inquiry may lead to a heretofore undiscovered mechanism. The ability to recognize and utilize serendipity and the role of the importance of the differences between experimental results is a sign of maturity in an investigator. This does not mean that every unusual result should be followed and the original direction of inquiry dropped. This maturity requires a trained mind and training always requires some waste; some mistakes. In this way, science is not a mysterious society, but, in fact, little different from any other occupation.

What are we doing at The University of Wisconsin to increase awareness and to help ensure that abuses will not take place? We believe very strongly in education, as opposed to oversight which smacks of policing. We have a program of mandatory certification. This program is oriented to making each person who uses, cares for, or supervises the use of animals in research and teaching aware of his or her responsibilities under the current laws and regulations. The program also deals with the historical perspective of animal regulation, development of ethical considerations, and the zoonotic disease potential of contact with research animals. There is a test associated with the document entitled "The Responsible Care and Use of Laboratory Animals." This test is not intended to be a test of anyone's intelligence, but rather acts as a form of certification demonstrating that the people who will be using animals have taken the time to read the document and are aware of their responsibilities under the current laws and the University policy. Thus far, we have certified more than 1600 people on the Madison campus alone. Variations of this program are in place at each of the 26 components of the University of Wisconsin System. At present, this certification is the only mandatory requirement. We have offered seminars and have now erected 21 poster boards in the largest animal units on campus where we are attempting passive teaching through attractive displays. Our goal is to raise the level of awareness and to increase the level of expertise of all those who require animals in research and teaching.

Another question that arises is, "Why not use alternatives, which are in most cases, really adjunct methods?" I and other authors have addressed this issue at length in previous publications (Smyth 1978; Will 1985; Fox 1986). The first argument is *for* the use of adjunct methods. Examples of adjunct methods that can be very useful are tissue culture and computer models. These provide different kinds of information. The computer models usually provide more general kinds of information than does tissue culture. For example, at our present state of knowledge, a computer can tell us if it is probable that an enzyme system is present, what the system appears to do, and at what metabolic site it may act. The computer can be right or it can be entirely wrong, depending upon our state of knowledge. By this I mean that a computer can only make decisions based on the data we are able to supply. These data usually come from experiments that have been performed in the whole animal first to make the original observation that a certain phenomenon occurs, then from more definitive experiments that let us test hypotheses in experimental animals. At this point, perhaps, critical experiments using an adjunct method are used to define a mechanism, and finally the hypothesis is most probably tested in the heterogeneous environment of the whole animal once again to see if it really works in the way we have surmised. Many times when whole animals are used, the experiments do not result in severe pathology or mortality and, as in the case of large domesticated animals, they are returned to the herd or flock.

As I have indicated, the adjunct method may play a very important role in defining the mechanism; however, the fact that the mechanism works in a certain way in tissue culture, for instance, does not always mean that it works this way in the whole animal. In the whole animal, many other systems may modify the action of the mechanism. These mechanisms may only work under certain disease conditions and not in the normal laboratory animal. It is as important to understand when the mechanism will not work as it is to know when the mechanism is operative. Tissue culture has its strong and weak points. The term "tissue culture" is a broad one, and encompasses several types of organ and cell culture techniques. If organ culture is used, it means that an animal is killed, and the organs removed and studied, either whole or in parts in the isolated state. Presumably organ culture may decrease the numbers of animals used, but this is not always the case.

Primary cell cultures are a second type of tissue culture, and these cultures may be quite different from established cell lines. Primary cell cultures are established by killing an animal, harvesting the cells required, and growing the cells in a culture medium. As long as these cells stay alive, they usually respond as they would in vivo. However, when the cells divide or reproduce, they may revert to a more primitive cell type with properties that are no longer the same as those of the cells when present in the animals or tissue (or organ). Cell lines established in this manner are available as frozen cells that researchers can order from a cell bank or collection. These banked cells are useful in that they are predictable in response to various environmental and other exogenous influences, but these cell lines may bear no resemblance to primary cell cultures or to the cells as they are in vivo.

There are some diseases in which the causative organisms will not grow in tissue culture. Examples are the organisms that cause leprosy, foot and mouth disease, herpes virus infections of man and animals, and many respiratory viruses. It seems amazing that we still haven't conquered leprosy, a disease well described in biblical times. Peculiarly enough, the only good model to work with in this disease is the armadillo. The results of a diagnostic test for leprosy in the armadillo are directly transferable to man.

In other situations the fact that the response is not the same as in man is equally important. Foot and mouth disease is a scourge of cattle and other ruminants in many parts of the world. In the research with this disease, there are many instances of a complete lack of correlation between the in vitro and in vivo responses to antigens or vaccines. Schistosomiasis (see figure 1) is a major disease of the world and in this particular disease, no correlation is demonstrated between the presence of the causative organism, the intensity of the disease, and immune status of the victim. For example, one of the most frequent maladies of schistosomiasis is a kidney disorder, and it is difficult to associate the severity of kidney disorder with disease intensity or immune status.

What should we conclude about whether the whole animal or an adjunct method is most appropriate to use in a specific instance? The most appropriate method to answer the question is that method which offers the best results, regardless of the cost or time involved. In the practical situation, it does often not work this way because equipment, expertise, and money to change technologies to use an adjunct method may not be available. In this instance, adjunct methodology may not be cheaper. Furthermore, granting agencies are reluctant to fund an individual who proposes to change technology because agencies believe that the investigator may not have the requisite expertise to make the grant worthwhile and productive using this new technology. All of these factors tend to impede the use of adjunct methods. In virtually all documented cases of development of new technology, the development has occurred because the new method improves research capability, i.e., improves resolution by having greater specificity, increased sensitivity, or lower cost. Most investigators would be eager to use any method that would allow them to use fewer or no animals at all, but somewhere along the line the drug or mechanism proposed must be tested in the whole animal. In cases where the organs must be collected, this obviously must be done in an experimental animal.

I have attempted to provide, in an unemotional way, a perspective that justifies the prudent and responsible use of animals in research and teaching. I would remind the reader of what I perceive to be the responsibility of those of us in the world who are more fortunate than others. I believe the era for the need to use animals in science is with us now and will not end in the foreseeable future, but as our knowledge increases, we will have less dependence on animals. In the meantime, it is imperative that every investigator follow the principle of the three Rs in animal use—reduction, refinement, and replacement—wherever possible.

Endnotes

[1] Paper presented at the national conference, "Animals and Humans: Ethical Perspectives," Moorhead State University, Moorhead, MN, April 21-23, 1986.

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