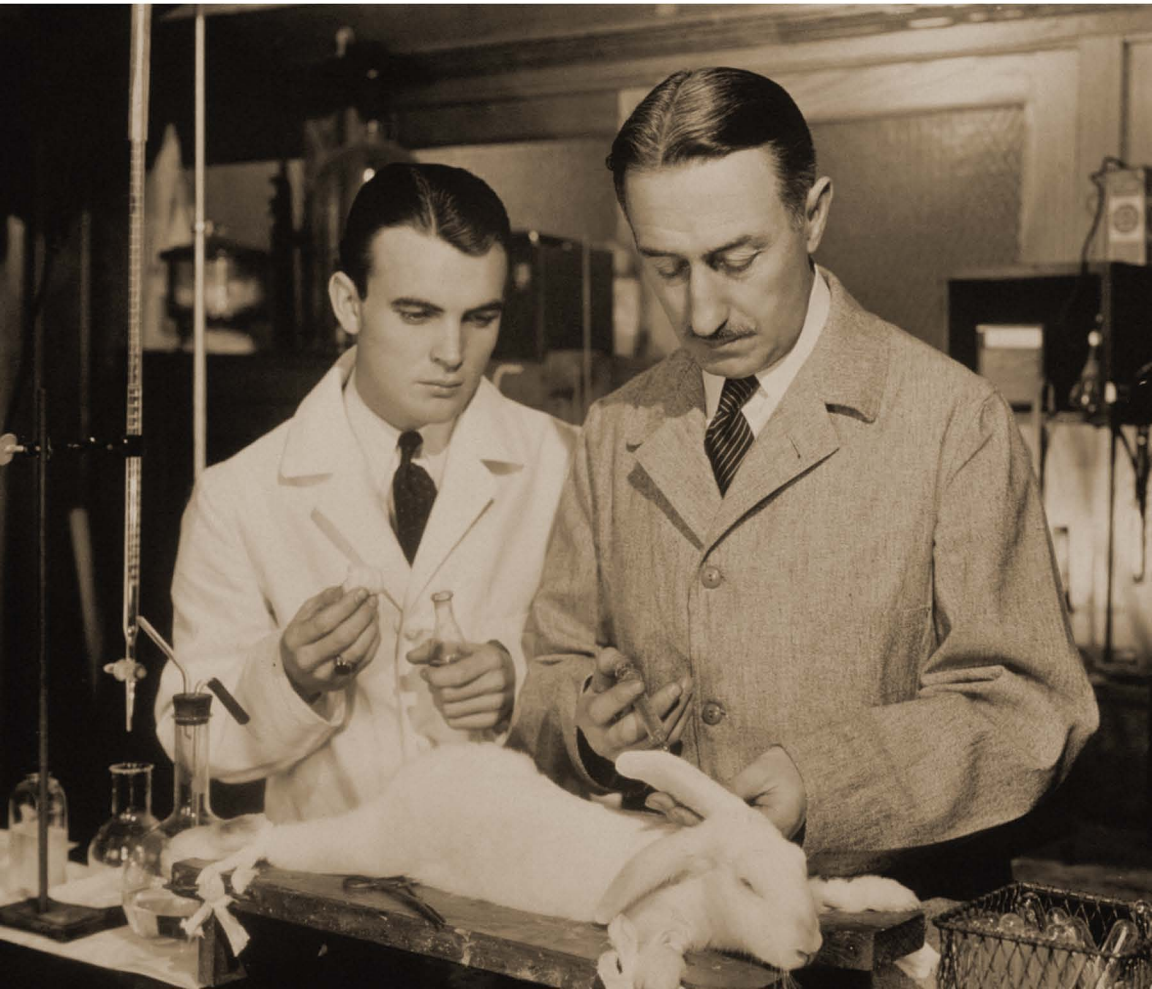
A HISTORY OF THE DEVELOPMENT OF ALTERNATIVES TO ANIMALS IN RESEARCH AND TESTING

John Parascandola



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IN RESEARCH AND TESTING

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To my sons, Adam and Mark,
who first got me interested in animal welfare issues

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Preface

MY AIM IN THIS BOOK IS TO TRACE THE HISTORY OF THE CONCEPT OF ALTERNATIVES to the use of animals in research and testing from its beginnings until it had become firmly established in the scientific and animal protection communities by the end of the 1980s. The story of alternatives is set within the context of developments in science, animal welfare, and politics. Although some earlier scientists had on occasion put forth suggestions for reducing the number and suffering of animals used in experimentation, and even in rare instances replacing them entirely, the origin of the alternatives movement is generally traced to the publication of *The Principles of Humane Experimental Technique* in 1959 by W. M. S. Russell and R. L. Burch. Russell and Burch introduced the Three Rs framework for humane animal experimentation that included the principle of replacement (substituting non-sentient materials such as tissue cultures for animals), reduction (reducing the number of animals used through appropriate strategies in the planning and performance of experiments), and refinement (reducing to an absolute minimum the amount of stress on the animals used). The Three Rs framework came to dominate the definition of the term "alternatives" in the period covered in this book and beyond.

The history of the development of alternatives has never been fully told. There is no book-length study of the subject. There have been a number of insightful articles on various aspects of the subject, most notably by Andrew Rowan and Michael Balls, both of whom have been involved personally in the alternatives story. Their publications and those of others have been useful to me in my own research and will be cited where appropriate. I believe, therefore, that my book fills a significant lacuna in the literature of the history of science, medicine, and animal welfare.

Let me offer a few caveats at the outset. First of all, this work is not a technical history of the development of specific alternative methods, although some of these are discussed in passing. My focus is on alternatives as a concept and a field of research and application. Significant attention has therefore been devoted to the origins and development of views on alternatives, controversy and cooperation between scientists and animal welfare advocates over alternatives, and the ways in which alternatives have entered legislation and experimental and regulatory practice.

I have also restricted my account to Britain and the United States, largely in order to keep the project manageable. I believe this is a reasonable approach. The choice of Britain hardly requires justification as the country played a major role in creating and advancing the field. The United States was slower to embrace the concept of alternatives, but it eventually emerged as a leader in the area. In addition, it offers a revealing contrast to Britain in terms of its greater resistance to regulation of animal research and the impact of this attitude on the adoption of alternatives.

Finally, I have chosen to carry my account only through the end of the 1980s. I have selected this cutoff point because I believe, as I elaborate in the book, that by the end of this decade the field of alternatives had become firmly established. I have included, however, a short epilogue that briefly considers some of the major developments in alternatives over the past few decades.

One of the major themes of the book is the crucial role played by the animal protection movement in promoting alternatives. Advances in science, such as tissue culture techniques, were of course necessary before animals could be replaced in research and testing, but it was animal welfare advocates who pressed scientists to develop such methods, even before there were many concrete examples of these procedures available. Initially, scientists often resisted these calls to devote substantial resources to research on alternatives. Organizations such as the Universities Federation for Animal Welfare (UFAW) and the Fund for the Replacement of Animals in Medical Experiments (FRAME) in Britain and the Animal Welfare Institute (AWI) and the Humane Society of the United States (HSUS) in America were instrumental in advancing the alternatives movement. In contrast to the support of the more moderate animal welfare groups, however, some more extreme elements of the animal rights movement, such as People for the Ethical Treatment of Animals (PETA), were often indifferent or even opposed, at least initially, to efforts to focus on alternatives, preferring instead to continue to press for abolition of animal research as opposed to collaborating with scientists on reform of animal experimentation.

The publication of Russell and Burch's book in 1959, although it did not have an immediate impact, provided the Three Rs approach that was to dominate the field of alternatives for decades, another theme of the book. The Three Rs focused attention not solely on the replacement of animals in medical research and testing, but also on the development of methods to reduce the number of animals used in medical experiments and the suffering and distress that they endured in these procedures, thus broadening the definition of what constituted alternatives.

In the nineteenth and the first half of the twentieth centuries, the battle against animal experimentation was concentrated in the hands of antivivisectionists, who

demanded an immediate cessation of the use of animals in the laboratory. There was little room for compromise between these groups and the scientific community. More moderate groups such as the Royal Society for Prevention of Cruelty to Animals in Britain and the American Society for the Prevention of Cruelty to Animals in the United States, which were founded in the nineteenth century, did play a role in efforts to regulate animal experimentation. In Britain, for example, the former group was involved, along with antivivisectionists in this case, in the campaign that led to the passage of the 1876 Cruelty to Animals Act. These organizations did not specifically deal to any significant extent, however, with the issue of alternatives. Another theme of my book is that it was the development of a specific group of moderate animal welfare groups around the middle part of the twentieth century that enabled an eventual cooperation with scientists that was to advance the concept of alternatives.

The first organization to encourage the development of alternatives to animals in research was the Universities Federation for Animal Welfare (UFAW). Although UFAW was founded in London in 1926, it did not become involved with laboratory animal welfare until the 1940s, and in the following decade sponsored the work that led to the publication of *The Principles of Humane Experimental Technique* in 1959. Under its founder and leader, Major Charles Hume, UFAW had distanced itself from antivivisectionists and took a sympathetic but unsentimental approach to animal welfare. The group was eager to work with scientists to better the conditions of laboratory animals. Alternatives provided an area where moderate animal welfare advocates and sympathetic scientists could come together in a compromise with a goal of possible eventual replacement of animals without demanding immediate cessation of their use. The Three Rs helped to make such a compromise even more viable, as it expanded the definition of alternatives to include methods that reduced the number of animals used or their level of their suffering in animal experiments.

In the United States, the establishment in the 1950s of moderate animal welfare groups such as the Animal Welfare Institute (AWI) and the Humane Society of the United States (HSUS) opened the door to working with scientists on the development of regulations concerning animal experimentation and the promotion of alternatives. The first organization devoted specifically to the field of alternatives was the Fund for the Replacement of Animals in Medical Experiments (FRAME) in Britain in 1969. In spite of its name, FRAME quickly expanded its scope to include not just replacement, but the Three Rs in general.

The book is divided into five chapters. Chapter 1 considers alternatives and the background to the concept before the emergence of the Three Rs model. The chapter covers the development of antivivisection movements in Britain and the United States

and the efforts to regulate animal research, culminating in the passage in Britain of the 1876 Cruelty to Animals Act. It also considers early efforts to identify alternatives, especially in terms of reduction and refinement; the development of the promising method of tissue culture research in the early twentieth century; and the promotion of laboratory animal welfare and alternatives by Robert Gesell and his daughter, Christine Stevens (the founder of AWI). The chapter concludes with a discussion of the conflict between AWI and NSMR (the National Society for Medical Research) in the 1950s and the efforts of American scientists to prevent the establishment of British-style animal research regulation in this same period.

Chapter 2 deals with the development of the Three Rs framework of alternatives by Russell and Burch and the publication of their seminal book, *The Principles of Humane Experimental Technique* in 1959. It begins with a discussion of UFAW becoming involved with laboratory animal welfare in the late 1940s, leading in the following decade to the project on humane animal experimentation. The chapter discusses the work of Russell and Burch on this project and the publication of the book. It concludes with a detailed description and analysis of *The Principles*.

Chapter 3 examines developments in the 1960s and the initial underwhelming response to the Russell and Burch book and the Three Rs. It begins with a discussion of the lukewarm reviews of the book. The chapter considers the limited references to the book during the decade, how it was largely ignored, and the career of Russell, the principal author, after the work was published. It discusses the efforts in Britain and the United States to enact animal protection legislation, culminating in America in the passage of the Animal Welfare Act in 1966. Britain, of course, already had an animal protection law in the form of the 1876 act, but efforts to strengthen this legislation in the 1960s failed. The chapter concludes with an analysis of why *The Principles* had so little initial impact.

Chapter 4 discusses the increased attention given to alternatives in the 1970s. It begins with a discussion of the animal rights movement of the 1970s and its influence on laboratory animal issues. The chapter then goes on to discuss the founding (1969) and early history of FRAME in Britain, tracing its growth and increasing significance, as well as the initial reaction of the scientific community to it. It covers the unsuccessful efforts in Britain and the United States to amend and strengthen animal protections legislation and concludes with a detailed description and analysis of David Smyth's important 1978 book *Alternatives to Animal Experiments*.

Chapter 5 discusses the developments of the 1980s that resulted in alternatives becoming a firmly established concept and field in the scientific and animal protection communities. The chapter begins with a detailed discussion of the campaign against

toxicity testing of cosmetics in the United States, led by Henry Spira and others. The pressure that this campaign exerted on the industry led it to fund the creation of the Johns Hopkins Center for Alternatives to Animals Testing in 1981. The chapter discusses the founding of the center, the initial skeptical reaction to it on the part of some members of the scientific community, and the center's activities over its first decade. It then discusses similar pressure on the cosmetics industry in Britain and the role of the FRAME Toxicity Committee in promoting alternatives to animal testing. The chapter also considers the successful campaigns in Britain and the United States to amend existing animal protection legislation and concludes with remarks summarizing how the concepts of alternatives and the Three Rs had become firmly established in the scientific and animal protection communities by the end of the 1980s.

The book ends with a brief epilogue summarizing some of the major developments that took place in alternatives near the end of the twentieth century and in the early decades of the twenty-first century. These developments include the creation of the Russell and Burch Award, the founding of centers for alternatives akin to the one at Johns Hopkins in several countries, the efforts of government agencies in various nations to promote an end to cosmetics toxicity testing in animals, and a significant increase in international cooperation as reflected in the establishment of the European Center for the Validation of Alternative Methods (ECVAM) and the World Congress on Alternatives and Animal Use in the Life Sciences. The epilogue concludes with a discussion of the status of the Three Rs concept today and how it may be modified or even replaced.

Finally, I wish to express my hope that this book will increase interest in and understanding of alternatives and stimulate further historical and scientific research on the subject. The development of alternative methods and the principles of humane experimentation embodied by the Three Rs have reduced the amount of suffering of untold numbers of laboratory animals in the past and will continue to do so in the future.

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THIS BOOK WOULD NOT HAVE BEEN POSSIBLE WITHOUT THE CONTRIBUTIONS of many people. I particularly wish to thank Andrew Rowan, Michael Balls, Bernard Unti, Alan Goldberg and the late Martin Stephens, all of whom read and provided valuable comments on various chapters of the manuscript, as well as sharing with me their expertise and wisdom on many questions related to alternatives. My conversations with Andrew and Michael throughout the process of my research and writing were especially helpful. The book also benefited from the input of two anonymous referees.

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My research for the book took me to many libraries and archives, where I benefited from the efforts of staff members too numerous to name individually in conducting this research. Several organizations also allowed me access to historical files and/or provided me with copies of relevant materials from these files. I would like to specifically thank the following institutions for their assistance: Animal Welfare Institute; Archives and Special Collections, University of Minnesota Libraries; Bentley Historical Library, University of Michigan; Center for Alternatives to Animal Testing, Johns Hopkins University; Chesney Archives, Johns Hopkins University; Fund for the Replacement of Animals in Medical Experiments (FRAME); History of Medicine Division, National Library of Medicine; Humane Society of the United States; Manuscripts and Special Collections, University of Nottingham; Special Collections, North Carolina State University Libraries; Universities Federation for Animal Welfare; Wellcome Collection Library.

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My apologies to anyone whom I inadvertently left out. Needless to say, I am solely responsible for any shortcomings of the work.

1

Alternatives Before the Three Rs

The use of animals in life sciences research may be traced back to the beginnings of Western medicine in ancient Greece. For example, a Hippocratic treatise from the first century BCE describes cutting the throat of a pig that was drinking to observe the act of swallowing and cutting open the chest of a living animal to observe the actions of the heart. As Maehle and Tröhler noted in their study of early animal experimentation: "It seems to have been obvious to these ancient physicians that knowledge of the bodily functions could best be obtained by studying the interior of living organisms."[1]

Vivisection, a term whose literal and original meaning referred to dissection of a living animal but eventually came to refer to all animal experimentation, was a relatively uncommon practice in ancient and medieval times. Animal experimentation achieved greater significance during the scientific revolution of the sixteenth and seventeenth centuries when discoveries like the circulation of the blood clearly demonstrated that experiments on animals could lead to useful physiological knowledge. With the emergence of modern biomedical sciences such as physiology and pharmacology in the nineteenth century, the use of animals in experimentation became much more widespread. Although concerns about vivisection, whether of a medical or moral nature, had been expressed to some extent essentially since the practice was introduced, the issue did not, in the words of Rupke, "develop into a major, public controversy until the second half of the nineteenth century. By then, experimentation on living animals had become a quintessential part of physiology as an institutionalized profession."[2]

Marshall Hall and Rules of Animal Experimentation

Although an organized antivivisection movement did not begin to flourish until the second half of the nineteenth century, the increasing use of animal experimentation in the emerging science of physiology in the first half of the century led to heightened concerns about the practice, especially in Britain. The work of the French scientist Francois Magendie, one of the pioneers of the new science of physiology, came in for particular criticism. Magendie conducted numerous experiments on living animals, often involving radical surgical procedures that must have caused a great deal of suffering in the days before anesthetics. A series of lecture-demonstrations by Magendie during a visit to London in 1824 created an uproar about the practice of vivisection. Even many British physicians who defended animal experimentation as a tool that could sometimes be useful in biomedical research attacked Magendie for what they considered to be excessively cruel and unnecessary vivisection research.[3]

Among those few British physicians who actively pursued experimental physiology during this period was Marshall Hall. His research on the phenomenon of reflex action, which involved vivisection, led to accusations of cruelty. In one instance, an attack in a medical journal on his experiments on the brain of a dog referred to the "poor tortured animal" and called vivisection experiments "horrible butcheries."[4]

Likely in response to the criticisms, Hall published rules for animal experimentation, perhaps the first medical investigator to do so.[5] In 1835, Hall published *A Critical and Experimental Essay on the Circulation of the Blood*. Perhaps because of the criticism his experiments received, he began the work with an introduction on the principles of investigation in physiology in which he directly addressed the question of the use of animals in research. He acknowledged the "peculiar difficulties" confronting the physiologist: "Unhappily for the physiologist, the subjects of the principal department of his science, that of animal physiology, are sentient beings; and every experiment, every new or unusual situation of such a being, is necessarily attended by pain or suffering of a bodily or mental kind."[6]

For this reason, he believed that physiological investigations should "be regulated by peculiar laws," or else the physiologist might be charged with cruelty. Hall was not thinking of any kind of government legislation, but rules developed by the profession. He enumerated the principles that he believed should guide physiological research. These principles were intended to reduce the use of animals and minimize their suffering. Although of course Hall did not use the term "alternatives" or refer specifically to the modern concept of the Three Rs (replacement, reduction, refinement),

his principles did foreshadow these general concepts. For example, his first principle stated that one should never have recourse to experiment in cases where observation could provide the information required. Related to this principle was one stating that no experiment should be performed without "a distinct and definite object," and with some confidence that the object could be obtained by the experiment. Eliminating experiments that were unnecessary or useless, and thus unjustifiable, would reduce the use of animals in research.[7]

Hall also argued that the needless repetition of an experiment was unjustifiable, unless there was a clear scientific reason for doing so. Physiologists should have a knowledge of the work done by their colleagues, and "should not needlessly repeat experiments which have already been performed by physiologists of reputation" unless there is some doubt about their accuracy. Hall's fourth principle was that any experiment "should be instituted with the least possible infliction of suffering." In this connection, he suggested that for some cases a newly dead animal might be substituted for a living one. He also added that the subject chosen by the investigator should be "from the lowest order of animal appropriate to our purpose, as the least sentient." His fifth principle was that physiological experiments should be performed under "such circumstances as will secure a due observation and attestation of its results, and so obviate, as much as possible, the necessity for its repetition."[8]

Hall believed that if physiology was pursued in this manner, it could escape charges of uncertainty and cruelty. He argued that medicine and surgery are dependent on physiology and that excluding physiological experiments would hinder the progress of the healing arts. He claimed that he had tried to steer a course "equally distinct from the heartless cruelties practiced by some soi-disant [self-styled] physiologists, and the senseless declamations of others against what they are pleased to call vivisection." Finally, he enunciated his sixth principle, that facts should be laid before the public in the simplest, plainest terms, and that controversy could be of little service to science.[9]

Hall's principles clearly addressed methods of reducing the number of animals used in research and in refining experiments to reduce the suffering of experimental subjects, two of the Three Rs. He could not address the replacement of animals in physiological investigation in a meaningful way because there were no adequate replacement methods at the time. He could only suggest the use of observation instead of experimentation in cases where that was appropriate. Alternative methods such as tissue culture and the use of microorganisms in physiological experiments would not be available for decades.

The case of Marshall Hall illustrates one of the major themes of this book, that is, that the movement for alternatives was consistently advanced by pressure from animal protectionists on scientists. Hall's efforts to develop rules of animal experimentation

and to suggest ways to reduce or refine the use of animals in research were clearly a response to attacks by antivivisectionists. This pattern of animal welfare advocates pushing scientific investigators to find ways to reduce the use and suffering of animals in experiments, and where possible to replace them, continued throughout the history of alternatives.

Hall's proposal did not lead to any broad, sustained discussion in the scientific community about establishing rules for animal research. Nor did ardent antivivisectionists, whose goal was the total abolition of the use of animals in research, show any interest in promoting the development of such rules. Some interest in this approach, however, was exhibited by the Society for the Prevention of Cruelty to Animals (SPCA), which was founded in England in 1824 as the world's first animal welfare organization. The society was granted royal status by Queen Victoria in 1840, becoming the Royal Society for the Prevention of Cruelty to Animals (RSPCA). Animal experimentation was only one of the concerns of the society, which worked to prevent cruelty to animals in general. Although critical of vivisection, the SPCA acknowledged in its first prospectus that in some cases such experiments were justified (when under the control of "benevolent minds").

In 1827, the society published a pamphlet on vivisection, which included contributions from physicians and surgeons designed to prevent and discourage "physiological butchery." In this publication, the SPCA suggested that a system be set up whereby all proposed vivisection experiments would have to be submitted to and approved by a board composed of the most "humane and eminent" members of the medical profession. Like Marshall, they were suggesting a mechanism internal to the profession for regulating animal experimentation. The proposal, however, did not lead to any action. Over time, the society came to focus on preventing specifically painful vivisection, that is, vivisection experiments carried out without anesthesia. As prominent British physician and medical researcher Benjamin Ward Richardson noted, experiments under anesthesia were permissible because there could be no cruelty without pain.[10]

Antivivisectionists and the Cruelty to Animals Act of 1876 in Britain

Some individuals concerned about animal experimentation were not convinced that self-policing by the scientific community would work and suggested that there was a need for legislation. In 1843, for example, physician Robert Hull argued in the *London Medical Gazette* that it was necessary to ultimately look "to legislative remedies for the correction of these monstrous abuses."[11] There were sporadic discussions about the

possibility of legislation regulating the use of animals in experimentation, but no serious campaign for such a law until the 1870s.[12]

It is beyond the scope of this book to give a detailed account of the battle resulting in the eventual passage of the Cruelty to Animals Act of 1876, but it is necessary to provide a summary of the events leading to the act and its provisions. Readers interested in learning more about this topic are referred to Richard French's excellent study, *Antivivisection and Medical Science in Victorian Society*.[13]

Several factors led to increased public pressure for an act to regulate animal experimentation in the early 1870s. For one thing, the growth of physiology and experimental medicine in Britain, culminating in the formation of the Physiological Society in 1876, significantly expanded the number of investigators carrying out vivisection experiments. The publication of a *Handbook for the Physiological Laboratory* in 1873 embodied vivisection methodology and publicized the practice. The handbook made no specific mention of the use of anesthetics, raising concerns about laboratory procedures on animals that were painful. Accounts in British newspapers in late 1873 of painful vivisection experiments by Moritz Schiff, professor of physiology at the Royal Institute in Florence, Italy, also stimulated public discussions about the morality of vivisection. The following year the RSPCA brought charges against a French investigator and three British physicians for wanton cruelty to a dog during an experimental demonstration at the annual meeting of the British Medical Association in Norwich. The charge was made under Martin's Act, an 1822 law that outlawed cruelty to large domestic animals and was later amended to cover all domestic animals. Although the defense prevailed, the case brought further attention to the vivisection controversy.[14]

Antivivisectionists stepped up their campaign for legislation. A powerful figure in the movement was Frances Power Cobbe, an Anglo-Irish journalist who had become interested in the vivisection debate in the 1860s. In 1863, she led the English community in Florence in protesting Schiff's experiments there. After the 1874 Norwich trial, Cobbe became convinced that Martin's Act was not sufficiently strong to protect against vivisection abuses and she supported special legislation for this purpose. In late 1875, she founded the Society for the Protection of Animals Liable to Vivisection (more popularly known as the Victoria Street Society).[15]

The antivivisectionists, led by Cobbe, managed to get an animal experimentation bill introduced into the House of Lords in May 1875. Moved to action by this development, the scientific lobby responded by promoting a less restrictive bill. In reaction to this controversy, the Home Secretary announced on May 24, 1875, the formation of a royal commission to examine the practice of subjecting live animals to experiments for scientific purposes. The commission issued its report in January 1876. Although the members of the commission differed on the question of whether or not animals were

being abused in scientific experiments, the report acknowledged that the practice itself was liable to abuse. The report went on to conclude that vivisection should be subjected to "due regulation and control."[16]

The Cruelty to Animals Act was passed in August 1876. Although it did not go as far as antivivisectionists such as Cobbe had wished, it was the first law regulating animal research. The act provided that any individual wishing to perform experiments on living vertebrate animals had to apply, with the support of the president of one of Britain's scientific or medical bodies and a professor of medicine or medical sciences, to the Home Secretary for a license. The individual had to perform the experiments at a place subject to inspection at any time and registered with the Home Secretary. Licenses were valid for one year, after which time they had to be renewed. Experiments had to be performed with the purpose of advancing a new discovery in physiological knowledge or developing knowledge that would be useful in medical practice. Experiments could not be performed for public demonstration or to acquire manual dexterity. There were also further restrictions on experiments carried out without anesthesia. The Home Secretary was authorized to require reports from licensees and to appoint inspectors, and penalties for offenses were established.[17]

Benjamin Ward Richardson on Biological Experimentation

The passage of the 1876 act, introducing some regulation of animal experimentation, did not end the debate over vivisection in Britain. Antivivisection and animal protection advocates continued to press for further reforms. However, experimental biology and medicine, which depended heavily on animal research, were firmly established in Victorian society and offered the promise of significant health benefits. The opponents of animal research were not able to offer an alternative program for advancing medicine. As French has noted: "The movement never succeeded, however, in articulating a research program of its own that proved convincing to any significant proportion of the orthodox profession."[18]

A further step toward improving the welfare of laboratory animals was the establishment of the Leigh Browne Trust in London in the 1890s. The trust had the object of promoting and encouraging original research in physiology and biology that did not involve experiments on animals that caused pain. The trust commissioned physician and medical researcher Benjamin Ward Richardson to prepare a work exploring the possibilities for painless research and related topics. Richardson himself had earlier in

his career carried out a significant number of vivisection experiments, although by this point in his life he had become more sympathetic to the cause of animal protection. In the case of Marshall Hall, criticism of his research by antivivisectionists had stimulated him to develop his rules of animal experimentation. In Richardson's case, it was an animal protectionist organization that directly ordered and funded his efforts to investigate experimental methods that did not cause pain to animals.[19]

Richardson published the results of his study in 1896 under the title *Biological Experimentation: Its Functions and Limits, Including Answers to Nine Questions Submitted from the Leigh Browne Trust*. In his introduction, he stated his general belief: "In an imperfect civilization like the present, when pain and disease exist everywhere, systematic experiments, even on sentient beings, may be exceptionally justifiable; but the admission need not imply the necessity for the infliction of more pain, or a physiological *crux crucis* [cross]."[20]

Several of the questions addressed by Richardson are relevant to the issue of seeking alternatives to animal research. In the broadest sense, the first question asked whether Richardson considered "*that painful experiment has played an indispensable part in the study of medical substances and methods for the cure of disease*." Richardson responded coyly that he did not believe there was any one method in science that could be considered indispensable. Methods may be convenient, useful, and expedient, but not indispensable. He noted that experiments on animals appear to have led to discoveries in the past, but this fact did not mean that these methods were indispensable. If a particular method had never been thought of, the inventive human mind might well have come up with an equally good plan that might have led to the same results. He also added a caution about painful experiments, warning that the disturbing influence of suffering on the subject could lead to deceptive results, thus indicating an awareness of the limits of this type of research.[21]

Some of the other questions dealt more directly with the possibility of developing research methods that did not involve painful experimentation, which was the objective of the trust. The third question, for example, asked: "In the study of human functions can you suggest promising lines of research without resort to painful experimentation?" Richardson responded that he was "embarrassed by the richness of the field of promise that lies before me," although in the end he was not able to offer much in the way of substantive alternatives that would have appealed to physiologists.[22]

He began by pointing out that the human mind tends to get on a beaten track and to focus on familiar paths. "Meanwhile it fails to discern all paths save that it is on, and so while one path towards successful discovery is crowded, other paths of bright promise are left untenanted." In his view, physiology had been "so bent on making discovery

by vital experiment, and that alone, the world has ceased to think of its work by any other name than vivisection." But experimentation means much more than "cutting into the bodies of living animals," and many experimenters "who never took a scalpel into their hands" have done good experimental work.[23]

His first example of an alternative method was not really new, although he believed that medical researchers did not give it sufficient attention. He advocated a "physiology with nature as the experimentalist, and man as the observer and chronicler." Richardson argues that there was no experiment of a physiological kind that could not be found in nature "would men industriously seek for it." For example, much could be learned about the nervous system (or any other body system) by comparing difference of function with difference of structure in different species without resorting to vivisection. Much could also be learned, Richardson claimed, by studying why certain behaviors, such as hibernation, are exhibited by some animals and not others. Studying the influence of external conditions on living things also offered a rich field for physiological study, as did experiments on dead tissues. Contemporary physiologists could counter, however, that centuries of observing and chronicling nature had added relatively little to physiological knowledge when compared to animal experimentation.[24]

The fourth question was related to the previous one, asking Richardson whether he could enumerate sound methods of research for studying the causes and treatment of disease that did not rely on painful experiments. His first suggestion was similar to his previous answer, namely observation of the effects of external influences on living beings, for example, clinical observation of the effects of atmospheric conditions on a disease. His second example was undoubtedly more appealing to laboratory scientists. The late nineteenth century was a period of increasing interest in physiological chemistry, especially in the action of ferments, or enzymes (as they came to be called). Richardson argued that one could study the phenomenon of zymosis (enzyme action) "equally well out of the animal body as in it." The action of ferments could also be studied in a senseless organism. In passing, he mentioned, but did not elaborate specifically on, microorganisms (at a time when the germ theory of disease was becoming firmly established).[25]

Richardson admitted, however, that while much can be accomplished in the field of therapeutics by experience alone, some advances "can only be effected by experimental pursuit, which, however, need not be painful." He gave as one example his own discovery of the therapeutic action of amyl nitrite, where "vital experiments on the inferior animal were unquestionably of service, and the probabilities are that in their absence the results discovered would have been lost." He noted: "Some remedies which, on the physiological argument promise the best results, are too dangerous to be tried at once

through the disease, and with them, therefore, preliminary experiment on a lower animal has been considered essential."[26]

Richardson was hopeful that therapeutics would become more rational, reducing the amount of empirical trial of remedies through the study of the effect of chemical structure on physiological action. Advances in organic chemistry and pharmacology promoted interest in this field during this period, and Richardson himself was involved in such studies. He pointed out that his own discovery of the therapeutic value of amyl nitrate "came from thinking of the principle of chemical constitution of remedies in respect to their applicability in practice for remedial objects."[27]

Richardson emphasized that his hope was "to bring about a reconciliation between extremists of both schools" (animal protectionists and scientists) and that the aim of "all earnest men and women" should be to come to a common understanding. His call for a reform in physiology, however, was critical of experimental physiology and probably did not endear him to many practitioners of the discipline.

> The reform that is called for is the enlargement, or the widening, of the boundaries of physiology; the turning of crude physiology into accomplished biology; the destroyal [*sic*] of the absurd fashion that has grown up among physiologists of looking with a kind of scorn on all physiology that is not vitally experimental, and with contempt on all physiologists who avoid experimenting on living animals. Plainly, what is wanted in practical physiology is not more knowledge, but wisdom, with the strongest leaning towards all that is most humane. I may not go with some who contend in argument for the abolition of all vital experiment, but I quite agree that the grandest physiology and physiological discovery could exist outside every shade of painful experiment, and I am now as opposed as anyone to methods of research that would take a living animal to pieces in order to discover its mechanism as if it were a watch, and means which, in the case of a watch itself, would be rude and ridiculous attempts for purposes of discovery.[28]

Beginnings of Alternative Methods

Aside from his discussion of the study of the action of enzymes in vitro, Richardson could not expand upon the suggestions of Hall with respect to alternatives to vivisection experiments in physiology. Richardson was writing, however, at a time when modern biomedical science was just emerging. Disciplines such as pharmacology and bacteriology were becoming established in the late nineteenth and early twentieth centuries.

Physiological chemistry was being transformed into biochemistry. By the turn of the twentieth century, cell theory was firmly established, and scientists were probing the internal structures of cells and studying their functions. Researchers were also investigating the pathogenic effects of microorganisms and ways to neutralize them. Like physiology, which led the way, these field relied heavily on animal experimentation. As Duncan Wilson has stated:

> It originated in physiology, but soon permeated bacteriology, embryology, pathology and zoology. This experimental ethos treated organisms as raw materials that could be dismantled and reformed in novel ways, and during the late nineteenth and early twentieth centuries, experimental biologists began to re-assess the nature of living material with a view to controlling natural phenomena. They isolated and disrupted the cells of developing embryos, grafted healthy or cancerous parts between animals, and induced unfertilized eggs to divide by altering the chemical composition of their environment.[29]

Although the development of these new experimental sciences led to a substantial increase in the number of animals used in research and increased confidence on the part of scientists in the value of vivisection, they were also eventually to serve as the breeding ground for alternative methods. Arguably the first of these breakthroughs was the technique of tissue culture. Although the principle of tissue culture was established by the German scientist Wilhelm Roux in 1885 when he removed a portion of the medullary plate of a chick embryo and maintained it in a saline solution for a few days, the true birth of the method is generally dated to 1907. In that year, Yale embryologist Ross Harrison, studying the mechanism of formation of nerve cells, was able to culture the cells in vitro and get them to continue to grow. Wilson emphasized the pioneering importance of this work as follows: "Though biologists had maintained organs apart from the body before, they generally assumed that they would only survive briefly after their removal. Harrison, on the other hand, demonstrated that cells could be induced to thrive apart from the body—to grow and divide as *in vivo*. His experiments opened the possibility that the body was no longer essential to the survival of its constituent parts."[30]

The potential of the tissue culture technique for biological research was immediately recognized and many other investigators adopted it. Expectations were high, but at first the method led to few major achievements. Tissue culture studies involved significant technical difficulties and, for various reasons, developed a reputation for being even more difficult than they were. Over the course of the twentieth century, many of these difficulties were overcome, and tissue (and cell) culture became a widespread technique in biological research following the Second World War.[31]

Perhaps the earliest person to suggest that tissue culture might be an alternative to vivisection was the British physicist and spiritualist Sir Oliver Lodge. As Wilson has reported, Lodge wrote in a 1930 article in the *Sunday Express* extolling the virtues of tissue culture that it "offered a better means of experimenting than 'watching the comfort or discomfort of live animals subjected to treatment.'"[32] In his research on the history of tissue culture, however, Wilson found, aside from Lodge's article, no evidence that it was seriously considered as an alternative to animal experimentation in the 1920s and 1930s. "No other newspapers carried a similar argument, and no antivivisection or animal welfare organization promoted tissue culture."[33] Tissue culture was not seen as a viable alternative in this period. Honor Fell, director of the Strangeways Research Laboratory in Cambridge, England, for example, wrote in an article in 1935 that tissue culture, while a valuable biological technique, could never replace experimental animals because we could not generally expect to obtain the same results in vitro as we do in vivo. The impact of Harrison's discovery on the field of alternatives was not felt for several decades.[34]

Rob Boddice has argued that tissue culture research raised new ethical objections to biological research because it "threatened the very sanctity of life, of the boundaries of the individual, considered as a temporally bound existence attached to subjective experience." He wrote that scientists "using tissue culture to examine and manipulate life at the cellular level were playing God." He pointed to Julian Huxley's 1926 short story "The Tissue-Culture King" as an exemplar of such concerns. The story involves an English researcher who endears himself to the king of an African tribe that captures him by culturing and mass-producing the king's tissue cells to, he claims, increase the safety of the life that was in him and to ensure that some of their protective power could reside everywhere in the country. This bizarre story goes on to depict the scientist creating (not necessarily through tissue culture methods) animal monstrosities such as two-headed toads and human oddities such as eight-foot-tall bodyguards. He even experiments with a device to control minds and caps of metal foil to protect against the mind control signals (the first "tinfoil" hats). As Duncan Wilson has discussed, ethical concerns did arise about creating hybrid cells between animals and especially about human tissue culture research involving controversial issues such as fetal tissue culture research and the ownership of tissue culture lines. Neither Boddice nor Wilson present any evidence that concerns of this type significantly impeded animal experimentation involving tissue cultures, nor did I find any in my own research.[35]

The establishment of the germ theory of disease and the science of microbiology in the late nineteenth century would also have ultimate consequences for the study of alternative methods, but not for many years. It is true that once the cause of an infectious

disease had been identified, scientists could initially test the effects of chemicals against pathogenic microorganisms in vitro. This methodology was most clearly expressed by the German researcher Paul Ehrlich, who established the concept of chemotherapy in the early twentieth century. Chemotherapy was based on the principle that certain chemical agents were more toxic to specific pathogenic microorganisms than they were to animal or human cells, and thus could be given internally to treat disease. Finding such "magic bullets," as Ehrlich termed them, turned out to be more difficult than originally anticipated. Using a process of chemical modification of drugs and testing them in vitro against pathogenic microorganisms, Ehrlich was able to identify potentially useful therapeutic agents, such as Salvarsan, which he introduced for the treatment of syphilis in 1910.[36]

Chemotherapeutic research, however, did not eliminate the use of animals, although it could perhaps reduce the number used through a more rational approach to finding drugs (along the lines of the structure-activity research advocated by Richardson and others) and initial testing of drugs in vitro. Ultimately the drugs had to be tested in animals. Ehrlich himself emphasized that in experimental therapeutics, one had to investigate the effects of drugs in vivo, and specifically in animals with the disease being studied. He criticized the field of pharmacology for concentrating on the study of the effects of drugs on healthy animals rather than those with a disease, a method that he argued would not solve the problems of curing disease.[37]

Antivivisection and Animal Welfare in America

The first animal welfare organization in the United States was the American Society for the Prevention of Cruelty to Animals (ASPCA), founded in 1866 by Henry Bergh after a visit to London where he attended several meetings of the RSPCA. Shortly thereafter, a number of states and cities established local societies for the prevention of cruelty to animals. Vivisection was only one of the concerns of these organizations, which focused on a variety of animal protection issues. After the death in 1888 of Bergh, who had been committed to the abolition of all experiments on living animals, the ASPCA began to retreat from his hard-line position. Conflicts developed in several humane societies, such as the American Humane Association (AHA), founded in 1877, between antivivisectionists and animal protectionists who were not opposed to all experiments on animals. The AHA, for example, passed a resolution in 1892 calling for state laws prohibiting painful experiments on animals solely for demonstration purposes. Tensions between the two factions led those who wanted the humane societies to take

a stronger stand against all animal experimentation to establish several exclusively antivivisection societies, beginning with the American Anti-Vivisection Society in 1883.[38]

Moderates in the animal protection movement emphasized the reform, rather than the abolition, of animal experimentation. They favored legal safeguards to ensure the welfare of laboratory animals. Even a majority of physicians, according to an 1895 poll conducted by the AHA, supported some regulation of vivisection. Physician Alfred Leffingwell, according to Bernard Unti, "was the nation's most active medical critical of animal experimentation during the years 1885–1915," and "he consistently advocated the regulation of vivisection, not its abolition." Unlike their British counterparts, however, American humane societies did not succeed at this time in their effort to have legislation regulating animal experimentation enacted.[39]

It is ironic that the key figure in the development of what was probably the first code of ethics for animal experimentation in the United States was the Harvard physiologist Walter Cannon, one of the strongest American defenders of animal research. As chair of the American Medical Association's Council on the Defense of Medical Research, Cannon circulated in 1909 a set of voluntary rules to all American laboratories and medical schools that had reported using animals in research. As Susan Lederer has noted: "The committee did not expect that the regulations would alter the care that the animals already received in the best institutions." By the next year, Cannon was able to report that thirty-seven medical institutions had agreed to adopt the rules, and many others had expressed a willingness to do so. Bernard Unti has commented on Cannon's motivation and raised doubts about how strictly the code was enforced: "In developing the code, Cannon was motivated by his desire to defuse antivivisectionist criticism as well as to convince legislators and the public that the scientific community was earnest about self-regulation. However, beyond the initial endorsements of the institutions to which Cannon appealed, there is a lack of historical evidence of compliance of higher standards of animal care within these institutions. Without such documentation, there simply is no ground for the claims of the medical science community to a long tradition of successful self-regulation."[40]

Once again we see that it was the pressures exerted by animal protectionists that prompted Cannon and the American Medical Association to propose a code for the conduct of animal experimentation. This proposed system of self-policing did not satisfy animal welfare advocates, who probably viewed it as putting the fox in charge of the henhouse. They undoubtedly felt justified in their concerns when just a few years later, in 1913, the New York Medical Society opposed an amendment to a proposed animal welfare bill in the New York legislature that would have incorporated the Council on the Defense of Medical Research's rules into the state's penal code.[41]

The antivivisection movement in the United States probably peaked around the turn of the twentieth century, although the claim by William Welch of Johns Hopkins University in 1926 that it was by then a "lost cause" was an exaggeration. Susan Lederer has pointed out that antivivisectionists waged a continuous campaign in the 1920s and 1930s to try to enact legislation prohibiting experimentation with living dogs, although these bills routinely failed to pass. Lederer admits that antivivisection no longer commanded the broad public support that it did in the late nineteenth century. Bernard Unti argues that the antivivisection movement, although not dead, was certainly not robust in the period between 1920 and 1950. He cites as evidence the facts that the dog exemption bills never "made it out of committee, nor did they generate great alarm on the part of experimenters."[42]

The conflict between animal welfare advocates and scientists became more intense again around the middle of the twentieth century. A major issue fueling the controversy was the question of the provision of animals for research by animal pounds or shelters. The need for laboratory animals greatly increased after the Second World War due to the rapid expansion of biomedical research, stimulated in large part in the United States by massive funding from the federal government. The burgeoning biomedical research enterprise required a substantially greater supply of laboratory animals. Pound animals had long been one source of supply for investigators, but the burst of research activity after the Second World War significantly increased the importance of the pound as a source of inexpensive animals.[43]

On the eve of this dramatic expansion in research, biomedical scientists were already becoming more concerned about the activities of antivivisectionists. As previously noted, laws to restrict medical research on animals, especially dogs, had been introduced in a number of state legislatures. Although none of these bills had passed, the scientific community, concerned about what they viewed as a threat to biomedical research, saw a need to educate the public about the importance of animal experimentation. At the 1944 meeting of the Association of American Medical Colleges in Detroit, a special committee was appointed to consider the sponsorship by the association of an organization to conduct a national education campaign on the necessity for and contributions of animal experimentation. The committee recommended, and the association approved at its 1945 meeting, that the association sponsor a national commission for the protection of medical science. The new organization, called the National Society for Medical Research (NSMR), was established with its headquarters in Chicago. The society's statement of purpose was as follows: "To inform the public regarding the necessity, humane character and accomplishments of animal experimentation."[44]

The major thrust of the NSMR in its early years was to combat legislation restricting animal experimentation and to work for the passage of animal seizure or animal procurement laws. These laws required animal shelters or pounds to make available, upon request, unwanted stray animals to scientific institutions. The first such law was passed in 1948 in Minnesota, and soon several other states enacted similar legislation. These pound seizure laws brought the NSMR into conflict with local humane societies, which operated many of the animal shelters and viewed the practice of mandatory seizure as compromising their mission and integrity. To the NSMR and its supporters, opposition to these laws was absurd and counterproductive since the animals to be turned over to laboratories were destined for euthanasia in any case. They failed to understand that the main goal of local humane societies was to prevent the suffering of animals, and they would rather euthanize unwanted animals than allow them to die on the streets from hunger or cold or from being run over by an automobile. People who turned in animals to shelters believed that they could at least be assured that their pet would die a painless and peaceful death if a home could not be found for it. Most of them would have been horrified to think that their pets might be turned over to laboratories to be subjects of possibly painful experiments. As Bernard Unti has noted, the pound seizure laws "precipitated the transformation and revitalization of organized animal protection in the early 1950s."[45]

When the American Humane Association (AHA), which served as an umbrella society for the local humane societies, declined to take part in the controversy, New York businessman Roger Stevens and his wife Christine founded the Animal Welfare Institute (AWI). The AWI opposed the mandatory turning over of pound animals that were destined for euthanasia to research laboratories (although it did not object to voluntary agreements between shelters and medical institutions provided that the animals would only be used in experiments under anesthesia from which they would not be permitted to recover). I have discussed in detail elsewhere the controversy between the NSMR and the AWI over pound seizure laws and laws regulating medical research.[46]

Robert Gesell and Alternatives

Christine Stevens, the force behind the AWI, was the daughter of physiologist Robert Gesell, chair of the Physiology Department of the University of Michigan. Although Gesell made extensive use of animals, especially dogs, in his research, he apparently was concerned with the welfare of his laboratory animals from relatively early in his career.

His dogs were housed in heated kennels on the roof of the building, with access to outside runways that allowed for exercise. Gesell emphasized to his animal caretakers, coworkers, and students that there was to be no maltreatment of the animals, either in their housing or in the experimentation. The animals were generally anesthetized with morphine followed by urethane, and they were euthanized without recovering consciousness at the end of an experiment.[47]

Gesell was not of the opinion that there was no need for improvement in the conditions of animal experimentation. He believed that some system of regulating animal research was desirable. In 1946, he wrote to University of Chicago physiologist Anton Carlson, then president of the NSMR, supporting the new organization but expressing his hope that it would address issues of laboratory animal welfare.

> It is my experience that there are always a number of us who may be too sure of man's privileges to experiment on the lower forms. Some system of scrutinizing the soundness of biological problems and the skill and wisdom and consideration of the scientist would do much to convince the public that our minds are open to all sides of the problem. I doubt the wisdom of a policy which offers no supervision of animal experimentation whatever. The surest way of preventing interference from the outside by enactment of laws restricting experimentation is to convince the public that we ourselves see the soundness of proper supervision.[48]

His hopes for the NSMR were soon dashed, however. He never received a response from Carlson, nor did his daughter Christine Stevens receive one when she sent Carlson a copy of the prospectus for the AWI for comment in 1951.[49] Gesell may have sensed early on that the NSMR was not likely to work for a system of supervision of animal experimentation, even from within the scientific community, and did not pin all of his hopes on this strategy. In 1947, he wrote to the chair of the Public Health Committee of the Michigan Senate to support a bill concerning the use of animals for the advancement of medicine and public health. He added that he hoped that if the bill passed, the chair would use his influence to see that sound rules were promulgated for animal use and that "every possible consideration is given to laboratory animals, the proper use of anaesthetics, proper care and comfortable quarters for animals before and after experimental procedures."[50]

By this time, Gesell was also lecturing medical students not only on the proper care of laboratory animals, but also on ways to reduce animal use and suffering. He discussed techniques of substituting less sentient for more sentient organisms and replacing biological with physical and chemical methods where possible. One of his former

students, W. A. Freyburger, wrote in 1980 that Gesell "became a strong advocate of use of less sentient animals and non-sentient methods for attainment of scientific data. When I took the medical school course in physiology in 1947, this position was espoused by Dr. Gesell."[51]

Gesell apparently did not publish his call for alternatives, at least not under his name. There is little doubt, however, that he was responsible for the scientific aspects of the initial prospectus of the AWI (on whose board he served), including the discussion of alternatives. In the summer of 1951, a typescript document entitled "Notes for a Prospectus for the Animal Welfare Institute" (under the name of Christine Stevens) was prepared and distributed to various individuals for comment. The document includes two sections relevant to alternatives.[52]

Among the basic principles set forth for the institute is one that states: "Criteria for pain-infliction in scientific experimentation and standards for its justification must be established as clearly as possible." Experimenters must take into account in each case the intensity and duration of suffering involved, the number of animals affected, the ultimate value of the experiment, the feasibility of using other less painful methods, and the extent and degree of mental suffering involved. The end justifies the means only if these means fall within reasonable limits.[53]

The second example deals directly with alternatives. The prospectus expresses the hope that new developments may mitigate animal suffering. The institute intended to investigate and foster the development of experimental methods that would minimize animal suffering. These fields of investigation might include:

a. Practical *replacement of the higher mammals by much lower forms of life* or life in lower stages of embryonic development (such as chick embryos) with a view to reducing the suffering undergone by animals with highly developed nervous systems.
b. Practical *replacement of chronic experiments involving protracted physical or mental suffering* by properly conducted sacrifice experiments with a view to reducing the number of painful experiments.
c. The *efficient statistical design of experiments* so as to affect a systematic economy in sampling. For example, methods whereby limitations in the number of variables introduced in an experiment makes possible the reduction of the number of animals necessary.
d. The *substitution of chemical and physical methods*, whenever possible, for biological methods in experiments or tests.
e. The means of *avoiding unnecessary repetition of experiments*.[54]

This statement, issued by the AWI and reflecting the views of Gesell, would appear to be the clearest exposition of the idea of alternatives before the development of the concept of the Three Rs (replacement, reduction, refinement) by W. M. S. Russell and Rex Burch in the period 1955–1957 and the publication in 1959 of their seminal work *The Principles of Humane Experimental Technique* (discussed in the next chapter). The AWI statement does not specifically use the term "alternatives," nor does it explicitly refer to the Three Rs, but it does express these principles. A printed version of the prospectus, including without change the two sections referenced above, was published on October 1, 1951. There is no evidence, however, that it had any influence in the biomedical community with respect to alternatives, which is not surprising given the suspicion with which the NSMR, for example, viewed the AWI and Gesell. As we shall see in future chapters, the scientific community was originally decidedly cool and sometimes even hostile to the idea of alternatives.[55]

The first issue of the AWI's *Information Report*, published in December 1951, included an invitation to scientific research workers to correspond with the institute with their suggestions for "possible methods whereby practical replacements made be made of higher mammals by lower forms of life or life in lower stages of embryonic development, or whereby properly conducted sacrifice experiments might replace some types of chronic experiments." The statement also expressed an interest on the part of the AWI in "methods whereby greater economy of sampling may be affected, chemical and physical testing methods, and means whereby unnecessary repetition of painful experiments may be avoided."[56]

Gesell never had a chance to read or comment on the work of Russell and Burch published later in the decade, for he died suddenly of a heart attack in April 1954. In his last few years, his strong views on animal experimentation brought him into conflict with his fellow physiologists. Since I have discussed this controversy in detail elsewhere, here I will just summarize it and refer readers to my publication on the subject for further details and references.[57]

As early as 1951 he clashed with University of Minnesota physiologist Maurice Visscher about a comment in an article by Gesell about the problems created by human population expansion. One of the points that Gesell made in this publication was that for every increase in population of 10 million there would be an additional 500,000 cases of cancer, and that in the meantime countless animals would be subjected to painful experiments in an effort to eradicate the disease. Visscher wrote to Gesell expressing his concern that the reference to painful animal experimentation would be seized upon by antivivisectionists as evidence that Gesell did not believe that these experimental investigations were necessary. He suggested that Gesell might forestall such a tactic

by publishing a positive statement about animal experimentation in the *Bulletin of the National Society for Medical Research*. Gesell declined this suggestion and instead sent Visscher a copy of his 1946 letter to Carlson cited above, in which he expressed his view that the present condition of animal experimentation was not ideal.

The disagreement between Gesell and his colleagues came to a head in February 1952 when he sent a printed memo to all members of the Federation of American Societies for Experimental Biology (FASEB), of which the American Physiological Society was a member. The communication expressed his concerns about animal experimentation. Gesell reproduced an article and two letters from the British medical journal *Lancet* in 1949 that criticized certain studies published in American and Canadian medical journals for inflicting unnecessary and unjustifiable pain on the experimental animals involved. Gesell also attacked a more recent article involving the drowning of 160 dogs, charging that such experiments "remind us so inescapably of the 'Doctors of Infamy' (Henry Schuman, New York), who performed terminal experiments on men and women without the use of anesthesia." Finally, Gesell defended the AWI against attacks by both scientific groups and antivivisectionists.

Gesell's letter was followed by a statement at the business meeting of the American Physiological Society (APS) on April 15, 1952. Gesell expressed his concerns about some of the types of animal experimentation being carried out, but used most of his remarks to criticize the NSMR. His remarks, unsurprisingly, were not received warmly by his colleagues, and he barely escaped a vote of censure. To make matters worse, Gesell sent out another mailing to FASEB members in March 1953 reproducing his remarks from the APS meeting. His colleagues were not quite sure what to make of his views or how to deal with them. His position was considered to be misguided and even absurd. The fact that antivivisectionists made use of Gesell's views to show that at least one prominent biomedical scientist was concerned about how animals were being treated in laboratories only exacerbated the matter in the eyes of his colleagues. Finding it hard to believe that a reputable physiologist could make such charges, Gesell's colleagues apparently thought that some health problem must have clouded his judgment. Gesell's death in 1954 ended the matter. Visscher uncharitably referred to him at the 1955 APS meeting as "the late unlamented Gesell."

Gesell was unusual for his time as a prominent scientist involved in animal experimentation who was critical of how this experimentation was often carried out and believed in the need to regulate it. Although his daughter Christine became an influential animal welfare advocate, Gesell's concerns about animals in research predated her involvement in the field, and it seems likely that she was influenced to become involved in animal protection work by her father rather than vice versa. Gesell's efforts to reduce

animal use and suffering and to replace animals where possible in experimentation were apparently not motivated (as, e.g., were those of Hall or Cannon) by concerns about appeasing antivivisectionists and animal protectionists, but by his own concerns about the state of animal experimentation. For voicing these concerns, he was castigated by his scientific colleagues.

The British Boogeyman

Although the death of Gesell terminated his conflict with the American Physiological Society, it did not end the disagreements between animal welfare advocates and biomedical researchers. From about the time of Gesell's death through the mid-1960s, a chief bone of contention was the effort by humane organizations to get a federal law regulating animal research enacted. The principal voice of the scientists in this conflict was the NSMR; its chief national opponents were the AWI and, after it was founded in 1954, the Humane Society of the United States (HSUS). The NSMR referred to both organizations as "neo-antivivisectionists." The HSUS was created by four dissidents from the AHA, led by Fred Myers, who believed that the organization had become too conservative in its approach to animal issues and unwilling to take any action that it believed to be controversial. As noted above, for example, the AHA declined to become involved in the battle over pound seizure laws. In its guiding principles, the newly created HSUS stated that it "opposes and seeks to prevent all use of exploitation of animals that causes pain, suffering, or fear." Like the AWI, the HSUS did not adopt an antivivisectionist stance, but sought practical, incremental solutions to prevent or mitigate the suffering of animals in the laboratory and elsewhere. In his history of the HSUS, Unti states: "While determined to be aggressive in the struggle against cruelty, those who formed the HSUS were equally resolute in their conviction that the organization must pursue a practical, effective course that accepted the path of incremental improvements. They committed themselves to 'action that will actually help animals and achieve practical humane education.'"[58]

Animal welfare advocates argued that housing and care for research animals were poor in many laboratories and that more could be done to reduce suffering in experimental procedures. From its founding in 1951, the AWI favored placing some kind of licensing and oversight restrictions on animal experimentation. The AWI's model was the 1876 British Cruelty to Animals Act. For its part, the NSMR rejected the view that there was a significant amount of abuse in the care and use of laboratory animals and was opposed to any kind of government regulation.[59]

The British law in particular was anathema to the NSMR and many American biomedical scientists. In their view, the law had hampered scientific research and education in Britain, and they used this as an argument against the enactment of a law regulating animal research. In a letter to Christine Stevens in February 1952, executive secretary of the NSMR Ralph Rohweder responded to a claim that the United States lagged behind Britain with regard to regulation of vivisection, stating:

> Not if you consider the rate of medical discovery important, it doesn't. The United States is the scene of more medical research and more medical discoveries than all the other countries on earth put together. America's capacity in this regard, like America's great productive capacity, is in part due to the fact that we are not quite yet strangled with regulations, bureaucracy and red tape. Have you talked to British scientists about the extra cost and the extra effort of the extra paper work? Have you heard the stories about the "understandings" with inspectors and all of the other bureaucratic shenanigans that characterize the "control everything" type of society?[60]

Stevens consulted with the Universities Federation for Animal Welfare (UFAW) about the British legislation. The UFAW was founded by Major Charles Hume in 1926 as the University of London Animal Welfare Society. Its aim was to mobilize science and scientists to help solve problems over the whole spectrum of animal welfare. By 1938, the organization had spread to a number of other British universities and changed its name to the Universities Federation for Animal Welfare. In 1947, the UFAW published its first handbook on the care of laboratory animals, followed by revised editions over the years. The federation declined to take a position on the question of the legitimacy of animal experimentation, but concerned itself with fostering the mitigation of physical and mental discomfort of laboratory animals.[61]

In 1950, Hume drafted a new model act for the protection of laboratory animals (which never went anywhere), a copy of which was sent to Stevens by a member of the Massachusetts Society for the Prevention of Cruelty to Animals. At about the same time, another colleague sent her a copy of the UFAW booklet "How to Befriend Laboratory Animals." These documents appear to have introduced Stevens to UFAW, which she first contacted in a letter of December 1950, asking for multiple copies of these publications and for advice on legislation. She wrote: "I feel there is urgent need for proper regulation of the use of laboratory animals in the United States. How to achieve it is a most difficult problem, and I should be very grateful to you for any suggestions which you might care to make on the basis of your experience in this work."[62]

Stevens and the UFAW were soon in regular contact. She traveled to Britain and met Hume and others in the organization, as well as visiting, at the suggestion of her father, the laboratories of several British medical researchers, including Alexander Fleming, the discoverer of penicillin. In the very first issue of the AWI's *Information Report*, published in December 1951, Stevens included a quotation from Hume on animal experimentation and welfare. The following year, the publication included a report on her observations on animal experimentation in Britain and an invited letter from Hume on the vivisection controversy there, in which he defended the British legislation on animal research. In 1953, the *Information Report* published "U.F.A.W. Suggestions for Protection of Laboratory Animals," which provided a "summary of the Cruelty to Animals Act, 1876, and of the practices which have gradually come to be based upon it." The document was prepared in response to a query from researchers in another country (which the AWI stated was not the United States) asking for suggestions for legislation for the protection of laboratory animals that they might urge their government to adopt.[63]

Stevens, undoubtedly influenced to a significant extent by Hume and the UFAW, strongly supported the British law and system of regulation of animal research. She stubbornly fought for American legislation based on this model throughout the 1950s and 1960s in the campaign leading to the passage of the Animal Welfare Act of 1966. A detailed discussion of this campaign is beyond the scope of this book, but it is important to consider the resistance of the American biomedical science community to a British-style law. The negativity of many American scientists and their organizations toward the British system of regulation may well have colored their initial response to the Three Rs concept of alternatives developed by Russell and Burch (see chapter 2), coming as it did out of Britain and the UFAW, as discussed later in the present book.[64]

Stevens had sent Rohweder a copy of a proposed model "Act for the Protection of Laboratory Animals" developed by Hume in March 1952, requesting input from scientists on this proposal. One of those to whom Rohweder circulated the model law was Maurice Visscher, who objected to several sections of the act. More broadly, however, Visscher noted that he was opposed "in principle to the establishment of any new and peculiar mechanism for the control of the treatment of animals in scientific research." He believed that the generic anti-cruelty acts in place in the United States were adequate to deal with any abuse of laboratory animals. Visscher also complained that in a "day and age when governments are tending to invade private lives," there was no need for "the establishment of more and more bureaucratic mechanisms for regulation."[65]

Visscher, who was later in his career to serve as president of NSMR, was a vehement opponent of legislation to regulate animal research, especially anything based on the

British model. He frequently made claims about the negative effects of the 1876 law on animal research in Britain. In an article in the NSMR's *Bulletin of Medical Research* in 1954, for example, he argued that the new twist to the antivivisection campaign was to argue for regulation rather than abolition of animal experimentation. He went on to state: "American antivivisectionists point to the long history of government regulation in Great Britain and ask when the U.S.A. will imitate this 'advanced' humanitarianism. They do not, of course, add that much of Britain's difficulty in training medical students in surgery comes from these laws; that British scientists have had to go to other countries to make certain important studies; that the great humanitarian Adolph Hitler also put through a similar decree."[66]

A decade later, when Hume was invited to testify at a congressional hearing on an animal research bill and cited numerous British scientists who supported that country's approach, Visscher pointed to what he claimed was "the general backwardness of British surgery" in defending the view that the British act hindered scientific advances. He recognized, however, that "the question of whether the British law does or does not impede scientific research and teaching has become a question of some importance" and that more evidence on the matter was needed. He also argued that the proposed American legislation was even stricter than the British act.[67]

Visscher was reluctant to concede, even when presented with evidence to the contrary, that the British act had not impeded medical research there. He reported in a letter, for example, on a conversation with a physiologist from University College, London, "who reiterated the general consensus in Britain that their animal experimentation act has more merit than demerit, and that they would not want to repeal it." This colleague informed him that the administration of the act was in the hands of very sensible men and "that the scientists are really not impeded in any noticeable ways." Visscher's reaction to these views was as follows: "Actually, I cannot believe this to be true, because there certainly is great impediment to the performance of experiments by people in such categories as medical students and graduate students. However, the British seem to think that they can live with it. I hope that we do not have to."[68]

Visscher's concerns about the British law were reflected by other leading biomedical scientists and organizations, as reflected in the following examples. Prominent surgeon Lester Dragstedt of the University of Florida expressed his view to Visscher in 1961 that he was convinced that governmental regulation of research in Britain hampered the work of surgeons and surgical research. In that same year, in response to animal legislation introduced into the US Congress, the American Physiological Society made an appeal to its members to provide it with any specific case evidence they had of impediments to scientific research under the British law. At that same time, Minnesota

physiologist H. J. C. Swan wrote to a member of the House of Representatives expressing concern about two bills before Congress. Noting that he had firsthand experience with work in Britain under their system of licensing and regulation, he stated that it presented real obstacles to medical research. He added: "Particularly in application to problems of disease and their surgical treatment, work in Britain has lagged behind this country."[69]

In 1963, Andrew Ryan, dean of students at the Chicago Medical School, wrote an article on the history of the British act of 1876 in the *Journal of Medical Education* in which he claimed that it had been detrimental to research in that country. Although he admitted that it was difficult to quantify the loss in productivity of British science due to this law, he confidently stated that "there is evidence that science has suffered." He then went on to criticize the animal welfare bills before Congress at the time, arguing that the proposed restrictions went beyond the British law. The British story, he concluded, should serve as a lesson warning against the proposed American legislation.[70]

Another strong critic of the British law was Ralph Rohweder, executive secretary of the NSMR, whose letter to Christine Stevens criticizing the British system was cited above. In general, the NSMR made frequent use of the British "boogeyman" in their efforts to derail any legislation regulating animal research. Like Visscher, Rohweder saw this effort as part of a broader "police-state" mentality with its emphasis on trying to solve issues by passing laws. He expressed this view, for example, in a letter that he wrote to a colleague in 1960 complaining that Stevens's emphasis on the British regulatory approach was "right in tune with popular thinking." He added: "If there is a problem, pass a law against it. Set up a new police agency to enforce it." Rohweder argued that the best way to improve laboratory animal care was through training, information, and persuasion, not "cops-and-robbers regulation."[71]

In an effort to counter these arguments and support the case for regulation in the United States, the UFAW sent a circular letter in 1960 to biologist fellows of the Royal Society asking them to respond to three questions. The scientists were asked whether they believed that the British animal law prevented research of the highest quality from being carried out in Britain, whether they favored abolishment of the British system of regulation, and whether in their own experience the system seriously frustrated legitimate research. Seventeen fellows replied "no" to all three questions without offering any comments, indicating their support of the British system. Another sixty-six fellows responded "no" to the questionnaire and also added comments, only a few of which offered minor criticisms on matters of detail. Only one of the eighty-eight scientists who replied expressed frustration with the system, believing that experiments on the brain, his field of research, were inhibited by the section of the law dealing with the minimizing of pain.[72]

Among the comments made in the replies were the following. James Craigie of the Imperial Cancer Research Fund stated that "it is nonsense" to claim that the British system of regulation interfered with high-quality research. C. A. Hoare of the Wellcome Laboratories of Tropical Medicine asserted that he had "never come across any instance which might indicate that the system had any adverse effect upon medical or biological research of the highest order." Retired physician and researcher Leonard Colebrook, who had been the first in Britain to carry out clinical tests with sulfa drugs, said that in his opinion the British law did not "seriously frustrate legitimate research." All three of these men, as well as others who replied to the survey, emphasized that the British system of animal regulation was a positive factor in biomedical research, providing, in the words of Hoare, "conditions for research that are beyond reproach." Rohweder of the NSMR dismissed the results of the survey on the grounds that the questions were "loaded."[73]

Several respondents commented that they believed there was a need for some kind of regulation in the United States. Nobel laureate Hans Krebs of the University of Oxford, for example, said he was glad to support the introduction of such legislation in the United States. R. J. C. Harris of the Imperial Cancer Research Fund noted that from what he had read about the conditions under which some work in American laboratories was carried out without adequate supervision, "that it is high time that the Americans put their house in order."[74]

These comments reflect a broader tension between American and British scientists over the animal welfare issue. Many British scientists and other individuals resented the American characterization of some areas of British biomedical research as "backward" due to the restrictions of the 1876 law. In the letter cited above by R. J. C. Harris of the Imperial Cancer Research Fund, he argued that the record of medical research in Britain since the passage of the 1876 legislation was sufficient proof that the suggestion that British biomedical science had been hindered by this law was worthless. Sir Arthur Porritt, president of the Royal College of Surgeons of England, stated in reply to a query from Major C. W. Hume that "very considerable advances in medical and scientific knowledge have been made in this country during the last fifty years," many of which involved experiments on animals. In a letter to the British journal *The New Scientist* published in 1961, Hume raised the following point: "If this restraint has really impaired the quality of British research it does seem odd that *in proportion to population* more Nobel Prizes for medicine or physiology have been awarded to British scientists than to those of any other nation."[75]

Even William Lane-Petter, secretary of the Research Defence Society (Britain's counterpart to the NSMR), expressed his concerns about some of the views voiced by Americans about British medical research in a letter to Ralph Rohweder in December

1960. He criticized the views of Rohweder and other Americans about surgical training in Britain, characterizing them as "a gratuitous misrepresentation" and "a most unworthy slur." He added: "We do not like it any more than we like the implication of some of the more extreme criticisms of our control of animal experimentation, which seem to imply that we cannot conduct decent research in this country because of these restrictions. We seem to have a sufficient number of Nobel Prize winners and other eminent scientists to ground that kite. I doubt if we would have had any more, if there had never been an act of 1876."[76]

On the other hand, the NSMR resented the fact that some of their British colleagues openly expressed their concerns about the state of animal welfare in the United States or their support for legislation to regulate animal research there. In the letter to Lane-Petter that provoked the reply cited above, Rohweder complained about "the efforts of a few British scientists to help sell British-type regulation in the United States." Lane-Petter felt compelled to respond to this. He argued that while most of his colleagues supported the British law, this was very far from trying to "sell" it to the United States, and he challenged Rohweder to name the scientists he had in mind. Lane-Petter also noted that he felt "bound to add that there are animal houses in the United States where the conditions surrounding the animals are not what they should be." An editorial in the Research Defence Society's publication *Conquest* a couple of years later reinforced this point, stating that it would be foolish, even impudent, for Britain to say to the United States "do as we do" with respect to the regulation of animal research. However, the editorial went on to defend the British system and to say that Britain could help in the discussion by showing how a working system evolved in that nation.[77]

Just as the author of the editorial in *Conquest* recognized that any British involvement in efforts to pass animal regulation legislation in the United States was a touchy subject, Americans were well aware that their own claim that the British law had hindered research in that country was a sensitive issue as well. As Rohweder expressed it in his letter to Lane-Petter, "the more pointedly we state the case against the negative police approach to progress the more likely we are to be interpreted by some Britons as attacking 'their' system."[78]

As the debate over animal regulation legislation in the United States continued, Russell and Burch's seminal book, *The Principles of Humane Experimental Technique*, to be discussed in the next chapter, was published in 1959.

2

Russell, Burch, and the Three Rs

The beginnings of a formal alternatives movement based on the three Rs (replacement, reduction, and refinement) can be traced back to a project sponsored by the Universities Federation for Animal Welfare (UFAW) which resulted in the publication of *The Principles of Humane Experimental Technique* in 1959. UFAW had been established as the University of London Animal Welfare Society (ULAWS) in 1926 by British Army captain (later major) Charles Westley Hume. Hume believed that issues of animal welfare should be handled with a maximum of sympathy and a minimum of sentimentality. He was anxious to distance his organization from antivivisectionists, as he believed that "fanatics" often inadvertently did more harm than good. He later explained that the society "came into existence in order to focus attention on the importance of authentic knowledge and accurate thought for effectively befriending animals." In an effort to advance this goal, he arranged a meeting at Birkbeck College, University of London (from which he had graduated with training in science) on February 12, 1926. Although there were apparently only two others present, Hume was commissioned to form a university society, ULAWS. Sir Frederick Hobday, principal of the Royal Veterinary College, was appointed president, lending a scientific cachet to the new organization.[1]

Over succeeding decades, the society focused on a variety of animal welfare issues, for example, humane animal trapping methods, the use of cruelty-free perfumes, and the welfare of animals used in films. In 1938, the name of the organization was changed to the Universities Federation for Animal Welfare. The new name better reflected the

increasingly wide range of people and institutions the former ULAWS dealt with. For example, UFAW branches were formed at a number of universities besides the University of London, such as Cambridge, Oxford, Durham, Reading, and Glasgow. The specific stimulus for this change in the organization was the University of London's refusal to grant ULAWS permission to broadcast an appeal for funds on the BBC. The refusal had nothing to do with the aims of ULAWS, but was due to the University Senate's desire to avoid any confusion with an appeal that the university itself was planning. With University of London removed from its name, UFAW did not require the permission of the senate to go ahead with its fundraising efforts.[2]

UFAW and Laboratory Animal Welfare

UFAW's first substantial foray into the field of laboratory animal welfare appears to have come with the publication of *The Care and Management of Laboratory Animals: Handbook of the Universities Federation for Animal Welfare* in 1947. Work on the book, which was edited by Professor Alastair N. Worden of the Institute of Animal Pathology at the University of Cambridge, had begun in 1943. In a 1944 letter to *JAMA*, Worden announced that UFAW was compiling a handbook for the care and management of laboratory animals designed to be of use to both scientists and technicians. He stated that the aim of the book was "to provide a concise, practical manual which will facilitate the uniform and humanitarian care of the smaller laboratory species" and that he hoped it would be used in Canada and the United States as well as in Britain. The book appears to have been the first guide to the husbandry of laboratory animals. The manual, now called *The UFAW Handbook on the Care and Management of Laboratory and Other Research Animals*, has gone through eight editions and is still in use today.[3]

In reviewing the book, Dr. Egbert Morland, retired editor of *Lancet*, praised the work for "mediating with rare insight between two irreconcilable combatants" (namely, the opponents and defenders of the use of animals in research). He added, with respect to this controversy: "It relieved my mind of the misery of watching it go on year in and year out, and it seemed for ever." Morland was overly optimistic as the controversy over animal research did not disappear, but the publication of the handbook and the emergence of an active role for UFAW in this area did contribute to more meaningful discussions between animal welfare advocates and scientists, at least in Britain.[4]

Major Hume himself later reflected on the success of the book. In a lecture before the Animal Care Panel in 1959, he stated: "At first, the anti-vivisectionists viewed it

with suspicion, but as time went on came to see that, since experimentation will continue whether they like it or not, there is everything to be said for making the animals as comfortable as possible. On the other side of the fence research workers were quick to see that this *Handbook* would help them to fulfil their own wishes, by improving both the humaneness and the technical efficiency of their laboratory work. This disarmed the suspicion with which many scientists viewed UFAW."[5]

Perhaps because British scientists had been used to some level of government regulation of animal experimentation since 1876, they were much more responsive to working with UFAW than American scientists in general were to collaborating with groups such as the Animal Welfare Institute (AWI). For example, Dr. William Lane-Petter, honorary secretary of the Research Defence Society (Britain's primary defender of animal research), coedited the second edition of the *UFAW Handbook* with Worden in 1957.

The interest in laboratory animal welfare stimulated by UFAW in the wake of the publication of the first edition of its *Handbook* in 1947 likely played a role in the decision of Britain's Medical Research Council to establish a Laboratory Animals Centre in that year. Three years later, the Animal Technicians Association (now the Institute of Animal Technology) was founded. In 1959, Hume expressed the view that "this change of climate made possible what we had always hoped for—a calm and objective discussion of the problem of vivisection, as opposed to the cut and thrust of controversy in which each side has to make as striking a case as it can, and nobody dare concede a point or yield an inch of ground."[6]

In the early 1950s, UFAW decided to move beyond issues of animal husbandry to tackle the more controversial subject of experimental techniques used on animals in the laboratory. As noted in the previous chapter, the number of animals used in laboratories increased substantially in the United States with the dramatic growth in biomedical research following the Second World War. These numbers also grew significantly in Britain in this period, a development that concerned Hume and other animal welfare activists. In a 1959 lecture, Hume pointed out that British experimenters were using "possibly half a million rats and some two million mice every year." He expressed the concern that these large numbers entailed "an obvious risk that an experimenter may begin to think of animals as if they were things" and "of no more consequence than a test-tube." He worried that animals might be being used in unnecessarily large numbers in research.[7]

Hume had already begun to express concerns about some animal experimentation practices by the end of the 1940s. He was one of the co-signers of a letter to the *Lancet* in 1949 criticizing some recent papers that described Canadian and American

experiments "calculated to inflict the maximum of injury consistent with the temporary survival of the animals, which were then studied physiologically." The signers of the letter emphasized that they were not questioning the importance of experiments on animals, but rather the particular procedures used. They closed by suggesting that "in planning his procedure every experimenter should earnestly consider whether the infliction of the pain involved is really justifiable in the interests of medicine or science, and try to devise techniques that will reduce suffering to a minimum."[8]

That same year UFAW published Hume's pamphlet on *How to Befriend Laboratory Animals*. In this little work, Hume touched on some issues that would be incorporated into the Three Rs. For example, he discussed the importance of reducing the number of animals used in research through statistical analysis and other methods. He also talked about choosing the method that caused the least suffering and developing new and better techniques (such as improved anesthesia). In 1950, Hume sent a draft of a model Act for the Protection of Laboratory Animals to the *British Medical Journal*, explaining in a cover note that the purpose of the draft was to enable UFAW to assist foreign colleagues who wished to promote such legislation in their own countries. Although applauding Hume's intentions, the *Journal* was critical of the details of the bill.[9]

Origins of UFAW's Humane Experimental Techniques Program

As early as March 1953, Hume informed the UFAW Executive Committee that for some time he had been "taking soundings" on the subject of research on "the humanitarian aspect of experimental techniques," although he indicated that this was not likely to become urgent "until the right combination of research worker, facilities, and funds should materialize." In May, Hume decided that the appropriate time had come, and he suggested to the Executive Committee that upon the upcoming retirement of Dr. Phyllis Croft, whose research on anesthesia and euthanasia UFAW had been supporting, the organization should appoint a young researcher "to study the ways in which experimental methods could be rendered increasingly humane." The proposal was referred to the Scientific Subcommittee.[10]

By September, Hume was ready to move forward with the project and obtained the approval of the Executive Committee for UFAW to advertise for a research fellow on the subject of humanitarian aspects of experimental methods and procedures. In a statement published about the proposed project in May 1954, UFAW commented that the research worker who would head such an effort "would need practical wisdom

and tact." An application for the position from W. M. S. Russell was received by UFAW in June 1954.[11]

William Russell graduated with honors from Oxford in 1948, where he began his studies in classics but then switched to zoology. He then pursued graduate research on the mating behavior of the African clawed frog in the laboratory of A. C. Hardy in the Department of Zoology and Comparative Anatomy at Oxford, leading to a DPhil in 1952. At the time of his application to UFAW, he was an Agricultural Council research fellow at Oxford. Russell may have learned of the position from Peter Medawar, professor of zoology and comparative anatomy at University College London, who was then serving as chair of UFAW's Scientific Subcommittee and who played a significant role in the promotion of the concept of alternatives. Medawar had been impressed by Russell when he served as the latter's tutor in zoology during Russell's undergraduate days at Oxford, where Medawar held an appointment at the time. Russell was also well known, as reported in the minutes of the Executive Committee, to other friends of UFAW. Another factor that likely influenced UFAW in his favor was that during his graduate research, he had developed with Richard Murray a more humane method of killing the frogs involved in the study. In fact, Russell and Murray published a brief note on the method in UFAW's *Courier* in 1951.[12]

In October 1954, Russell was hired on a year-to-year contract "to undertake research into the history and progress of the introduction of humane methods into biological research, with a view to encouraging further such progress." He was to work in close collaboration with a Consultative Committee appointed by UFAW, with Medawar as chair and Hume as secretary. One of the other members was William Lane-Petter, head of the Laboratory Animals Bureau and, as previously mentioned, honorary secretary of the Research Defence Society. The right of publication of the research was vested in UFAW. Russell also arranged, with the assistance of Medawar, an appointment as an honorary research fellow at University College, London, which UFAW welcomed as it provided an opportunity for him to remain in close touch with research laboratories.[13]

Russell immediately convinced UFAW that he needed an assistant for the project. Alistair Worden, who had edited *The Care and Management of Laboratory Animals: Handbook of the Universities Federation for Animal Welfare*, learned of this opportunity and called it to the attention of Rex L. Burch. In the early part of World War II, Burch had worked in a British Army laboratory of pathology and public health in Yorkshire. There, one of his duties was to kill guinea pigs used in a diagnostic procedure for tubercle bacilli in milk with a sharp blow to the nape of the neck using a specially designed wooden instrument. He recalled years later that before taking charge of the work he wanted to make sure that the method of killing was humane. After practicing the

method on dead guinea pigs, he became proficient enough that the first live animal he tried it on died instantly, presumably setting his mind at ease.[14]

Burch soon joined the army and continued to carry out the diagnostic work with guinea pigs. After the war, he studied medicine at Guy's Hospital Medical School in London, but he had to drop out for financial reasons. He was then hired by the Boots Pure Drug Company as an assistant in tropical medicine and went on to set up a diagnostic laboratory for all of the research animals. His work at Boots, he later stated, "gave me wide experience in animal husbandry and experimental procedures, because I became deeply involved with work in breeding units and with all those working experimentally in different disciplines."[15]

A few years later, Burch established his own research and breeding unit. His bank manager called his attention to the presence of Professor Alastair Worden at the nearby National Research Unit at Huntingdon because he believed the two men had some similar scientific interests. Burch called upon Worden and later recalled that at their first meeting "he invited me to carry out histological and microbiological work for him on a casual basis." When Worden learned of the position at UFAW, he concluded that Burch's background was suitable and encouraged him to contact Hume and apply, which he did. Burch was appointed to the part-time paid position, partly on the basis of a strong recommendation from Worden, and was made a member of the UFAW Consultative Committee. He also continued his work with Somerset Pharmaceuticals, which UFAW regarded as a positive situation because it took him into laboratories across the country and thus kept him in touch with experimental work.[16]

Christine Stevens and the Animal Welfare Institute in the United States became involved with the project from its beginnings. The AWI contributed $500 toward the work in its earliest stages and indicated that it would consider further contributions in the future. In recognition of her support and interest, Hume asked that Stevens be appointed a member of the Consultative Committee. When she first met Russell at a lunch with Hume and him during one of her visits to Britain, however, she did not react positively to the project head. In her notes on the meeting, she commented: "Russell's program seems too vague, and he did not impress me as being trustworthy." She added that he wanted "to get a 'slave,' a girl who has done nutrition work at Mill Hill, to be a secretary for him," a comment that may not have sat well with her. Stevens asked him to send her a copy of the questionnaire that he planned to send to laboratory scientists. Her impression of him likely became more favorable over time, as she was an enthusiastic supporter of Russell and Burch's book on the project when it was eventually published.[17]

Work on the Humane Experimental Techniques Project

As envisioned by UFAW, two main techniques were to be employed in the work: "a historical study of the literature of experimental biology and a survey of the present trends in the field." Russell undertook the former effort and immediately developed strategies for the literature review. He indicated in notes on the project that he would focus on the introduction of new techniques, scanning the literature for examples that might seem optimal for the purposes of the study (i.e., might seem most promising from the point of view of humane experimentation). After choosing appropriate areas, he would then examine changes in the techniques employed and seek to answer questions such as these: When the technique was introduced, could it have been introduced earlier from knowledge already available? What sort of lag was there between publication and widespread adoption? What objections were raised to its use? Was it an improvement in humanity and/or efficiency? In order to limit this large task, he also planned to concentrate on the literature of recent decades, which he believed would yield more fruitful results. In fact, he stated that he would "pay considerable attention to developments occurring during the actual period of the investigation."[18]

Burch was tasked with conducting the survey under the supervision of Russell and the Consultative Committee, which would involve him personally visiting various laboratories and interviewing scientists. The Consultative Committee decided that the work should begin with a study of bioassay, "in view of the fact that more animals are used in this than in pure research and that it offers a fruitful and concrete point of attack." Early in the project, Burch made a tentative approach to the University of Cambridge, but it became obvious to him that the "usual formalities" (e.g., going through department heads) had to be observed before he could interview any members of the departments. With the assistance of Cambridge physiologist B. A. Cross, he prepared a draft of a possible letter to department heads and sent it to Russell. The draft was brief, basically just mentioning that Burch was assisting on a UFAW project on humane practices in biological research with a focus on bioassay methods. It also requested permission for him to interview members of the department involved with assay methods.[19]

Michael Balls has pointed out that this draft letter from Burch appears to have been the first time that the term "alternatives" was used in connection with humane experimentation methods. Burch had altered the original wording of his draft to change a sentence stating that UFAW hoped, as a result of the information they collected, that they

might be able to suggest improvements in routine methods of bioassay. Burch's handwritten comments on the typed draft suggested changing "improvements" to "some possible alternatives." In revising Burch's draft, Russell (who was to be the signer of the letter) crossed out "some possible alternatives" and instead wrote that UFAW hoped "to produce a review of progress in the development of humane techniques." Hume agreed with Russell, expressing concern that a reference to suggesting alternatives, even though that was what UFAW was hoping to do, might create a defensive "who are you to tell me how to do my job" attitude on the part of the scientists being interviewed. Medawar approved the draft letter, although he commented that it might have been useful to make clear that UFAW had nothing to do with antivivisection. Worden also wondered "if it might not also be helpful to make quite clear that there is no inkling of antivivisection" as there would always be some who were suspicious.[20]

Twenty-two letters were sent to selected departments in fields such as pathology, pharmacology, biochemistry, physiology, and experimental and veterinary medicine in early December. Within a few days, Russell had already received ten replies, which he passed on to Burch. All of these replies indicated a willingness to cooperate. Russell urged Burch to read all the letters carefully and "adjust your behavior accordingly." He was anxious to keep the goodwill of the scientists involved. Russell also encouraged Burch to make every effort to observe actual conditions and practices in the laboratory in addition to speaking with the scientists. He instructed him to be especially careful in discussing the psychological aspects of the study, by which he meant their interest in assessing attitudes toward humane approaches. This topic, he counseled, "should be introduced with caution after you have sized up the individual dept. member" being interviewed. He added: "It is in any case useful to start with factual discussion, especially from the point of view of possible differences between principle and practice, where it is essential to get the chap to 'give himself away' unsuspectingly. (Thus a man may express strong conscious humane attitudes, and show by negligence or avoidable inefficiency in practice that there are unconscious complications)."[21]

In December, Russell submitted a progress report to the Executive Committee indicating that the number of responses to the twenty-two letters had now increased to fifteen, all favorable. UFAW's publication *Courier* also published a short piece by Russell describing the project. In it, he emphasized the need to collect information on existing humane techniques for animal experimentation and to make them more widely known. He argued that humanity and efficiency tended to advance together, and that avoidable discomfort to laboratory animals could have physiological effects that interfered with the results of the experiment. He reiterated his belief that it was important

to study not only the techniques, but also "how the complex attitudes of individuals toward the lower animals interact with all the other variables."[22]

By the time Burch began his visits in early 1955 to the departments contacted by letter, twenty out of twenty-two of them had responded favorably. As soon as possible after his interviews, Burch would dictate his reports onto tape, and the tapes were then transcribed by a typist. One example of these reports is the transcript of his interview with virologist F. Kingsley. Burch reported that Kingsley assured him that virus workers "were only too anxious to eliminate the use of whole animals altogether, and have made considerable strides towards doing so." The use of tissue cultures, Kingsley said, involved fewer variables and produced more information. He added that there were only two purposes for which live animals had to be used: in the production of antiviral sera and for testing the virulence of a virus at certain stages of vaccine production or in some research problems. Because of the recent widespread use of tissue cultures, the report stated, in this field "humanity and efficiency are indissolubly linked." There appeared to be "no need to spur virus workers to further efforts for discovering culture methods for more viruses."[23]

Meanwhile, Russell had taken the opportunity of administering a specially designed attitudes questionnaire to fifty-three subjects at a club meeting. He considered this effort to be a valuable pilot study for his proposed investigation of "irrational attitudes to animals and the unconscious determinants of inhumanity." He reported to the Executive Committee and the Consultative Committee in March 1955 on the preliminary results of his analysis of the questionnaires. He found, for example, that "a 'hostile' attitude to certain animal species correlated significantly with a high score on what is known as the 'Authoritarian Score.'" Russell saw this as a beginning in linking "irrational attitudes to animals with previous work on personality variables." His inclusion of this topic as part of the project is not surprising, given his lifelong interest in behavioral science, which increased after he married Claire Hayes, whom he met in 1950 when she served as his psychoanalyst. He and Claire became research collaborators and published several books together, including *Human Behaviour: A New Approach* (1961).[24]

In addition to the literature research and interviews with laboratory scientists, the UFAW project also involved to some extent encouraging and supporting work by scientists on the development of humane methods of animal experimentation. For example, UFAW funded research by M. R. A. Chance at the Department of Pharmacology of the University of Birmingham on controlling variability in animal responses, thus reducing the number of animals required to obtain precise results in procedures such as bioassay. UFAW also employed veterinary surgeon Phyllis Croft as a research fellow

to study the possible replacement of conscious animals by anesthetized ones in the bioassay of certain drugs.[25]

At the UFAW annual meeting in February 1955 at University College, London, Russell gave his first public presentation on the project. Although he made no reference to the Three Rs in this talk, which was subsequently published in the *UFAW Courier*, he did discuss humane methods that essentially represented the concepts embodied by the Three Rs. In his words: "Humanity in the biological sciences can increase in two main ways. First, increasingly humane procedures can be developed, so that the animals actually studied are exposed to less and less pain, fear and discomfort. . . . The second way in which humanity may increase in our field is by the reduction in numbers of the animals used in biological research."[26]

Clearly Russell is discussing here the principles of refinement and reduction. He also, however, made reference to what is essentially the concept of replacement, but considered it at this point to be a subcategory of reduction. He notes that reduction can be accomplished in two ways. One of these methods is what we ordinarily associate with reduction, increased efficiency in methods and techniques (e.g., statistical analysis) that allow fewer animals to be used to obtain the same amount of information. The second method is what later became the third R, replacement, defined by Russell as the use of "other objects of study" to "replace animals in the study of a given problem, or at least in the pilot approaches to such a study." Russell gives two examples. The first is methods of testing drugs, hormones, and the like that utilize chemical methods or microorganisms rather than biological assays on higher organisms. He viewed this technique as especially important because "it accounts for something approaching half the total of all experimentation on animals in this country." Russell was encouraged by the fact that methods of testing had already been developed for some substances that did not require the use of animals at all. The second example was the testing of some simpler biological hypotheses on "mechanical or electronic brains" (although he cautioned that such "model animals are vastly simpler than the originals"). As one example, he pointed to the development by psychiatrist William Ross Ashby in 1948 of the homeostat, popularly referred to as a "thinking machine."[27]

In his presentation Russell described the progress that he and Burch had made to find and publicize humane methods in use or development by literature searches and interviews with laboratory scientists. He also discussed his interest in studying "the psychological factors affecting attitudes to animals, especially among scientists." He expressed his conviction that conscious cruelty in the laboratory was rare, and that problems in the humane treatment of animals were based on a lack of understanding of the needs and fears of animals. Increased understanding of animal behavior, he believed,

would help to breed respect and humanity. Finally, Russell emphasized the need for further study of the unconscious factors "which may warp the judgement and pervert the actions of the most well-intentioned person." For example, "unconscious mechanisms in ourselves may blur our vision and interfere with our discrimination and our appreciation of information about animals which is already available."[28]

Years later, Russell stated the Three Rs must have been developed by Burch and him some time between 1955 and May 1957, but that neither of them "can now remember how, or more exactly, when, they first appeared." They had to conclude that "like Topsy in *Uncle Tom's Cabin*, they just 'growed.'" He recognized that the Three Rs were "present in essence, but not explicitly as such, in a short paper published in 1955," referring to the above-mentioned publication of his remarks at the 1955 UFAW annual meeting. That is, as I have shown, the concepts were clearly there, but there was no specific mention of the Three Rs. As Russell himself has noted, he formally announced them at a 1957 symposium on "Humane Technique in the Laboratory" organized by UFAW. Therefore, he added, they "must have evolved them in the interim" between these two meetings. Russell gave the same explanation in a 1993 letter to Andrew Rowan in which he commented about the origins of the Three Rs: "If we had known then that they would still be talked about in 1993, we would have taken more careful note!"[29]

However, an outline of the proposed book that Russell sent to Burch on June 3, 1956, a copy of which is in the Russell Archive at the University of Nottingham, lists the Three Rs. Russell's suggested title at that time was *Man and Animals in the Laboratory*. He divided the work into three sections: "Animals in the Laboratory"; "Animal Welfare as a Problem in Applied Science"; and "Humanity and Efficiency in the Laboratory." In the last section, on humanity and efficiency, he outlined a subtopic on increasing humanity in experimentation. Here he clearly cited "Replacement, Reduction and Refinement" (although without using the term "Three Rs"). Thus it appears that the Three Rs concept, at least in terms of spelling out replacement, reduction, and refinement, was developed between early 1955 and June 1956 (rather than as late as 1957, as stated by Russell).[30]

The UFAW symposium to which Russell referred took place at Birbeck College, University of London on May 8, 1957. By that time, Hume had presumably decided that there had been enough progress on the study of alternatives for UFAW to sponsor a meeting on "Humane Techniques in the Laboratory." The meeting included two papers by Russell, the main one of which first clearly expressed in print the Three Rs, which were even identified in the title, "The Increase of Humanity in Experimentation: Replacement, Reduction and Refinement." His other paper dealt specifically with refinement. There were also papers at the symposium by Hume, Lane-Petter, Croft,

Chance, and others. Abstracts of the symposium presentations were published in volume 6 (1957) of the *Laboratory Animals Bureau Collected Papers*.[31]

Peter Medawar wrote the foreword to the published volume. Medawar claimed that no country had higher standards of laboratory animal welfare than Britain, and that because these standards prevailed, there was a will to make them better. He also voiced the following view:

> What is at once clear from this Symposium is that improvements in the care of animals are not now likely to come of their own accord, merely by wishing for them: there must be research on methods of research; and it is in sponsoring research of this kind, and making its results widely known, that UFAW performs one of its most valuable services.[32]

Medawar commented that advances in laboratory animal welfare could be expected along three lines, namely, "Russell's three Rs of humane practice." While optimistic that the further development of more humane techniques would reduce the numbers and suffering of animals used in research and testing, Medawar at this point was not fully convinced that animal experimentation would ever be totally abolished. As he stated: "If science and medicine are to continue to advance, I do not think there will ever come a time when animal experimentation can be done away with altogether. One can, however, foresee the time when it will become something of a rarity, and when people look back with the same incredulous taste upon the use of animals for standardization and bio-assay, as we do now upon, say, the crudities of surgery as it was before the days of Simpson and Lister." Fifteen years later, while still arguing that animal experimentation was necessary for the advance of medical science, Medawar correctly forecast that "its peak will be reached in ten years time, or perhaps even sooner."[33]

Curiously enough, the abstract of Russell's main paper, while discussing replacement, reduction, and refinement, does not explicitly use the term "Three Rs," as Medawar had done in his foreword. In spite of the broad title of the paper, in Russell's own words, it "chiefly concerns replacement," which Russell divided into relative and absolute replacement. Relative replacement was further subdivided into two categories: "Non-recovery experiments on living, intact but totally anesthetized animals" and "Experiments which required only cells, tissues, organs or physiological preparations from animals previously painlessly killed." He noted that these methods still involved the use of animals, although not "for experimentation in a sentient state." Russell's first example of relative replacement, which involves the use of intact live animals and killing them during the experiment while they are under anesthesia, would not be considered to

be replacement today (as will be discussed further later in this chapter). As examples of absolute replacement, Russell cited "the culture *in vitro* of metazoan endoparasites, the use of higher plants as test objects, the substitution of micro-organisms for animals, and physico-chemical techniques employing no organisms at all."[34]

Russell makes no mention in this abstract (which is a little over two pages in length) of his interest in the behavioral factors that influence the attitudes of humans toward animals, a subject he had discussed in the past and would return to again in the future. The rest of the paper is largely devoted to a discussion of the imperfection of all models (animal or otherwise) of the human organism, other than the human organism itself. Russell points out that one can assess the relation of a model to the origin in one of two independent ways: it may be of higher or lower fidelity and of greater or less discrimination. He defined these terms as follows: "High fidelity means that all properties of the original are copied in the model equally well—or, it may also be said, equally badly. Great discrimination means that a model resembles the original very closely in respect of one or more particular properties; such a model gives a particularly good response over one sector of the physiological spectrum."[35]

Russell pointed out that while high fidelity is sometimes desirable, discrimination is often preferred in practice. For example, a microorganism, which is totally unlike a human, may be a more convenient model than a mammal in some nutrition research. He then identified what he called the "hi-fi fallacy," an assumption that he believed hindered the progress of replacement methods. This fallacy is based on two premises, that high fidelity is desirable in general and that mammals are of exceptionally high fidelity as models of the human organism. These premises lead to the conclusion that mammals should be used as much as possible, especially in screening and toxicity tests. Russell, however, disputes this conclusion on two grounds. He argues that the fidelity of mammals is open to question in several respects and that "the advantages of discrimination are insufficiently appreciated, even in the toxicity field, where scout testing on organ cultures offers considerable promise."[36] He was to further emphasize the significance of the high fidelity factor in the *Principles*, as will be discussed later.

Russell's second paper in the symposium dealt with the subject of refinement, which he defined as "the reduction to a minimum of the distress or discomfort to be imposed upon animals used for experimentation." Refinement can take two forms, he noted. One is the use of a procedure such as anesthesia, which can be superimposed on the experimental technique being employed. The other method involves the choice among different procedures for reaching a given experimental objective. Here Russell placed particular emphasis on the correct choice of experimental animal and bemoaned the fact that our knowledge of the behavior of commonly used laboratory animals is

inadequate. He called for more intensive study of the behavior of the different types of laboratory animals, both those already in use and those that could potentially be used.[37]

As noted above, both Russell and Burch indicated that they could not recall exactly how they came up with the Three Rs. Michael Balls, however, has offered an intriguing speculation about the origins of the Three Rs term. Cleo Paskal, literary executor of the papers of W. M. S. and Claire Russell, called Balls's attention to a page from *The Observer* dated December 26, 1954. The page contained a short story by an author named Ursus, which was the pen name used by Russell for his science fiction writings. Next to Russell's story was an advertisement for United Steel Companies Limited entitled "the Three Rs of Industry." The advertisement identified three basic requirements of a successful industry: efficient technology, commercial vision, and vigorous scientific research. Curiously, these three factors do not begin with Rs at all, but perhaps the company meant to make a comparison to the three basic components of education, Reading, Writing, and Arithmetic (in the shortened form of Rithmetic), which have long been referred to as the Three Rs because each of them has a strong R sound at the beginning. As Balls concluded, however, unless new documentation surfaces, "we cannot know whether, consciously or subconsciously, this had any effect on WMSR [W. M. S. Russell]."[38]

Finding a Publisher for the Russell-Burch Book

Although Burch collaborated with Russell, who always credited him as an equal partner on the alternatives project, it was Russell who drafted the book resulting from the work. Russell also provided the intellectual framework and arguments for the book. In fact, Burch's formal affiliation with UFAW as a part-time assistant to Russell had ended in 1956, although Russell continued to consult him on the project and made him a co-author on the book. On July 10, 1957, he wrote to Burch to tell him that he finished the book that day and would have a copy of the manuscript posted to him. He asked Burch to read it carefully and offer any suggested additions or alterations, but there is no record of Burch having responded with any recommended revisions. Russell indicated that he had also given copies to Hume and Chance to comment on and would later ask others to review the manuscript.[39]

Kenneth Bird, then the chair of UFAW, informed Hume that he was willing to submit the manuscript on behalf of UFAW to the publisher, Methuen, for consideration

for publication. Russell sent Bird a copy of the book, indicating in a cover letter that it was primarily aimed at experimental biologists in particular and all biologists in general. He also believed that another important audience for the book would be undergraduate and graduate students just beginning laboratory work. Finally, he noted that it should also be of interest to other groups, such as historians of science. Russell added that the book was not a popular work, "but we have tried to write it in such a way that specialists of many different kinds will find it intelligible."[40]

The manuscript was submitted to Methuen, and on August 16, 1957, Peter Wait of Methuen sent a letter to Bird with his reaction to the proposed book. Wait indicated that he had sent the manuscript to a biologist for review. The reviewer stated that he did not find it easy to be definitive in his recommendation. His first reaction to the work was unfavorable. He found it to be often "carelessly and obscurely written," as well as verbose in some places. He also believed that the authors "seem a little optimistic when they write (p. 62): 'When the full results are available it will be exciting (my underlining) to follow the shifts which must surely be occurring in the details of the pattern as the objectives and methods change in particular fields.'" The reviewer admitted, however, that on more careful reading he thought it was a good deal better than on his initial skimming. He noted that it was "a not-uninteresting and in some ways unique book" that should be marketable in Britain and even to some extent overseas, "particularly in the U.S., where interest is growing in the subject."[41]

Wait informed Bird that he thought that if the book were revised along the general lines suggested by the reviewer, it "would be well worth publishing." He expressed some concern, however, about sales, asking Bird if Methuen could expect some sort of support from UFAW. He commented more specifically about the prospect for sales: "In England at any rate, I cannot see more than 100 or so copies finding their way into departmental libraries. I do not think many biologists would want to possess copies of their own, but many of them would read it if it were made available to them. The market is of course wider than just England. It is in fact biologists anywhere. But outside England, I wonder how much interest there is in the humane treatment of animals."[42]

Hume sent Russell a copy of the letter from Methuen, along with his own advice. He pointed out that Methuen's two concerns were the prospect of low sales and the need to revise the book to make it more readable. With respect to revision, Hume concluded that although the work contained important factual information and fundamental original ideas, "the style and presentation are really off-putting." He added more specifically: "The style is high-falutin' [*sic*], complicated and obscure, and too long-winded. The references to psychoanalysis are of great interest to psychoanalysts,

but hardly interesting to readers who have no knowledge of psychoanalysis, who are in the majority. Many of the sentences have to be read more than once before one can construe them and see the point. It is not that the wording is ungrammatical—on the contrary—but it makes too much of a demand on the reader's attention."[43]

Hume suggested that Russell not devote months of full-time effort to revision, but instead revise it little by little over the course of a year or two. In the meantime, Russell could devote much of his time to other matters that were of immediate practical importance to UFAW. Hume proposed that this would be a more effective way of revising a book of such importance. In this way the "whole thing matures," and he admonished Russell that "maturation means simplification and abridgement rather than proliferation."[44]

Russell obviously had revised the book sufficiently to satisfy Methuen by May 1958, because he signed a contract with Methuen for publication of the work at that time. As part of the revision process, Russell agreed to cut about 5,000 words. Methuen's financial concerns were eased by UFAW agreeing to forego any royalties on the first 1,000 copies. Royalties on copies sold above that number would be 12.5 percent and were to be shared by UFAW (80 percent) and Russell and Burch (10 percent each). Russell commented in a letter to Burch that "the sums involved will be so small (unless a miracle occurs) that our own remuneration can only be a token one, and more a matter of prestige."[45]

Publication of *The Principles of Humane Experimental Technique*

In June 1959, Methuen published *The Principles of Humane Experimental Technique* with a price of 30 shillings. The *UFAW Annual Report* for that year expressed the hope "that the deep thinking which has gone into this work will inaugurate a new era in biological research, in which the systematic study of problems in humane technique will rank as an essential part of every biologist's training, so that what has been done will lead in time to widespread practical results."[46]

In the following discussion of the book, I shall refer to Russell alone for the sake of simplicity. As I noted above, Russell was basically the sole author of the manuscript and responsible for its intellectual arguments, although Burch certainly contributed significantly to the research on which the volume was based. Comparing the published volume to the outline for the book that Russell sent Burch in 1956, we see that the title had been changed from *Man and Animals in the Laboratory* to the more specific *The*

Principles of Humane Experimental Technique. The three sections proposed in the outline were reduced to two parts in the book: "The Scope of Humane Technique" and "The Progress of Humane Technique." This was accomplished by combining the first two sections in the outline ("Animals in the Laboratory" and "Animal Welfare as a Problem in Applied Science") into part 1 of the published work.[47]

Part 1 on "The Scope of Humane Technique" provided general background information on such topics as the concept of inhumanity, the ecology of experimental animals, and the sources, incidence, and removal of inhumanity. After a brief introductory chapter, Russell tackled the question of humanity and inhumanity. Here he drew upon the statement of UFAW's aim for his definition of humanity with respect to animals, namely "to reduce the sum total of pain and fear inflicted on animals by man." The goal of humane experimental techniques therefore would be to reduce pain and fear (or, more broadly, distress) in the animals used in the laboratory. He then went on to discuss distress (a term which for him incorporated fear and pain) in animals and the criteria for and measurement of distress.[48]

In discussing the ecology of experimental animals, Russell made use of a 1952 survey by the Laboratory Animals Bureau to estimate the total number of animals used in laboratory research and testing in Britain as well as the specific numbers for individual species. The results revealed that about one and three-quarter million animals were used in British laboratories in a single year. By far the largest number were mice, just over one million, followed by rats and guinea pigs (about 250,000 and 200,000 respectively). Many other species such as rabbits, dogs, and cats were used in smaller numbers. Russell also mentioned the formation in 1957 of an International Committee on Laboratory Animals, which was arranging surveys in various countries to produce an international picture.[49]

The final chapter of part 1 discussed the sources, incidence, and removal of inhumanity. Russell distinguished here between direct inhumanity, in which the infliction of distress was an unavoidable consequence of the procedure employed, and contingent inhumanity, in which the infliction of distress was an incidental and inadvertent by-product of the procedure employed. Contingent inhumanity involves imperfect conditions in the husbandry of laboratory animals or in the way the experimental procedures are carried out. Direct inhumanity, however, occurs as the result of the nature of a particular experimental procedure, even if the experiment "is conducted with perfect efficiency completely freed of operations irrelevant to the object in view." Russell devotes most of this chapter to discussing the more vexing problem of direct inhumanity and briefly introduces at the end of it the Three Rs as the methods for the removal of inhumanity.[50]

The Three Rs: Replacement

Part 2 of the book contains a chapter on each of the Three Rs and a concluding chapter on "The Factors Governing Progress." Russell defined a replacement technique as "any scientific method employing non-sentient material which may in the history of experimentation replace methods which use conscious living vertebrates." Non-sentient material could include higher plants, microorganisms, and "the more degenerate metazoan endoparasites, in which nervous and sensory systems are almost atrophied." He added that to "shed obsessional tears over the fate of these organisms would bring the whole concept of humanity into contempt." He admitted that the free-living metazoan invertebrates, that is, multicellular invertebrates in which the cells are differentiated and form tissues, raised more difficult issues. Russell arbitrarily decided to exclude them "from consideration as objects of humanitarian concern." Nevertheless, he labeled the substitution of these organisms for vertebrate subjects as "comparative substitution," which he viewed as only a limited gain with respect to humane experimentation.[51]

Russell divided replacement into relative and absolute replacing techniques. In absolute replacement, animals are not required at any stage of the process, and he regarded this as the "absolute ideal." In relative replacement, "animals are still required, though in actual experiment they are exposed, probably or certainly, to no distress at all."[52]

Russell discussed relative replacement first and gave a number of examples, such as "non-recovery experiments on living and intact but completely anesthetized animals." Another case of relative replacement is where animals are only used to furnish preparations after being painlessly euthanized. This could include, for example, experiments on animals that have been "deprived of enough of their central nervous system to be reliably regarded as insentient." These types of techniques, where live intact animals are used in the experiment itself or are euthanized to furnish experimental materials, would not be considered to be replacement by most investigators working in the alternatives field today. They would instead likely be classified as examples of refinement.[53]

The final example of relative replacement given by Russell involves the use of isolated cells, tissues, or organs of vertebrates. Materials commonly used in such experiments are isolated organs (e.g., heart, uterus) and isolated nerve-muscle preparations in suitable perfusion fluids. These techniques are widely used in physiological and pharmacological research, and in the bioassay of substances. Tissue culture, Russell noted, forms a bridge to the category of absolute replacement, where vertebrate animals are not required at all.[54]

Russell divided absolute replacement into four subdivisions: the use outside the body of metazoan endoparasites (e.g., nematodes); higher plants; microorganisms

(e.g., protozoa, bacteria); and nonliving physical and chemical systems. He noted that replacement techniques have been widely used in some fields and hardly at all in others, and that "such developments have been largely empirical and largely independent of each other." There is as yet no general theory of replacement, Russell added, but he believed that "all the materials are by now available for someone with the requisite mathematical equipment to develop a systematic applied theory of replacement." As part of his discussion of a general theory, Russell once again explained the high fidelity fallacy that he had earlier outlined in his 1957 paper.[55]

In the rest of the chapter on replacement, Russell tried to make the discussion "a little more concrete," as he said, by considering in more detail "two of the major replacing techniques," the use of tissue culture and of microorganisms. With respect to the former procedure, he focused on tissue culture in virology and in bioassay and toxicity testing. Russell pointed out that when tissue culture was first developed in the early twentieth century, it had been (and here he quotes F. Sanders) "'the province of the artist in biological technique.'" As discussed in the previous chapter, successful tissue culture work involved fastidious and careful techniques, and was not attempted by most researchers. A major problem in culturing viruses was that strict precautions had to be taken to exclude contaminant microorganisms from the culture. With the advent of the antibiotics, however, these drugs could be added to cultures in sufficient quantities to suppress bacterial growth, without generally affecting the virus. An important turning point was the successful culture of the polio virus in vitro by Enders, Weller, and Robbins in 1949.[56]

Russell noted that while live animals were still needed for the study of virulence and the production of antiviral sera, for many purposes (e.g., growth, identification, serological study) tissue cultures could be used. This procedure was not only more humane, but more effective and less expensive. Even in the case of vaccines, he saw progress. For example, he reported that in Sweden, vaccinia vaccine had been produced from tissue cultures of bovine embryos obtained from pregnant cadavers in slaughterhouses. He cited a review by Sanders on tissue cultures as substitutes for experimental animals in which the author predicted with confidence that this type of replacement would continue unabated. Russell also noted that Sanders ended his review with a discussion of a relatively new development, "the maintenance of cell lines by transplantation *in vitro*, as in the case of the famous HeLa cell, isolated from human material in 1952, and since used all over the world in polio studies. By such means the use of animals (apart from the original human or animal donor) is eliminated altogether, thus converting relative into absolute replacement."[57]

Russell quotes Sanders as concluding with a statement that virologists had great cause to rejoice at their liberation from the hazards and uncertainties of animal

experimentation. To this statement, Russell adds, displaying his sense of humor: "'At this point'—to quote Alice in Wonderland—'one of the guinea-pigs cheered, and was removed by an officer of the court.'" With this bit of whimsy, Russell concluded his discussion of tissue cultures in virology.[58]

Russell next turned to other uses of tissue culture, noting that it was being developed to some extent, although not as much as in virology, oncology, pharmacology, chemotherapy, bioassay, and toxicity testing. He added that the method offered great advantages in these areas, "though its potentialities are far greater than its current usage." With respect to bioassay, where whole animals were still being employed to a large extent, he gave examples of developments where in vitro tests were being or could be used based on tissue culture research. For example, insulin could be measured by the increase in glucose uptake by the isolated rat diaphragm and steroids by their cytotoxic action on rabbit lymphocytes.[59]

In the case of toxicity testing, one example that Russell discussed was the use of tissue cultures to screen potential new therapeutic agents. He cited, for example, a study that found a good correlation between toxic effects of drugs on tissue cultures and their irritant effects on human and rabbit skin. In his view, this principle of "scouting," that is, screening, where potential new drugs are discarded if their effects on tissue cultures are such as to give a poor prognosis for their effects on whole organisms and humans, was gradually coming into use.[60]

Russell's last example of replacement was the use of microorganisms. A major aspect of this area is the use of microorganisms for the study, and especially the assay, of nutritional factors. For example, since many animal vitamins and microbiological growth factors are often the same, scientists could take advantage of this fact to use microorganisms to provide a quantitative or semiquantitative measure of a growth factor present. Russell also briefly discussed the use of microorganisms as a replacement technique in other areas, such as in the routine assay of antibiotics.[61]

Over time, definitions of the Three Rs have been offered that vary somewhat from those of Russell and Burch, and this has been most significant in the case of replacement. As noted earlier, Russell included under replacement "Non-recovery experiments on living, intact but totally anesthetized animals." Under most later definitions of replacement, this method, which involved the use of whole live animals in the experiment, would not meet the criteria for replacement. This point is clearly illustrated by the discussion of the definition of replacement by Andrew Rowan and Franklin Loew in a 1995 report sponsored by the Pew Charitable Trusts.

> *Replacement* originally referred to the use of insentient material for conscious, living, higher animals so that a fully-anesthetized animal that did not recover could be

> regarded as a replacement to a conscious animal. Today the idea of replacement is more restrictive and usually refers to the use of either tissue culture or some other experimental system that does not require killing or disturbing an animal. Thus the use of the new pregnancy test kits instead of rabbits is considered to be a replacement (despite the fact that the antibodies in these kits were probably raised in living animals).[62]

Tannenbaum and Bennett have also pointed out the difference between Russell and Burch's use of the term "replacement" and much current usage, as explained above. They also explain why they believe Russell and Burch chose their particular definition: "Importantly, replacement is *not* defined in the *Principles* as the use of nonanimal material instead of animals. Replacement is defined as the use of *insentient* (or nonsentient) material instead of sentient material. Russell and Burch do not define replacement as not using animals because they classify *the use of insentient animals as instances of replacement*."[63]

Tannenbaum and Bennett also note that many recent definitions "that claim to follow the *Principles* define replacement as not using animals, not using vertebrate animals, or using less-sentient animals." They cite examples of definitions of replacement promulgated by various organizations, such as the American Veterinary Association and the Institute of Animal Laboratory Research, that claim to follow the *Principles*, but which actually are not in complete agreement with Russell and Burch's definition. For example, they may restrict replacement to the use of procedures that do not involve animals or may include the use of less-sentient animal species, neither of which is a part of the original definition of replacement in the *Principles*.[64]

The Three Rs: Reduction

The next chapter dealt with reduction and began with the statement: "Desirable as replacement is, it would be a mistake to place all our humanitarian eggs in this basket alone." Russell noted that replacement progressed gradually, and he believed it was not likely that it would ever "absorb the whole of experimental biology." Even in the case of refinement, which he would discuss in the following chapter, he claimed that "in any given field there is bound to be a latent period before success is attained." Moreover, whatever progress was made in humane methods through replacement and refinement, the third R, reduction, would still be desirable with respect to any procedure, especially those employing large numbers of animals. He concluded: "For all these reasons reduction remains of great importance, and of all modes of progress it is the one most obviously, immediately, and universally advantageous in terms of efficiency."[65]

Russell discussed various means for reducing the numbers of animals employed in research and testing. His first example was choosing the best strategies in planning and performing lines of research. Citing Charles Hume, he stated: "The central problem is that of choosing between trial and error on a grand scale and deductively inspired research." Particular experiments should be selected on some basis other than tables of random numbers from a larger set of experiments that could be considered. To Russell, it was obvious that guided (what Hume called "insighted") research would be much less wasteful of animals. He discussed Hume's concern that trial and error methods were being used on a grand scale, especially in pharmacology and chemotherapy (e.g., large-scale testing, often random, of new chemical substances on animals to determine their possible therapeutic properties).[66]

One of the problems faced by biological scientists is that animals vary in their physiological responses to chemicals and other stimuli. Therefore, in research and testing, one has to use a sample of animals and infer from the mean response the effect of the chemical, for example, on the organism. The accuracy of the inference will depend upon various factors, including the size of the sample. From a humane point of view, one would naturally want to use as small a sample as would allow valid results to be obtained. Russell pointed out that an important advance in dealing with this problem was the development of modern statistical methods, which allowed the investigator to determine the minimum number of animals needed for an experiment. He then discussed the application of statistics to biological experimentation in some detail.[67]

With respect to reduction, Tannenbaum and Bennett note that a major discrepancy between Russell and Burch's definition and some recent ones involved the use of the term "minimization." A number of current definitions define reduction as the absolute minimization of the number of animals used. The definition in the *Principles*, however, involves only reducing the number of animals used, not necessarily to the minimum possible number. They speculate that the authors of the *Principles* wanted scientists to reduce numbers at the time however they could, recognizing that as statistical and experimental techniques were improved, they could move progressively toward minimization.[68]

The rest of the chapter was devoted to the sources of physiological variance and to ways these could be reduced, with the ultimate aim of decreasing the number of animals needed in a given experiment. One example of this approach given by Russell is to increase the phenotypic uniformity of the animals used in an experiment through appropriate breeding methods. Controlling the proximate environment of the experimental animals, such as the amount of crowding in the cages, is also important, as these

factors influence the social behavior and the physiological responses of the experimental animals. In fact, Russell concluded that "in the study of laboratory animal behaviour lie the richest prospects of reduction."[69]

The Three Rs: Refinement

The third R, refinement, was the subject of the next chapter. The object of refinement, according to Russell, was to "simply reduce to an absolute minimum the amount of distress" on the animals in the experiment. It comes into play if replacement cannot be used and after every effort has been made at reduction, and it "presents more formidable difficulties to the would-be taxonomist of techniques." Russell commented: "It is indeed so protean in its aspects, that it almost seems to require a separate solution in every single investigation, and refinement might be regarded as an art or an ability to improvise."[70]

Russell did try to make some generalizations, beginning with subdividing investigations into two categories with respect to efforts at refinement. The first category is stressful investigations, "which have as their main or subsidiary object the acquisition of knowledge about the mechanisms of pain and distress, and/or their autonomic and endocrine sequelae." This category presents the most difficulty in terms of refinement because there would seem to be "an irreconcilable conflict between the claims of humanity and efficiency." How could one, Russell asked, eliminate or reduce stress in such cases without prejudicing the very aim of the experiment? He saw grounds for hope, however, that when more is known about the pathways by which central nervous distress is translated into physiological stress responses, "the responses themselves may be evoked, as required, by intervention at a more peripheral or co-ordinative level . . . than that of the sites of integration distress itself." He referred to this as "stress without distress." The second category of refinement, to which Russell devoted most of the chapter, includes all other studies that do not have the above goal, and Russell designated them as neutral investigations.[71]

According to Russell, anesthesia was "the supreme refinement procedure," and in fact he called it "perhaps the greatest single advance in humane technique." He was optimistic about the recent development of preparations that maintained local anesthesia for relatively long periods, such as days. These anesthetics had been developed to cope with the problem of prolonged local pain, especially after operations, in humans. Russell saw great potential for their use in controlling prolonged pain in animals, both

during and after experimental procedures. He commented that concerns about harmful side effects of these substances in humans "might be of no consequence in animals soon to be sacrificed anyway."[72]

Other examples of refinements to reduce distress given by Russell included the recently developed restraining collar for dogs subjected to operations that was well tolerated by the animals and the administration of certain substances to animals by aerosols rather than by hypodermic injection. He also discussed the importance of giving serious attention to the choice of experimental procedures and the species of experimental animal to be used. The two are interrelated because in choosing between procedures, one important problem is matching the choice of species used with the requirements of the experiment. He summarized the significance of appropriate choice of procedure and experimental animal as follows: "This subtle matching of procedure to species, and species in turn to objectives, is more significant than appears at first sight for the humanity of technique. For the only alternative is to try to correct the mistaken choice of a wrong species by forcing it to conform to the requirements of the investigation. This results in just those roundabout methods we should guard against, and is all too liable to end in gross inhumanity."[73]

Russell ended the chapter with a discussion of a concrete example, the humane study of fear in experimental psychiatry. He begins with the recently introduced tranquilizers and the methods of screening for new drugs of this class, which he calls (quoting another scientist) the "'feverish search for a panacea for anxiety.'" Organic chemists can readily turn out compounds with potential tranquilizing or other psychopharmacological properties, but testing the effects of these substances on the brain is not an easy matter for they are likely to be complex and multiple. To Russell, rational use of animals in experimental psychiatry depends upon accurate knowledge of the behavior of each species of animal, a subject about which our knowledge is limited. This led, he stated, to "a miscellany of desperate methods." For example, in the study of fear, there is "a tendency already emerging to race for the electric grid, as the most Procrustean method for terrorizing rates." He added: "This is a rat-race better stopped before it starts in earnest."[74]

To Russell there were two solutions to this urgent problem. The first was to devote intensive and systematic study to the behavior of laboratory animals commonly in use. The second was to "recruit" species whose behavior was already well studied. Both solutions have a role to play with respect to humane experimentation. Russell was particularly interested in the possibilities of this latter approach. In his words: "Our ignorance of the behaviour of common laboratory animals is off-set by a wealth of knowledge about that of lower vertebrate species." Furthermore, "this knowledge is concentrated on precisely those aspects of behaviour likely to be of service in the screening of new

neurotropic drugs." He then provided a number of specific examples, one of which was Eckhard Hess's demonstration that meprobamate and chlorpromazine reduce or eliminate flight reactions in mallard ducklings.[75]

Tannenbaum and Bennett have called attention to deviations in some contemporary definitions of refinement from the definition given in the *Principles*. The key point they identify is the addition of the concept of well-being to Russell and Burch's definition of refinement as any decrease in the incidence or severity of inhumane procedures applied to experimental animals. They give examples of current definitions that include statements to the effect that refinement includes measures to enhance animal well-being, as well as to minimize pain and distress, although I believe that it is not unreasonable to argue that Russell and Burch's definition could be comfortably stretched to include well-being.[76]

Factors Governing Progress

In the final chapter of the *Principles*, "The Factors Governing Progress," Russell discusses personality, sociological, and related factors that influence the progress of humanity in animal experimentation. The chapter is relatively short, and the author admitted that he had provided only a sketch of these factors, which he stated deserved a fuller treatment.

Russell quickly dispensed with the personality factors. He identified two "pathological" personality factors that were important in determining attitudes to and treatment of animals. The first of these was the authoritarian factor, which he claimed was "known to correlate significantly with hostile attitudes to animals, as well as stereotyped preferential treatment of particular species." The second was a less understood factor, which he believed was at least partially independent of the first, tentatively called the revolutionary factor. He noted that it "finds its main expression *vis-à-vis* animals in a rigidly and fanatically antivivisectionist attitude."[77]

Russell postulated that experimental biologists were less likely than most people to respond irrationally to animals. Obviously, as biological researchers, they could not lean toward an antivivisectionist attitude. Their work compelled them to think in terms of many variables, which he claimed was the type of thinking that would be blocked by a high level of the authoritarian factor. Individuals who were strongly authoritarian therefore would not be likely to become or remain experimental biologists. Even if they did, as authoritarian personalities they would likely conform to the opinion of the majority of their colleagues, which would restrain them from acting inhumanely.

Russell admitted, however, "We have no quantitative data, but in a not inconsiderable acquaintance with British experimental biologists we have encountered only a minute proportion of individuals with markedly authoritarian traits." These conclusions would hardly stand up to the standards of modern experimental psychology as they are based on Russell's perceptions rather than on any empirical data.[78]

Russell next turned to sociological factors. Here he made a case that experimental efficiency (expressed as a balance between time, cost, and efficacy) would be promoted by following the Three Rs. For example, the use of in vitro cultures was much cheaper than the use of guinea pigs. Reduction in the number of animals used is another example of cost savings. Russell also argued more generally that the advantages of humane techniques applied almost universally with respect to efficacy (capacity of the experiment to provide the required information), reminding the reader that this point had been made many times throughout the book. For example, experimental results may be compromised due to pain, fear, or other forms of distress that affect the physiological response of the subject animals. He also addressed here what he considered to be a more fundamental aspect of the correlation between humanity and efficacy, especially important in research, involving the human exploratory drive. Russell discussed how the scientist's exploration may be blocked "on some front where his reactions to childhood social experiences are impinged upon," leading the experimental biologist to fail to truly explore but instead "in his experiments, act out on his animals, in a more or less symbolic and exaggerated way, some kind of treatment which he once experienced in social intercourse with his parents." Through what seems to me to be a very convoluted and dubious argument, he concludes that it "follows logically that, if we are to use a criterion for choosing experiments to perform, the criterion of *humanity* is the best we could possibly invent." Even if we could not trace the connection in any given research, Russell believed this to be "a fundamental and inescapable law founded on the key properties of human behaviour."[79]

Other factors that could hinder progress in the advancement of humanity in animal experimentation, according to Russell, were inadequate communication, inertia, and lack of education. He then gave brief descriptions of three organizations in Britain concerned with the progress of humane technique: the Laboratory Animals Bureau, the Animal Technicians' Association, and the Universities Federation for Animal Welfare.[80] Finally, the book ended with a brief conclusion, in which he emphasized that research in this field had barely begun as a systematic discipline. He closed with words expressing the hope that he and Burch had for *The Principles of Humane Experimental Technique*: "We hope the book may stimulate some experimentalists to devote special attention to the subject, and many others to work in full awareness of its existence and possibilities.

Above all, we hope it will serve to present to those beginning work a unified image of some of the most important aspects of their studies. If it does any of those things, this book will have amply served its purpose."[81]

The publication of this book was a crucial landmark in the history of alternatives, providing the Three Rs framework that came to dominate the field. The humanitarian impact of this rubric has undoubtedly spared millions of animals from suffering. The project leading to the book was sponsored and funded not by a scientific research institution, but by an animal welfare organization. UFAW recognized, of course, that advances in alternatives techniques would have to come from the scientific community and believed in working with this community to achieve these goals. Hume and the authors of the book hoped that this work would be well received by scientists and would stimulate further research in alternatives. As we shall see in the next chapter, however, the book was at first largely ignored. It would take many years for its impact to be significantly felt.

3

An Underwhelming Response

The 1960s

Although the three Rs eventually came to play a significant role in discussions about alternatives, the publication of Russell and Burch's *The Principles of Humane Experimental Technique* in 1959 had little immediate impact in the scientific and broader public community. There were, for example, relatively few reviews of the book. Reviewers in general viewed the book as a useful reference that collected together a mass of relevant information, but were critical of the writing style. Veterinary surgeon Phyllis Croft, who worked (as mentioned in the preceding chapter) as a research fellow at the Universities Federation for Animal Welfare (UFAW), complained about "the wordiness of the style, and the use of unnecessarily long and obscure words" in her review in *Veterinary Bulletin*. She went on to add that the average experimenter "did not use or readily understand words such as logistics, ethology, paralogism and to limn," and "he may feel that expressions such as 'the cuddlier species' are out of place in a scientific book." Pharmacologist Miles Weatherall of the London Hospital Medical College, writing in *Nature*, stated that the publication had value in providing a summary of humane experimental methods that had already been adopted, but was "not sufficiently informative to be used as a guide either to details of experimental design or to the husbandry of experimental animals." Both reviewers, however, had positive comments about the book as a basis for and hopefully a stimulus to further research.[1]

An anonymous review in *Veterinary Record* also cited the value of the book as an information source about and stimulus to humane experimentation techniques. This reviewer was also concerned, however, that the "deep philosophy" of the work would

discourage readers and cause them "to relegate it to the shelves merely for reference." The reviewer was overly optimistic about the current status of humane experimentation, stating that much of the information and analysis was already well known to most of those who work with animals and that the principles espoused were already being "actively pursued in most of the leading pharmacological laboratories and in University and hospital laboratories."[2] This was clearly an overstatement.

In a review in the *British Medical Journal*, Arthur St. George Huggett, chair of Physiology at St. Mary's Hospital Medical School, offered lukewarm praise, stating that the *Principles* "is an essentially useful book." He was skeptical, however, about the impact of the book on researchers, commenting that "if the operator is not intrinsically humane in technique before reading it, one doubts that it will convert him despite its patent desire to achieve this important and laudable end." Nutrition researcher Eleanor Margaret Hume of the Lister Institute of Medical Research noted in her review in *Science Progress* that the *Principles* was not a "book of recipes," that is, a collection of individual humane techniques, but "a scholarly treatise and much of it makes highly interesting reading for its own sake."[3]

An interesting feature of these reviews is that none of them makes any specific reference to the term "Three Rs" used by Russell and Burch in the book. All of them, however, do name replacement, reduction, and refinement as the basis of humane experimental techniques. As is probably to be expected in book reviews, there is little discussion of these terms. Even more striking is a discussion of the book in a review of reviews by American pharmacologist Chauncey Leake in 1963, where he did not mention the Three Rs individually or collectively at all. Leake stated that Russell and Burch provide a thorough discussion of the principles of humane experimental techniques, but he did not define what they meant by this term. The only other comment he had about the book is the vague statement that the authors "indicate the importance of adequate care and of gentle and kindly treatment of experimental animals in all phases of animal studies."[4]

A Decade of Dormancy

After the initial reviews of the book, little attention was paid to it or to its concepts for at least the next decade. Michael Balls, who has long been involved in the field of alternatives and been interested in its history, referred to the period following the publication of *Principles* as "The Dark Ages of the Three Rs," specifically comparing it to the period in Western civilization following the fall of Rome.[5] Three other key figures in

the alternatives field who have also studied its history, Martin Stephens, Alan Goldberg, and Andrew Rowan, called the 1960s and somewhat beyond a period of dormancy with respect to the Three Rs, when "the scientific community largely ignored Russell and Burch's book." They added: "By and large the animal protection literature did not pay much attention to the idea of alternatives and it was virtually absent from the technical literature."[6]

In a search of *Science Citation Index* for references to Russell and Burch, Andrew Rowan found none in the 1960s (other than book reviews of *Principles*), and I confirmed his results.[7] An analysis of 105 scientific journals by Philips and Sechzer found no mention of the term "alternatives" in the period 1966–1973. They did note, however, that one 1966 article briefly mentioned the concept and a 1971 editorial cited several examples of alternative techniques, but neither used the term.[8]

Ironically, one of the few early references to the Russell and Burch book (other than the reviews) in the scientific literature was in a 1960 book defending animal research. Geoffrey LaPage, a parasitologist at the University of Cambridge, in his *Achievement: Some Contributions of Animal Experiments to the Conquest of Disease*, referred to the previously mentioned 1957 UFAW meeting at which scientists discussed how the concepts of reduction and refinement could be implemented "and how far, as Russell and Burch (1959) also discuss, animals could be replaced, for certain kinds of experiments at any rate."[9] The 1959 book referred to here is *Principles*.

Animal welfare organizations also did not do much to promote the concept of alternatives in this period, as noted in the quotation above from Stephens, Goldberg, and Rowan. Given that there were relatively few concrete examples of alternative animal experimentation techniques available, focusing on them may not have seemed the most promising area in which to advance animal welfare at the time. Even UFAW, which sponsored Russell and Burch's work, did not at first follow up this effort in a serious way. Although the organization remained active in various areas of laboratory animal welfare, including publishing updated editions of its laboratory handbook, a staff member has confirmed that in this period there were "no real discernible activities that UFAW undertook to promote the 3Rs/alternatives approach other than to help the publishers to sell the [Russell and Burch] book." The retirement of Hume in 1965 also likely reduced interest in alternatives at UFAW. Andrew Rowan has commented that his successor, Walter Scott, "showed no real interest in animal research issues."[10]

The most significant step taken in Britain before the founding of the Fund for the Replacement of Animals in Medical Experiments (FRAME), discussed in the next chapter, at the end of the decade was the establishment in 1962 of the Lawson Tait Memorial Trust, designed to encourage and support researchers who did not use any

animals in their work. The trust was founded by the National Anti-Vivisection Society, the British Union Against Vivisection, and the Scottish Anti-Vivisection Society. It was named after Robert Lawson Tait, a prominent Victorian surgeon who had refused to use animals on moral and scientific grounds. The trust soon became independent of its founding societies and self-governing. Beginning with only £5,000, the trust provided grants to scientists who used replacements for animals in their research. Given the relative lack of alternative techniques, especially those actually replacing animals, available at the time, the creation of the trust represented a growing optimistic view in at least some corners of the animal protection movement that the development of nonanimal methods was a promising avenue of research and deserved support.

At first, the scientific community was hesitant to align itself with this new entity, given the role of antivivisection societies in its organization. Gradually, however, some scientists began to apply for grants from the trust. A major impediment to cooperation between scientists and the trust, however, was that the original rules of the organization only allowed it to support scientists who did not hold a Home Office license for animal research. Staunch antivivisectionists were opposed to supporting any scientist who had anything to do with animal research. This restriction ruled out the vast majority of biological and medical investigators in Britain, including those who were interested in researching and testing nonanimal methods. This problem was finally resolved in 1974 when the trustees of the Lawson Tait Memorial Trust formed the Humane Research Trust, which broadened the original aims of the trust to allow for the support of scientists interested in developing alternatives, regardless of whether or not they held Home Office licenses. This compromise allowed for cooperation between animal protectionists and scientists in the search for alternatives.[11]

In the United States, the Animal Welfare Institute (AWI), which had discussed alternative methods even before the publication of the Russell and Burch book and had supported their project, as previously discussed, continued to be interested in the subject. AWI became the principal distributor of the *Principles* in this country, ordering copies from Methuen, the British publisher, and sending leaflets offering the book for sale to thousands of laboratories and individuals. Beyond promotion of the *Principles*, however, there is relatively little attention given to alternatives in the newsletters and surviving archival records of AWI from the 1960s.[12]

The Humane Society of the United States (HSUS) also had limited activities related to alternatives in the 1960s, in spite of the expressed interest of its executive director, Fred Myers, in the subject. Frederick "Doc" Thompson, an HSUS board member from 1963 to 1966, recalled that Myers thought of the Russell and Burch book as a kind of bible as he prepared various legislative efforts concerning the humane treatment

of laboratory animals in this period. As early as 1961, Myers wrote to a colleague: "We recognize that animals are going to be used in research until scientists themselves find other and better ways of accomplishing the ends that animals now serve. We think, however, that it is possible to improve the care of animals in many laboratories and that, through careful design of experiments it would be possible to reduce the number of animals necessarily used."[13]

With this in mind, Myers indicated that he wished to fund a project involving the careful analysis of the statistical design of animal experiments, the objective of which would be "to determine whether, in the analyzed group of projects, the number of animals used could have been reduced without impairing the validity of the results." The focus of this study would thus involve one of the Three Rs, that is, reduction.[14] HSUS did fund such a study, contracting with Westat Research Analysts. In its report, Westat explained that the study was based on an analysis of 173 articles from the scientific literature involving experimental animals published in 1961 and carried out in American laboratories. After careful statistical analysis of these studies, they concluded that 75 percent of them "could have, by use of proper statistical design employed reduced numbers of animals with essentially no loss in statistical significance." The Westat study, however, was not widely distributed and apparently had no significant influence in promoting the concept of alternatives. The report also did not specifically reference Russell and Burch or the Three Rs.[15] Even given Myers's support of alternatives, however, HSUS did not devote substantial effort to the topic in this period. The organization, along with the AWI, was, however, influential in the passage of the Animal Welfare Act in 1966 (discussed below).

Another effort to promote alternatives in the United States was the creation of United Action for Animals (UAA) in 1967 with the specific goal of promoting alternatives, with an emphasis on replacement. The organization was founded in New York by Eleanor Seiling. According to a *New York Times* obituary, Seiling became interested in animal issues in 1959 "shortly after she retired as a secretary on Wall Street, when she learned that her goldfish had died of fungus contracted at a pet shop" and the store proved reluctant to improve conditions. She worked on several research projects at HSUS for a time before establishing her own organization. Seiling spent many hours in the New York Public Library searching scientific journals for examples of alternatives and of what she considered to be unnecessary research. As Andrew Rowan noted, however, "she appears to have been a lone voice in the United States."[16]

As for Russell and Burch themselves, they went their separate ways and moved into other areas of work. For three decades there was little contact between them, and, as

Burch noted, they "knew little of what was going on in the field of humane experimental technique."[17] Burch had left UFAW in 1956 and spent most of the rest of his life running a one-man microbiological testing laboratory in the town of Sheringham.[18]

When the project was over in 1959, Russell, the principal author of the book, apparently had difficulty finding a position. He spent the next five years in private practice as a psychoanalyst, a field in which the only training he received was given to him by his wife Claire and her previous husband, James Hayes. Russell also continued work begun with Claire on human ethology, the study of human behavior especially in relation to evolution, a newly emerging field in which Nikolaas Tinbergen was one of the pioneers.[19]

In 1963, perhaps tired of being a psychoanalyst, Russell began actively applying for jobs in a wide variety of fields. Letters in the Russell Archive at the University of Nottingham reveal, for example, that he applied for positions as an assistant editor at the magazine *New Scientist*, as a translator for the World Health Organization, and as a research fellow in management studies at the London School of Economics. There is almost a sense of desperation in these applications, some of which were only peripherally, if at all, related to his areas of academic expertise and/or seemed not to require his level of education. In one case he received a letter from the Computer Science Department at the University of Western Ontario asking if he could recommend someone for a faculty position in the theory of systems. Russell responded by recommending himself, citing his interest and publications in the area of evolution concepts in behavioral science. The head of the department wrote back, however, "I believe our needs require someone with a more definite mathematical background." When Russell inquired about a possible position at the University of Sussex, he was informed by John Maynard Smith that he had "decided that there will not be a place for someone of your particular interests" in the Biology School.[20]

Of particular interest is Russell's application for a position at UFAW. In October 1963, Russell saw a notice that UFAW was looking for a new secretary-general as Hume was preparing to retire from that position. He wrote to Hume informing him that he was in the process of looking for a full-time position and stated that the UFAW job "enormously appeals to me, and is exactly what I would most like to take on now." If the position were still open, he noted, he would very much like to talk to Hume about it. Hume replied that while UFAW was "greatly honoured by your application, unfortunately we have already made an appointment." He added in confidence that the person hired was the research director of a large pharmaceutical company. The fact that Hume and UFAW had apparently not thought to inform Russell about the opening

is further confirmation that their activities in this period were not focused on alternatives. One can only speculate about what direction UFAW might have taken in this regard if Russell had become its secretary-general.[21]

In 1964, Russell wound up taking a position as a scientific information officer at the Commonwealth Bureau of Pastures and Field Crops, reflecting his difficulty in securing employment more suitable to his level of education.[22] Why should a zoologist with a PhD from Oxford not have been able to obtain a position in an academic department at a time when biology and biomedical science were rapidly expanding in universities and elsewhere? Especially one who had been associated at Oxford with two distinguished scientists and future Nobel laureates, Peter Medawar and Nikolaas Tinbergen, as previously mentioned.

It is true that Russell had an unconventional background for a young biologist. The fact that he had studied classics and literature as an undergraduate at Oxford before switching to zoology is indicative of Russell's broad range of interests. In a curriculum vitae prepared about 1959, Russell listed his scientific interests as: "All aspects of human and lower animal behaviour, and also reproductive endocrinology."[23] In the years since receiving his doctoral degree, Russell had spent most of his time first on the UFAW book project, which involved no laboratory research, and then in private practice in psychoanalysis. From the early 1950s he had also been working on a book on the comparative physiology of the vertebrate under contract with Sir Isaac Pitman and Sons, but it was never published, and in 1961 he and Claire published *Human Behavior: A New Approach*.[24] In 1963 it had been a little over a decade since Russell had obtained his PhD, and his activities during that time would not have counted in his favor in applying for most academic jobs, at least in biology. As Cleo Paskal, a close friend of the Russells, later wrote about Bill: "As this point, his seemingly disparate interests were becoming an impediment to an academic career."[25]

Russell's interest in ethology and his friendship with the sociologist Stanislav Andreski finally led to an academic appointment in 1966. Andreski, who had just founded the Department of Sociology at the University of Reading, apparently appreciated Russell's broad interests and saw him as a welcome addition to his staff. Russell accepted a position at Reading and remained there, rising eventually to the level of professor, until his retirement in 1990, when he became an emeritus professor. While there, he taught a wide variety of subjects: primate sociology, statistics, demography, genetics, ecology, cultural evolution, and the social stratification of city-states.[26] During that period, he also published various papers and books, often in collaboration with Claire. Their joint publications included *Violence, Monkeys and Man* (1968) and *Population Crises and Population Cycles* (1999).[27]

Legislative Efforts

During the decade of the 1960s, there were efforts to revise the 1876 Cruelty to Animals Act in Britain and to pass animal welfare legislation at the federal level in the United States. What role, if any, did the newly introduced concepts of alternatives and the Three Rs play in these events?

In Britain, as in the United States, the significant increase in the use of animals in experimentation and testing in the mid-twentieth century led to growing concerns on the part of antivivisection and animal welfare groups. In 1948, antivivisection groups such as the National Anti-Vivisection Society and the British Union for the Abolition of Vivisection pressed the government to review and possibly revise the 1876 act, but without success. In the late 1950s and early 1960s, there were renewed efforts on the part of both the abolitionist and the animal welfare communities to convince the government to address the issue. Eventually pressure from various organizations, such as the Lawson Tait Memorial Trust, UFAW, and the Royal Society for the Prevention of Cruelty to Animals (RSPCA), compelled the Home Secretary to agree to establish an inquiry into the workings of the 1876 act in late 1962. On May 23, 1963, he appointed the Departmental Committee on Experiments on Animals, chaired by Sir Sydney Littlewood, a prominent lawyer.[28]

During the parliamentary discussions leading up to the appointment of the Littlewood Committee (as it was generally referred to), House of Commons member F. A. Burden referred to Russell and Burch's book on two occasions in 1962. His use of the book was largely for the purpose of justifying the need for reforms in the field of animal experimentation, and he did not make any explicit reference to the Three Rs. The only alternative technique that he mentions in discussing *The Principles of Humane Experimental Technique* is the use of films to replace experiments in teaching. Burden also refers, however, to a UFAW pamphlet by Charles Hume, *Experiments on Animals in Great Britain*, and in this case, he does quote the author's discussion of certain alternative experimental techniques. For example, he cites Hume's suggestions about the possibilities of substituting simple organisms such as protozoa for higher animals in drug screening and standardization and the use of a less empirical strategy that would result in a decrease in the numbers of animals used in these processes. His comments, however, did not lead to any significant discussion of alternatives.[29]

The British Union for the Abolition of Vivisection (BUAV) debated whether or not to weigh in on the deliberations of the Littlewood Committee. The charge to the committee was limited to a consideration of the present control over experiments on living animals and what changes, if any, were desirable. The committee therefore explained

to those invited to give evidence that they did not intend to consider the question of whether or not experiments should be performed at all. Since the aim of the BUAV was the total abolition of vivisection, and the leaders of the organization were required to oppose any regulation short of prohibition, in theory they should have boycotted the work of the Littlewood Committee. Yet not engaging with the committee did not seem advisable. BUAV approached the committee and worked out an arrangement whereby the organization was allowed to submit a 7,000-word "Memorandum of Agreement" wherein they were able to state the group's fundamental opposition to vivisection. The main focus of the document, however, was on attempting to show that the 1876 act had failed to prevent or even mitigate the suffering of experimental animals. The memorandum was later supplemented by oral evidence.[30]

BUAV argued that there "seemed to be both considerable repetition of experiments and excessive persistence with biological research when results were demonstrable by other means." They believed that this trend was encouraged "by the relatively small cost of animals compared with chemical and other forms of experimental materials." The Scottish Anti-Vivisection Society, citing in its statement to the Littlewood Committee the increase in the number of animals vivisected, raised the question of whether "experiments on animals have become a mania." They called for the setting up of a procedure for investigation of methods not involving living animals.[31]

The final report of the committee in 1965 acknowledged that the position of BUAV and other antivivisection societies was the total abolition of animal experimentation, but expressed appreciation for their willingness to offer constructive comments. The report summarized the views expressed by these groups. Among their claims was that vivisection "was the experimenter's method of choice because it was accessible and cheap" and that there was unnecessary duplication of experiments (as noted above for BUAV). They argued that what was required was a change in strategy to concentrate more on "alternative methods," thus indicating an increased interest in these techniques on the part of British animal protectionists. They also advocated for greater use of clinical observations and experiments on humans, preventive medicine, and "fringe" disciplines such as homeopathy.[32]

In a booklet issued in 1965, the Research Defence Society (RDS) sought to counter these claims and to downplay the value of alternatives, pointing out that they were not available or suitable in the case of many procedures. They also challenged the statement that animals were often used because they were cheaper than chemical assay, calling it nonsense. They emphasized that modern medicine used all available methods of research and stated that "we cannot afford to neglect any reasonable approach to advances."[33]

The committee's report barely mentions alternatives and does not refer at all to the Three Rs or to Russell and Burch's book. Even when referring to the suggestions received from correspondents asking them to consider "alternative ways to achieve the purposes" of animal experimentation, the only examples given in one section of the report are "more extensive education on health, hygiene and diet, and encouragement of medico-spiritual systems of treatment." In another section where suggestions from correspondents about alternative approaches are discussed, the two examples given are limiting the number of animals used in experiments, including prohibiting their use in the testing of cosmetics, and replacing teaching demonstrations involving animals by films and books. The only recommendations made by the committee that relate to, but do not specifically reference, the Three Rs are ones that encourage the design of experiments to avoid wasteful use of animals (reduction) and reduce pain and suffering (refinement). Although there are no specific recommendations concerning replacement methods, the report did comment that there seemed to be general agreement that animals should not be used in experiments where insentient material would serve.[34]

The Littlewood Report did not lead to any hearings in Parliament or any introduced legislation throughout the rest of the 1960s. As Robert Garner has pointed out, the report's conclusions themselves were at least partly responsible for this inertia. The Littlewood Committee indicated that it was satisfied with the Home Office's administration of the 1876 act and found no evidence of extensive public demands for reform. Garner added: "Given these conclusions, it is not surprising that Labour and Conservative governments during this period, with many pressing problems on their plates and no one within their ranks who was particularly concerned with the issue of animal research, were reluctant to commit themselves to legislative reform which would not only take up valuable parliamentary time but would also incur inevitable controversy."[35]

In the United States, there was a serious campaign for legislative action, led by two relatively new animal welfare organizations previously mentioned, AWI and HSUS. Although there were some proposals for regulating animal experimentation in the 1950s, the main focus of animal welfare advocates in that period was on the passage of the federal Humane Slaughter Act in 1958. According to Bernard Unti, the first serious federal bill on animal experimentation was introduced in Congress by Senator John Sherman of Kentucky in May 1960. The bill "established basic record-keeping requirements, mandated comfortable and decent housing and nourishment, and called for pre- and postprocedural anesthetic relief when it would not interfere with experimental outcomes. Painful procedures could not be conducted without proper licensure."[36]

The story of the struggle to pass what eventually became the Animal Welfare Act in 1966 is a long and complicated one, which has been discussed elsewhere in some detail.[37]

I will therefore provide only a brief summary of the events, focusing especially on issues related to alternatives. Numerous bills on animal care were introduced in Congress in the years immediately following the Sherman bill as animal welfare groups, the research community, and laboratory animal dealers lobbied Congress on the subject.

Animal welfare groups such as AWI and HSUS, unlike the antivivisectionists, did not seek to end animal experimentation, but rather to regulate it in order to reduce the suffering of laboratory animals. American scientists, led by the National Society for Medical Research, were opposed to any significant regulation of experimentation. As discussed in chapter 1, they were especially concerned about the suggestion of licensing researchers and laboratories that was part of the British act, a policy that was advocated by Christine Stevens of AWI. Some members of the biomedical community were concerned that the passage of "any animal welfare bill might serve as an opening wedge for additional legislative restrictions on research."[38]

In September 1962, hearings were held in the House of Representatives on two bills dealing with the humane treatment of animals in research by recipients of federal grants or by federal agencies. One of the bills stated at the beginning:

> That it is declared to be the policy of the United States that animals used in experiments, tests, the teaching of scientific methods and techniques, and the production of medical and pharmaceutical materials, shall be spared avoidable pain, stress, discomfort and fear, that they shall be used only when no other feasible and satisfactory method can be used to obtain necessary scientific information for the cure of disease, alleviation of suffering, prolongation of life, or for military requirements, that the number of animals used for these purposes shall be reduced as far as possible, and that all animals so used shall be comfortably housed, well fed, and humanely treated.[39]

The other bill included essentially the same statement, except that it referred specifically to living vertebrate animals rather than the more generic term "animals." Numerous witnesses representing both the animal welfare and scientific communities testified. One of the animal advocates who appeared was Major Charles Hume of UFAW, who was introduced by Christine Stevens. Hume largely devoted his time to rebutting the claim by many American scientists that biomedical research had been hampered in Britain because of the regulation of animal research there. He read into the record letters sent to him by prominent British scientists, such as Peter Medawar, stating that the British law had not hindered their research in any significant way. In his comments, Hume did mention Russell and Burch's *Principles*, although he did little more than cite its publication. Aside from this brief comment by Hume, there was no other reference

in the hearings to Russell and Burch and the Three Rs in spite of the fact that the bill, in the statement quoted above, clearly stated the principles embodied by the Three Rs in mandating that animals used in research should be spared pain and distress, that they should only be used when no other satisfactory method was available, and that the number used should be reduced as far as possible.[40]

Efforts by AWI, HSUS, and other animal advocates to publicize abuses in some laboratories and the shady dealings of many in the dog dealer trade increased pressure on Congress to act. Bernard Unti has pointed out, however, that by 1966 the focus of the campaign had shifted from the use and treatment of animals in research to the trade in animals, undoubtedly spurred in part by two well-publicized incidents involving dog traders. In the summer of 1965, a family dog named Pepper disappeared from the backyard of her home and was later found to have been sold by a dealer to a laboratory for experimentation. By the time Pepper's whereabouts were discovered, she had been sacrificed and cremated. HSUS estimated at the time that nearly half of all lost pets in the previous year had been rounded up by dealers and sold to laboratories. New York congressman Joseph Resnick, who represented the district where the dealer who had sold Pepper resided, was incensed enough to introduce a bill making it a federal crime to purchase or transport dogs or cats in interstate commerce without a license from the US Department of Agriculture. The bill also required research laboratories to purchase animals from licensed dealers. Resnick coupled his bill to laboratory animal legislation. Hearings on the bill were held in September.[41]

Public pressure for an animal welfare bill swelled to a head with the publication of a story in the February 4, 1966, edition of *Life* magazine, provocatively titled "Concentration Camps for Dogs." The article reported on the raid of the facilities of a notorious Maryland dog dealer, organized by HSUS and the Maryland State Police, with *Life* reporters accompanying them. It described the horrible conditions in which the dogs were housed, graphically depicted by dramatic black and white photographs. The story caused a sensation, and outraged readers deluged the magazine and members of Congress with thousands of letters. In early March, the House held hearings on the regulation of the transportation, sale, and handling of animals used in research and experimentation. The Senate followed later that month with hearings on animal dealer regulation.[42]

Since by this time the focus of attention had shifted to the trade in animals, with special attention to stolen pets, rather than how they were used in research laboratories, it is not surprising that the various bills considered in these hearings dealt almost exclusively with the regulation of this trade. In fact, each of the bills stated its purpose in essentially the same words, as in this example from H.R. 12488: "That, in order to

protect the owners of dogs and cats and other animals from thefts of such pets and to prevent the sale or use of stolen dogs and cats and other animals for purposes of research and experimentation, it is essential to regulate the transportation, purchase, sale, or handling of dogs, cats, and other animals by persons or organizations engaged in using them for research or experimental purposes or in transporting, buying, or selling them for such use."[43]

As Christine Stevens pointed out, some of the bills omitted "laboratories from the requirement of humane animal handling," applying it only to animal dealers. For this reason, Stevens preferred the bill cited above, H.R. 12488, which called for the licensing and inspection of dealers and laboratories, as well as authorizing the secretary of agriculture to promulgate humane standards for the handling and transportation of animals by dealers and research facilities.[44] Even this bill, however, explicitly stated that "this authority shall not be construed to authorize the Secretary to set standards for the handling of these animals during the actual research or experimentation."[45]

According to the testimony by HSUS president Oliver Evans at the March House hearings, his organization favored the idea of limiting the legislation to the business of supplying animals to laboratories. HSUS was certainly not opposed to regulation of laboratory animals, but Evans argued that the issues involving animal research were complex and went beyond those involving dealers. In his written testimony, he elaborated on this position, pointing out that laboratory animals were often confined for long periods of time and thus might have different requirements for cage size, ventilation, nutrition, and so on. He also raised the issue of reducing the number of animals to the lowest number required for the purposes of an experiment and the question of information retrieval. He did not explain this last point, but perhaps he was referring to the need to search the literature for possible alternatives to an experiment involving animals. For these reasons, Evans believed that the issue of protection of animals in the laboratory was best covered under other legislation that was being considered at the time.[46]

The House passed an amended version of H.R. 12488 on April 29, 1966. Responding to lobbying by the research community, the House limited the bill to dogs and cats and did not cover the laboratory environment itself. Meanwhile in the Senate, Senator Warren Magnuson introduced S. 2322, which was considered at hearings in March and May 1966, along with two other similar bills. The Magnuson bill had been stripped of any coverage of laboratories, and Senator Mike Monroney proposed an amendment to restore this coverage. HSUS once again opposed this step and continued to argue for two separate bills, one regulating animal dealers and one addressing the protection of animals in research laboratories. Bernard Unti summarized the HSUS concerns as follows: "The HSUS thought Monroney's proposals for regulating usage were

inadequate and feared that their adoption would 'foreclose for a number of years the additional legislation which would be needed for adequate coverage of all of the problems involved.'"[47]

In the end, Monroney prevailed and the coverage of laboratory animals was restored. Soon thereafter Congress passed the Laboratory Animal Welfare Act (P.L. 89-544), which was signed by President Johnson on August 16, 1966.[48] Diane Beers summarized the main provisions of the law as follows: "As enacted, the law prevented the use of stolen animals for research and established minimum standards of humane care for dogs, cats, primates, rabbits, hamsters and guinea pigs. Most notably, Congress authorized the USDA to register research facilities, license animal dealers, and periodically perform unannounced inspections of both. To discourage pet theft, the law stipulated that records were to be kept for all protected animals. Failure to strictly comply with these regulations would result in criminal penalties for animal dealers and civil penalties for laboratories."[49]

However, the act did exempt animals from coverage during actual research and experimentation. Humane care requirements applied to laboratory animals only prior to the experiment. In the words of Beer: "Once a scientist placed an animal on the operating table, government jurisdiction ended."[50]

Alternatives, Russell and Burch, and the Three Rs were not specifically mentioned in any of these hearings in 1965 and 1966 (except for the passing reference to reduction by Oliver Evans noted above) or in the act itself. Given the fact that the legislative efforts by this time had come to be largely devoted to the trade in animals, and that the act itself exempted animals from coverage during actual experimentation, it is perhaps not surprising that these topics did not receive attention.

Animal welfare groups such as AWI and HSUS, while pleased with the passage of the Laboratory Animal Welfare Act, were not satisfied with its provisions, especially with the lack of any regulation of experimentation itself, and continued to press for further reforms. In 1967, the very year after the passage of the act, Representative Paul Rogers (D-FL) and Senator Jacob Javits (R-NY) introduced legislation to expand the scope of the act to cover all warm-blooded animals, including throughout any experiment in which they were involved. Among its other provisions, the bill called for the use of non-sentient and less developed forms of life for higher mammals whenever possible. Thus the issue of alternatives was addressed in this bill.

HSUS backed the bill, including the provision of assigning responsibility for enforcement to the Department of Health, Education and Welfare (HEW), which seemed to the organization to be a more logical choice than USDA. Christine Stevens and the AWI, however, opposed the transfer of responsibility from USDA to HEW, causing a rift in the animal welfare community's support for the bill. Using her political

influence, she managed to prevent the bill from getting out of committee. In 1969, Rogers, in an effort to break this impasse, rewrote his bill to drop the provision repealing USDA authority under the act, but Stevens remained opposed to the bill because it divided authority between the two departments. In the end, it was a different bill that surfaced to eventually become law and amend the 1966 act, as discussed in the following chapter.[51]

Why Did the Three Rs Meet with So Little Initial Success?

Why were Russell and Burch's book and the Three Rs concept largely ignored during the 1960s and beyond, especially in the scientific community? In a thought-provoking article, historian Robert Kirk has proposed that a major factor for "the muted scientific interest in the 3Rs when they were first proposed" was the growing divide at the time between the humanities and the sciences as expressed by C. P. Snow. He goes on to say that even the relative success of the Three Rs in recent times "has done little to encourage engagement with their original text," that is, with *The Principles of Humane Experimental Technique*.[52] Kirk explains that his article "argues that one explanation for this distinction may be found in another, more celebrated, event of 1959, C. P. Snow's Rede lecture on *The Two Cultures*. The moral outlook of *The Principles of Humane Experimental Technique* derived from an earlier ethos wherein humanistic and scientific values occupied a shared culture."[53]

Kirk is certainly correct in stating that *The Principles* incorporated both humanistic and scientific perspectives. As we have seen, Russell was a polymath whose interests spanned classics, human behavior, psychoanalysis, folklore, and other disciplines as well as science, and the book devotes a great deal of attention to the concepts of humanity and inhumanity.[54] Russell was convinced that the most humane use of animals leads to the best science. Kirk's article provides an excellent discussion of these points.

I am not convinced, however, that Snow's two cultures concept is the major factor in explaining the initial lack of interest in the book and the Three Rs. Was the fact that the book was difficult reading, and not merely because of its synthesis of humanistic and scientific concepts, a major factor in this lack of interest? Russell's language and style were a challenge to most readers, including those sympathetic to the humane concepts expressed in the work. I have already discussed how an anonymous referee for Methuen when the publisher was considering the manuscript stated that it was often "carelessly and obscurely written," as well as verbose in some places.[55] As we have also seen,

Charles Hume himself, the head of UFAW and initiator of the project that led to the book, and who can fairly be described as sympathetic to the humanities, complained that the "style is high-falutin' [*sic*], complicated and obscure, and too long-winded."[56] As noted at the beginning of this chapter, Phyllis Croft, who worked on the UFAW project, wrote in her review of the book about "the wordiness of the style, and the use of unnecessarily long and obscure words."[57] Even Michael Balls, a pioneer in the field of alternatives and a great admirer of *The Principles*, has acknowledged that it "is a very difficult book to read. To say the least, its style is idiosyncratic, eccentric and very personal, reflecting the unique and complex character of its principal author."[58] The fact that the book made for difficult reading may have deterred certain potential readers from getting through it, but I do not believe that it can explain the lack of significant interest in the Three Rs concept.

The most important factor for the lack of interest of biological scientists in the concept of alternatives in the 1960s, in my view, was the crucial and entrenched place of animal research in biomedical research and testing. At the time, animal experimentation was the gold standard of biological and medical research, as it still is to a significant extent today. The vast majority of biomedical scientists were trained in and committed to animal research. Their education devoted relatively little, if any, attention to matters of animal care and handling, which were generally left to technicians. Supporters of science pointed to the great strides made in biology and medicine as a result of animal experimentation and vigorously opposed the attacks of antivivisectionists.[59]

What motivation did scientists have to turn from tried and true animal studies to untested procedures with which most had little or no experience? There were few replacements for animal procedures available in any case, as evidenced by the paucity of validated nonanimal replacements that Russell and Burch could point to in their book. This lack of available technology at the time the book was published no doubt also played a role in preventing the book from having an immediate impact with respect to the adoption of alternatives. True, scientific researchers could have paid greater attention to the reduction and refinement methods proposed by Russell and Burch, but again these were not subjects that were emphasized in their training and experience. It is not that they wished to use more animals than necessary or cause unnecessary pain to them, but these issues were not uppermost in their minds. As Bernard Dixon wrote with respect to the reluctance of medical researchers to consider nonanimal techniques, "there is the influence of fashion and familiarity, which leads people to retain well tried and tested methods." In a recent book on the history of animal experimentation, pharmacologist Richard Miller stated that in many respects scientists are conservative and "are not going to welcome somebody knocking on your door and

telling you that what you are doing is out of date and unethical and that you should be doing something else."[60]

In addition to opposing antivivisectionists, biomedical scientists, especially in the United States, tended to be suspicious of groups that did not totally oppose animal experimentation but promoted laboratory animal welfare. Organizations such as AWI and HSUS, for example, were constantly attacked by the National Society for Medical Research (NSMR), as discussed to some extent in chapter 1.[61] Ralph Rohweder, the NSMR's executive secretary, used terms such as "neo-vivisectionist" and "neo AV" [antivivisection] group to describe AWI and HSUS.[62] As Andrew Rowan has noted, in the 1950s (and I would add beyond) "anyone who dared to criticize animal research was regarded as an unwitting antivivisectionist, no matter how justified such criticism might have been."[63] Recall the vehemence of the attacks on Robert Gesell by his colleagues in the American Physiological Society (as discussed in chapter 1) for daring to publicly express concern about some of the types of animal experiments being carried out. Gesell foreshadowed Russell and Burch not only in talking about alternative methods, but also in insisting that the issue was not vivisection versus antivivisection (as the NSMR would have it) but humanity versus inhumanity.[64]

Biomedical researchers, however, did not think of their experiments in terms of humanity versus inhumanity, as Russell and Burch had framed the issue in their book. As Rob Boddice has pointed out, these scientists tended to view their laboratory work as a practice of humanity. A 1913 resolution adopted by the Federation of American Societies for Experimental Biology stated that medical experimenters "were self-sacrificing, high-minded men of science who are devoting their lives to the welfare of mankind in efforts to solve the complicated problems of living beings and their diseases." By its very nature, medical research was a humanitarian endeavor.[65]

Although Boddice was writing about the antivivisection controversy of the late nineteenth and early twentieth centuries, medical scientists in the period after the Russell and Burch book was published continued to defend the humanity and ethical nature of their animal research. Maurice Visscher claimed in 1967, for example, that the "position of the great majority of informed persons is that the humane use of lower animals to increase knowledge and to achieve practical advancement in medicine, agriculture, animal husbandry, and the like is highly ethical and should be promoted. Human welfare is placed first." Several decades later, neuroscientist Adrian Morrison expressed his position that "using animals in biomedical research is necessary scientifically, justified morally, and required ethically."[66]

Boddice further argued that the belief of scientists in the ethical, moral, and humanitarian nature of their research was real and not just a stance adopted to justify

their work. He wrote: "That medical scientists, whose work depended on the experimental destruction of animals, could really have been, or believed themselves to be, hard-working humanitarians, should be credited. The power of rhetoric, intertwined with practice, and compounded by the production of evidence, *makes* the experience so described. The humanitarian intent of medical scientists, and therefore their experience of their work as a humanitarian practice, should be taken seriously."[67]

I agree with Boddice that the belief of medical researchers in the humanity of their work should be credited, although no doubt their views were subconsciously reinforced by self-interest. They thus tended to view attempts to place restrictions on and in any way try to control the direction of their research as impeding the humanitarian goals of improving the lives of both humans and incidentally animals as well. Given this strong conviction of the humanitarian nature of their research on animals, it is not surprising that Russell and Burch's discussion of reducing inhumanity in animal experimentation did not resonate with most biomedical scientists.

Another argument against Kirk's thesis is that when antivivisection and animal welfare groups made efforts to promote alternative methods in connection with legislation in Britain and the United States in the 1960s and 1970s, in most cases without any specific reference to the Russell and Burch book, organizations representing biomedical researchers generally opposed them. I have mentioned earlier in this chapter that in the discussions surrounding the work of the Littlewood Committee, the Research Defence Society downplayed the value of alternatives, pointing out that they were not available or suitable in the case of many procedures. In 1973, the RDS successfully opposed an amendment to the Cruelty to Animals Act that would have "prevented any experiment using live animals if the purpose of the experiment could be achieved by alternate means not involving animals."[68] Two years earlier, NSMR had complained that the groups emphasizing the replacement of animals in experiments had as their "undisguised objective" the elimination of animals as biological models. These groups, according to NSMR, were seizing on recent advances in computer technology and tissue culture "as substitute methods rather than as adjuncts to modern biomedical research and training."[69] I will further discuss these conflicts over alternatives later in the book, but here I just want to make clear the suspicion with which alternatives were viewed by many scientists when they were first being significantly promoted, independent of the Russell and Burch book. As I stated earlier, I believe that this opposition owed more to the ingrained culture of animal models for biological research than to any split between the "two cultures."

I should add that Michael Balls and Andrew Rowan, both of whom have long been involved in the field of alternatives and students of its history, agree that it was the

predominance of the animal research model in biology and medicine, rather than the growing divide between the humanities and the sciences discussed by Snow, that inhibited interest about alternatives in the scientific community. Balls has stated "that Snow's two cultures concept was not a reason for lack of interest in the Three Rs. The real point is that animal users did not need to be interested in the Three Rs or concerned about their implications, because their reliance on animal experimentation was virtually unchallenged." Rowan has opined that although Snow's two cultures view was widely discussed, "I do not believe it had any noticeable impact on the 'alternatives' issue. I would argue that scientists then (and now) have a hard time with the notion that what they are doing to animals might be a moral issue."[70]

It is also true, as previously discussed, that animal welfare groups, including UFAW itself, did not show much interest in alternatives in the decade following the publication of the Russell and Burch book. These groups, which one would think would have been more sympathetic to the humanistic arguments expressed in the *Principles*, did relatively little to promote the concept of the Three Rs during the 1960s. Perhaps the lack of interest in and attention to alternatives on the part of the scientific community discouraged animal protectionists from seeing them as a viable strategy for reducing, or even eliminating, the use of animals in research. As we have seen, however, animal protectionists in both Britain and the United States did make some unsuccessful efforts to include provisions to promote the development and use of alternatives in legislation, and these efforts would increase in the following decades.

The decade of the 1960s closed, however, on a hopeful note for alternatives with the creation of the Fund for the Replacement of Animals in Medical Experiments (FRAME) in 1969. The activities of FRAME, the emergence of the animal rights movement, and other developments led to increased attention being paid to alternatives in the 1970s, as discussed in the next chapter.

4

Increased Attention to Alternatives

The 1970s

As discussed in the previous chapter, the concepts of alternatives and the Three Rs received little attention in both the scientific and animal welfare communities in the 1960s. There was, however, an extremely important development at the end of the decade, namely the creation of the Fund for the Replacement of Animals in Medical Experiments (FRAME) in 1969. The growth of FRAME was one of a number of factors that promoted increased attention to alternatives in the 1970s, as will be discussed in this chapter.

The Animal Rights Movement

One important development in the 1970s was the rise of the animal rights movement. The history of the animal rights movement is a complex story that is beyond the scope of this book, and in general did not have a specific and direct action on the development of alternatives. It did, however, have an indirect influence by stimulating greater public interest in animal protection issues broadly, thus increasing awareness of alternatives. The movement also had a direct influence, as we shall see, on some individuals, most prominently Henry Spira, who became involved in efforts that promoted alternatives. Therefore, it will be useful to briefly comment on the origins of the movement. There have been several published accounts of the history of the animal rights movement, and the interested reader is referred to these works for further information.[1]

The publication in 1975 by Australian philosopher Peter Singer of his book *Animal Liberation* is frequently cited as marking the birth of the modern animal rights movement.[2] Harold Guither, author of a history of the animal rights movement, wrote of Singer's book: "Some regard it as the bible of the new animal rights movement, since it presents many of the basic philosophical concepts for ethical treatment of animals."[3] Singer took the utilitarian concept of "the greatest good of the greatest number" as the only measure of ethical behavior and argued that there is no reason not to apply it to other animals. He popularized the concept of "speciesism," which had recently been introduced by Richard Ryder, who described it as "the widespread discrimination that is practiced by man against other species."[4] Both Ryder and Singer argued against speciesism and compared it to racism. In the words of Guither, the basic ethical principle involved "is one of equality, not necessarily treating animals and humans in the same way, but giving them equal consideration for the abilities that they possess."[5]

Singer's book did not appear in a vacuum, of course. He was part of a loose network of friends, most of them graduate students in philosophy, at the University of Oxford in the late 1960s and early 1970s that has been called the "Oxford Group" (not to be confused with the Christian organization founded in 1921) or the "Oxford Vegetarians." Singer first became interested in animal issues and converted to vegetarianism through his contact with the group. Members of the group developed a philosophical basis for animal rights and, to a greater or lesser degree, became involved in animal activism. As mentioned above, Singer adopted the concept of speciesism from Ryder, who was a member of the Oxford Group (although not a graduate student but a clinical psychologist at the Warneford psychiatric hospital in Oxford). Ryder had first used the term in a privately printed leaflet in 1970 and then again in an essay in the 1971 book discussed below.

Other members of the Oxford Group also played a significant role in the emergence of animal rights, as discussed in the recent history of the group and its influence by Robert Garner and Yewande Okuleye.[6] Here I will just mention a couple of examples. One important contribution was the publication in 1971 of the groundbreaking book of essays *Animals, Men and Morals: An Enquiry into the Maltreatment of Non-Humans*, edited by group members Stanley and Rosalind Godlovitch and John Harris. The book presented clear arguments for animal rights and included essays by several members of the Oxford Group as well as other authors, such as British novelist and journalist Brigid Brophy, who had close ties to the group and helped arrange for the publication of the book. Another essay in the volume by someone who was not a member of the group was Terence Hegarty's discussion of alternatives to animals in research, which is discussed below.[7] Another contribution to the animal rights movement

from a member of the Oxford Group was Richard Ryder's *Victims of Science: The Use of Animals in Research*, published in 1975, which aimed "to provide documentary evidence of the way man mistreats animals for the purposes of research, and to suggest reforms."[8]

Peter Singer helped call attention to the 1971 symposium volume by publishing a review article in the *New York Review of Books* based on the book, "but drawing the views of the several contributors into a single coherent philosophy of Animal Liberation." In fact, the article was titled "Animal Liberation." A New York publisher who saw Singer's review article wrote to him suggesting that he develop the views expressed in the piece into a full-length book, ultimately leading to his publication of his groundbreaking *Animal Liberation*.[9] This book had a profound influence on many individuals who became leaders in the animal rights movement. For example, Ingrid Newkirk, who co-founded the activist animal rights group People for the Ethical Treatment of Animals (PETA) in 1980, stated:

> After reading *Animal Liberation*, I realized that in the same way that racist and sexist views allowed us to discriminate against minorities and women, speciesism allowed us to inscribe an inferior status on animals and to regard them not as individuals, but as objects and means to fulfill our desires.
>
> I talked about the book, I wrote about it, I gave copies to everyone I knew. At that time, I was being honored as one of the Washingtonians of the Year for my work to create the country's first spay/neuter clinic as well as an adoption program. During my speech, I quoted extensively from *Animal Liberation*, trying to change other people's thinking the way Peter Singer had changed mine. It was then that I saw a need for an organization that would educate people about animal suffering and work to win their basic rights. That year I started PETA.[10]

Another important animal activist who was influenced by Singer, in this case directly, was Henry Spira. A veteran of labor and civil rights battles, Spira was working as an English teacher in the New York City public schools when he took a continuing education course on animal liberation at New York University in 1974. The course was taught by Peter Singer, who was at the time a visiting professor. Spira may have been stimulated to take the course after reading an essay that attacked an article of Singer's and finding himself more in agreement with Singer than with his critic. At the time, Singer was in the process of writing *Animal Liberation*, and he expounded on the views expressed in his manuscript to the class.[11] Spira was greatly influenced by this experience, and in a 1989 interview published in the magazine *Animal Liberation*, he told Singer: "I think what your essay did for me, what the class did for me, was to put the whole issue

of animal rights firstly within the context of liberation movements and, secondly, put it on a rational basis that can be defended in public debate on its own merits without reference to whether one does or doesn't like animals. What came out of the course was that animals are being harmed on a massive scale, and that it's wrong, it's an injustice."[12]

Desiring to act on this newfound interest in animal rights, Spira launched in 1976 a campaign to stop experiments by Dr. Lester Aronson at the American Museum of Natural History in New York on the sexual behavior of surgically altered cats. Spira believed that the experiments were inhumane and had no demonstrable practical value. Through letter and advertisements in the press and large-scale protests, he and his supporters pressured the museum to end this research project. In 1977, Aronson informed the National Institutes of Health (NIH), which had been supporting his research, that he would not be requesting a renewal of his grant when it terminated on August 31. He gave as his reasons his plans to retire in July and "the recent attacks by antivivisectionists groups." He requested that NIH extend his current grant for an additional year, but he was given an extension of only three months. Spira next turned his attention to other animal rights issues, and one of these, the toxicity testing of cosmetics on animals, will be discussed in the following chapter and is more directly concerned with alternatives.[13]

Founding of Fund for the Replacement of Animals in Medical Experiments (FRAME)

Fund for the Replacement of Animals in Medical Experiments (FRAME) was founded by Dorothy Hegarty, with the advice and assistance of Dr. Charles Foister, in London in 1969. Dorothy Hegarty was born in Shanghai in 1910. She left China during the unrest of the 1930s and moved to England. She and her husband Jack eventually settled in Wimbledon. Hegarty had always loved animals and by the early 1960s was becoming increasingly involved in animal welfare issues. She was particularly troubled by the use of animals in experimentation and their treatment in factory farms.

She was active in the National Antivivisection Society (NAVS) until she broke from the group, in part due to a confrontation with Lady Muriel Dowding, the then dominant figure in NAVS. Hegarty had become disillusioned by the insistence of antivivisection societies such as NAVS that all animal experimentation should be immediately abolished, what Hegarty's son Terry referred to as the "no-no" approach. This position was always refuted by the scientific community with the argument that there could be no medical progress without animal experiments. She reasoned that scientists did not look kindly on being told to simply abandon an approach that they believed had been

proved successful over many years in producing medical advances, but that they might be more sympathetic to being encouraged to try something new. That something new involved finding new experimental methods that could replace the use of animals.

To pursue this goal, she created Promoters of Animal Welfare (PAW) and began accumulating information on tissue culture, computer simulation, and other methods of research not involving the use of live, whole animals. She disseminated this information in leaflets distributed to the general public, the media, politicians, and research scientists. In 1969, she secured the patronage of Claude, Countess of Kinnoull, a wealthy supporter of animal welfare, who provided the financial support that allowed Hegarty to create a registered charity. With the collaboration of a friend, plant pathobiologist Charles Foister, the retired director of the Scottish Office's Agricultural Scientific Services, she founded FRAME.[14]

Although Bill Annett, secretary to the board of trustees of FRAME, said Hegarty and Foister had for some years been "inspired by Russell & Burch's book *The Principles of Humane Experimental Technique*" to publicize the concept of the Three Rs, this does not appear to be accurate.[15] Annett did not join FRAME as a consultant until 1978, just before Michael Balls became a trustee, and so was not involved in the early years of the organization.[16] If Hegarty and Foister had actually been inspired and guided by the work of Russell and Burch, it is curious that there appears to be no mention of them or their book in early documents from FRAME. Michael Balls, in preparing an appreciation of Hegarty for a 1995 special issue of *ATLA (Alternatives to Laboratory Animals)*, reported that he had read all of the minutes of the FRAME board of trustees and all of the organization's early *Progress Reports*. He remarked: "One thing which has struck me is that I have seen no mention of William Russell or Rex Burch, or of *The Principles of Humane Experimental Techniques*, published in 1959."[17] Balls concluded that while "Mrs. Hegarty may have heard of Russell & Burch and their book, I think she came quite independently to the conclusion that what she at first called 'substitutes' when creating FRAME's predecessor PAW, in the early 1960s, would provide an escape from the impasse created by the ongoing and fruitless confrontation between the antivivisectionists and the medical research community."[18]

Years later, when Balls himself first learned of the Russell and Burch book some years after he had become a member of the FRAME board of trustees (1978), he found that there was no copy of the volume at the FRAME library.[19] Andrew Rowan had also found that there was no copy of the book in the FRAME library when he arrived to take up the post of the organization's scientific administrator in early 1976.[20] It thus seems extremely unlikely that the *Principles* served in any specific way as a guiding document for the early work of FRAME. It was only later, as discussed below, that FRAME

became an active supporter of Russell and Burch's Three Rs, broadening its scope beyond replacement.

FRAME did, however, make use of the term "alternatives" from early on. The trust deed establishing the organization, dated September 1, 1969, refers to one of its aims as providing awards, scholarships, and prizes "for those discovering new and improved techniques as alternatives to the use of animals" in medical, biological, pharmaceutical, and related research. In a *Scientists' News Letter* issued by FRAME in October 1970, Charles Foister expressed satisfaction that "the B.B.C. and others approach us for information relating to alternatives to animals in medical experiments."[21] It is clear, however, that FRAME was using the term "alternatives" to refer specifically to replacements, only one of the Three Rs of Russell and Burch, and not in the way it has generally come to be used, which also includes refinement and reduction.

FRAME did not initially mention, let alone devote any attention to, the broader concept of the Three Rs. It is clear from the name of the organization and its early documents that it was focused solely on replacement, and no mention was made of Russell and Burch's Three Rs or of refinement or reduction techniques. It is true that the trust deed mentions that one of the objectives of FRAME was to give all possible encouragement, advice, and information to those engaged in medical, biological, pharmaceutical, and associated researches "involving experiments on animals so as to avoid unintentional cruelty and unnecessary suffering," but this was basically just paying lip service to the general idea of humane treatment of laboratory animals.[22] However, Mrs. Hegarty and others at FRAME were most likely at least aware of Russell and Burch's book by 1971 as it was mentioned in a published article that year by Mrs. Hegarty's son Terry, who served as one of the organization's trustees.[23]

It is not clear who introduced the term "alternatives" into these early FRAME documents. Mrs. Hegarty had originally used the term "substitutes." Terry Hegarty, who had a PhD in botany, appears to have been the first person associated with the organization to use the term in a published work, the 1971 article referred to above, which was in fact titled "Alternatives." In spite of the reference to Russell and Burch, however, it is clear that Terry Hegarty is using the term "alternatives" to refer only to replacement. He bemoaned the fact that the number of laboratory animals used each year continued to grow "due to the unfortunate trend against the rapid development of replacements, and results from resistance to change combined with familiarity in using existing techniques."[24]

FRAME was at first largely a family affair. As previously mentioned, Terry Hegarty served as one of the trustees, and he and his wife Sheona, both scientists, served as scientific consultants. Eventually, Mrs. Hegarty's husband Jack became the organization's

treasurer. Initially FRAME operated out of the Hegartys' home, but it moved to an office in Wimbledon in 1971. A full-time secretary and a full-time scientist (Peter Bell, a chemist with journalistic and business experience) were soon hired, as well as part-time help to assist with searching the literature for information on replacement techniques.[25]

In the early years, FRAME's activities centered around developing an information center on alternatives, publicizing the organization and the concept of alternatives, raising funds, publishing pamphlets and a bibliography on alternative techniques, and lobbying Parliament and other arms of the British government. These activities included the publication *Alternatives to Laboratory Animals*, which listed important papers relevant to alternatives. In 1972, FRAME established the *Journal of Abstracts of Alternatives to Laboratory Animals* (renamed *ATLA Abstracts* in 1974) to carry on this service of informing investigators about relevant publications about alternatives. FRAME's appeals to Parliament focused on proposals for speeding up research in the field of alternatives.[26] Hegarty said she was not in favor of seeking legislation to enforce the use of alternatives, believing that the best results would be obtained by supplying information to those researchers who sought it and encouraging the interest of others.[27]

In the same newsletter in which the above statement appeared, Hegarty emphasized that one of the main objectives of FRAME was "to try to bring together scientists and laymen in a common purpose, i.e., to see animals replaced in medical experiments whenever and as speedily as possible." She recognized in particular that a key factor in the organization's success would be to secure the support of the scientific community because, as she put it, "obviously the more scientists who hear of FRAME and will support its efforts the speedier will our aims be realised." Hegarty also expressed her appreciation to the *New Scientist* for a "splendid article about FRAME" by editor Bernard Dixon, who had only recently assumed that position. Dixon became a strong advocate for FRAME in the publication and in lectures that he delivered. He also briefly mentioned alternatives and FRAME in his 1973 book *What Is Science For?*[28]

Like the Animal Welfare Institute before it, FRAME found that taking a middle position and attempting to bring together scientists and animal advocates did not protect it against criticism from both sides. Many scientists were skeptical about the possibility of alternatives replacing animal experimentation, except in limited cases, in the foreseeable future. Some scientific and medical organizations in the United States were already skeptical about the true goals of animal welfare groups such as the Animal Welfare Institute (AWI) and the Humane Society of the United States (HSUS) and were suspicious of the newly created FRAME as well. In 1971, the American Medical Association expressed the view in an editorial in its journal that recent developments concerning alternatives "have an ominous portent." They specifically criticized FRAME in

harsh terms as follows: "FRAME might be better called 'FRAUDS' (Fund for the Replacement of Animals Used in the Discovery of Science); FRAME's intentions seem pure, but there is good reason to believe that its basic motives are antivivisectionist. FRAME would have us think that the time is near when tissue culture techniques, mathematical models, and computers can replace animal experiments. Just how these methods might substitute for animal experimentation in neurophysiology, for example, is difficult to comprehend."[29]

In that same year, the *NSMR Bulletin* claimed: "Today's anti-vivisectionists are placing more emphasis on replacement than on prohibition under the guise of furthering research in the life sciences without impeding progress, but their undisguised objective is still elimination of animals as biological models." They included FRAME in their discussion of these groups and added that antivivisectionist groups in the United States "have lacked the finesse to make this 'alternate methods' approach seem plausible."[30] Maurice Visscher, professor of physiology at the University of Minnesota and president of NSMR, was suspicious of FRAME's motives, noting that although FRAME publicly claimed it supported the progress of biological science, a recent debate in the House of Commons "attests to the likelihood that the new organization will attempt to put additional pressure on governments to write more restrictive laws governing the scientific study of living animals."[31] He clearly expressed his doubts about the potential of alternative techniques in a 1975 book on ethics in medical research. In a statement criticizing antivivisectionists, he stated: "Some of them, as already noted, are dressing up their opposition to the use of animals in scientific study with the wholly illusory claim that the use of animals in research is obsolete in an era of advanced computer technology and other powerful mathematical tools."[32]

In Britain, the Research Defence Society (RDS) also took a cautious approach to the efforts of FRAME and other animal welfare societies to promote alternatives, although they were less overtly hostile than their American counterparts. In a 1975 document, RDS council member J. D. Spink referred to animal welfare societies that had dropped the absolutist antivivisectionist approach and focused on reducing the amount of animal experimentation "mainly by promoting the use of the so-called Alternative Methods." He added that this approach made them less objectionable than the antivivisectionist societies, but also more formidable opponents "as their more moderate policy will be acceptable to a broader section of public opinion." On the other hand, he counseled the society to consider trying to find common ground with more moderate groups, specifically mentioning FRAME, and that alternative methods might be an area where the two sides had some common interests. In 1973 the organization's council expressed the opinion that the adoption of a proposed Council of Europe

recommendation, which called for the drafting of international legislation setting out the conditions for animal experimentation and establishing a clearinghouse on alternatives, would be "deplorable" and "severely restrictive on teaching and research."[33]

FRAME also received criticism from antivivisectionists who objected to its efforts to work with scientists to reduce, rather than immediately abolish, animal experimentation. In 1973, Dorothy Hegarty felt compelled to make the following statement in FRAME's *Progress Report* addressing this type of criticism: "We are all anxious to see animals replaced in medical experiments whenever and as speedily as possible. It must however be realized that animal experimentation has become so firmly entrenched that a change of system will only be affected by careful thought and planning and not by hurried and impetuous demands made without due consideration."[34] Writing in the early 1990s, Michael Balls, then chair of the FRAME board of trustees, and J. H. Fentem noted: "We still have to make similar statements several times each month—in reply to enquirers who have been misled by the simplistic literature of certain other organizations."[35]

Further Development of FRAME in the 1970s

FRAME struggled financially in its early years, but continued support from Lady Kinnoull, donations from some animal welfare groups and antivivisection societies, and even a few contributions from industry kept it going. In 1976 the position of scientific administrator was established, which was first filled by Andrew Rowan. Rowan was born in Zimbabwe and raised in Cape Town, South Africa. His mother was a professional ornithologist and his grandfather was a world-renowned entomologist, so he became interested in biological science at an early age. He received his DPhil in biochemistry from Oxford University in 1975 and worked briefly for Pergamon Press editing *International Abstracts of Biological Sciences*. Not being entirely satisfied with the position, he began seeking other employment opportunities. He came across an advertisement for the position of scientific administrator at FRAME. He had been intrigued by a brochure from FRAME that he had seen while a graduate student at Oxford, as well as by Bernard Dixon's *What Is Science For?* (1973), which he read at about that time and which briefly discusses alternatives.[36]

Rowan applied for and was appointed to the position. He believes that he was likely selected because of his doctorate in biochemistry and his experience editing an abstract journal, as one of his duties at FRAME was to serve as editor of *ATLA Abstracts*. Sheona Hegarty, who was editing the publication at the time, was anxious to turn the task over

to someone else, in part because of a strained relationship with her mother-in-law. As a number of former FRAME employees later commented, Mrs. Hegarty was a difficult person to work for.[37]

Rowan's appointment enhanced the scientific credibility of FRAME, which was important to Mrs. Hegarty. In announcing his appointment in one of her progress reports, she stressed his scientific credentials and announced that in addition to editing *ATLA Abstracts*, he would "be doing very useful and necessary public relations work, giving talks and participating in discussions on the use of replacement techniques."[38] Rowan later recalled how Mrs. Hegarty emphasized the scientific character of FRAME:

> One feature of my interview and my subsequent "work" was that Mrs. Hegarty (and her husband Jack) kept accentuating that FRAME was scientific and not an animal welfare organization. Mrs. Hegarty was very suspicious of any suggestion that we should attend a meeting organized by one of the other organizations promoting alternatives because we did not want to be confused with an animal welfare outfit. But any change from the Terry Hegarty/Charles Foister approach was viewed with great suspicion by Mrs. Hegarty. It took me six months to persuade Mrs. Hegarty that we should include papers and reports (not just abstracts) in *ATLA*. It only happened because Terry approved of the idea.[39]

Rowan remembers that he acquired a copy of Russell and Burch's book and read it during his first year at FRAME. Although he found the prose to be turgid, he was very interested in some of the ideas and information in the book, including the material on Chance's statistical work and the discussion of models, especially the difference between a high fidelity and a high discriminatory model. This book, along with Richard French's history of antivivisection in Victorian Britain, Peter Medawar's *The Art of the Soluble*, and the writings of Bernard Dixon all influenced his thinking on animal research and alternatives at this time. As he visited various academic and corporate laboratories, he was struck by the fact that academic scientists tended to attribute any inhumane experiments on animals to the industrial firms, while those firms pointed to academic laboratories as the places where any such practices might take place.[40]

During his time at FRAME, Rowan's major accomplishments included rewriting FRAME's alternatives booklet, testifying at the Home Office on the LD50 toxicity test, organizing a symposium on "The Use of Alternatives in Drug Research" at the Royal Society, and co-editing the volume of papers from this meeting. In his introduction to the volume of papers, Rowan indicated "drug discovery and testing and the testing of

other environmental chemicals" was chosen as the theme of the symposium as it was "one of the most promising areas for alternatives."[41] Large numbers of animals were used in these programs, and significant progress had been made in the development of in vitro screening techniques. It is also clear from his introduction that by this time FRAME was devoting attention to a second one of the Three Rs, reduction, in addition to replacement. Rowan explained that FRAME "uses the term 'alternatives' to describe any technique or system which could replace or reduce the demand for animals while at the same time providing information or results of comparable quality. This definition includes the idea of 'reduction' and, as such, accepts the fact that experimental animals have been and still are required in the biomedical laboratory."[42]

Rowan was instrumental in FRAME's campaign to promote the use of in vitro methods to replace animals in the testing of cosmetics and household and agricultural products. He wrote the scientific material for FRAME's leaflet "What Price Vanity," which specifically criticized the Draize eye irritancy test and the LD50 toxicity test (which will be discussed in the next chapter). The leaflet also included a list of firms providing products that were not tested on animals. Rowan also played a key role in laying the groundwork for the FRAME Toxicology Committee, which emerged as a result of the cosmetic campaign.[43] The FRAME *Progress Report* of May 1979 stated: "Following on from the cosmetic campaign, FRAME is approaching one relevant aspect of animal experimentation, that of toxicology, in a practical manner by establishing an Expert Committee to review current methods to assess the feasibility of introducing and developing alternative techniques which are generally cheaper and more effective than animal tests. Seven experts from relevant disciplines have kindly agreed to serve voluntarily on the Committee supported by a Research Officer whom we are in the process of recruiting."[44]

Finally, Rowan was responsible for getting Michael Balls, who was to play a crucial role in the further development of the organization, involved with FRAME by asking him to write an article for *ATLA Abstracts* in 1976. Balls became a trustee of FRAME in 1979 and in the same year was also elected chair of the newly established FRAME Toxicity Committee. Since that committee did not hold its first meeting until October 1979, its work is discussed in the following chapter.[45]

By 1978, however, Rowan was looking for other opportunities. Aside from the difficulty of working with Mrs. Hegarty, he was also interested in returning to the United States, where he had spent a year as an exchange student in 1964–1965 and which he felt was a bigger biomedical research arena. He learned from a colleague that HSUS was looking to hire somebody on the animal research issue, and he sent a letter of inquiry to Michael Fox, director of HSUS's Institute for the Study of Animal Problems.

A meeting was arranged with HSUS president John Hoyt on his next visit to London, and Rowan was hired for the position (see below).

Humane Society of the United States and Animal Research

In the United States, HSUS became increasingly interested in animal experimentation and alternatives in the 1970s and began to explore the establishment of a staff position specifically devoted to laboratory animal welfare. Early in the decade they hired a laboratory animal veterinarian, but his tenure was a short one. The creation of the Institute for the Study of Animal Problems (ISAP) as a research division within the organization in 1976 provided increased opportunities for investigation of animal research issues, among other topics such as pet overpopulation. The institute was funded by a $750,000 grant from the Whittell Trust. Veterinarian Michael W. Fox, then on the faculty of Washington University of St. Louis, was hired as director of the ISAP. In addition to his veterinary degree, Fox also held a PhD in medicine and a DSc in ethology/animal behavior from the University of London. His academic contacts and his position on two committees of the National Academy of Sciences that focused on laboratory use of animals gave him the expertise and contacts to continue to study the use of animals in research, testing, and education.[46]

In 1978, Andrew Rowan was hired as associate director of ISAP. Given Rowan's previously discussed experience at FRAME, he provided HSUS with special expertise in the area of alternatives, which was attracting increased interest. Rowan, in the words of Unti, "became HSUS's leading spokesperson on the potential of nonanimal methods." Rowan recalled that there was not much happening at HSUS concerning alternatives when he arrived. He was aware that the organization had at some point established an alternatives committee, but it was defunct by the time he was hired. Soon after Rowan's appointment, HSUS issued a report stemming from research in 1978, before Rowan arrived, assessing the attention given to animal care issues by investigators who had applied for and been awarded grants for work involving animal experimentation by the National Science Foundation and the National Institutes of Health (NIH). The 1979 report concluded that the grant applications did not provide sufficient information for review committees to make informed judgments about whether or not the proposals complied with NIH guidelines for the care and use of laboratory animals.

HSUS also became involved in this period with Henry Spira's campaign to ban the Draize test. Shortly after Rowan arrived at HSUS, Spira visited him to discuss

a possible follow-up campaign to the American Museum of Natural History effort. Rowan suggested that he focus on the Draize test, used to test the toxicity of cosmetics and other substances on the eye and generally involving rabbits as the experimental subjects. Others had also pointed Spira to the Draize eye irritancy test as a likely candidate for an animal protection campaign. In fact, Spira had first become aware of the test as early as 1974 when Peter Singer described it in the course in which Spira participated. Rowan became one of Spira's scientific advisors and thus he and HSUS became actively involved in the effort. Although the campaign began as the 1970s drew to a close, it culminated in the 1980s and will be discussed in the following chapter.[47]

Toward the end of 1982, the funding from the Whittell Trust for the ISAP expired and the unit was closed. Fox remained at HSUS, but Rowan moved at the beginning of 1983 to the Tufts University School of Veterinary Medicine where he established the Center for Animals and Public Policy, which he directed. His work on animal experimentation and alternatives at FRAME and HSUS provided him with much of the material for his 1984 book *Of Mice, Models, and Men: A Critical Evaluation of Animal Research*, which includes a chapter on alternatives.[48]

Efforts in Britain and the United States to Amend Animal Welfare Legislation

It was not until June 1971 that the British Parliament held a substantial debate about the failure to act on the 1965 Littlewood Report. As discussed in the last chapter, politicians had not seen any urgent need to act because the report itself indicated that it was satisfied with the Home Office's administration of the 1876 act and found no evidence of extensive public demands for reform. However, the previously discussed development of the animal rights movement stimulated greater public interest in the 1970s. As Robert Garner has written: "In the 1970s, it was less easy for governments to ignore the demands for reform. The public consciousness of the use of animals in research was raised by a reinvigorated and radicalized animal protection movement and a popular press which was prepared to sensationalize aspects of the issue."[49]

In 1973, Douglas (Lord) Houghton, a Labour Party peer, introduced a bill to amend the 1876 act dealing with only one single issue, namely alternative methods. Such a bill had been introduced twice before, in 1968 and 1971, but had gone nowhere. In a debate on the bill on May 11, 1973, Houghton explained that the purpose of the bill was "to encourage and, indeed, to enforce wherever possible the use of alternative methods" in research experiments. He went on to stress that the "search for alternative methods is not

a tiresome fad" and that those "who believe in this are not cranks or silly sentimentalists." The amendment proposed to add a statement to the licensing requirements under the 1876 act that "it shall be a condition of every such licence that no experiment on a living animal shall be performed under the authority thereof if the purpose of the experiment can be achieved by alternative means not involving an experiment on a living animal." During the debate, supporters of the bill pointed to what they considered to be trivial nonmedical uses of animals, such as for safety testing of cosmetics and detergents, while opponents argued that animal experimentation was still needed in the present state of medical knowledge and that the bill would make the work of medical researchers more difficult. The RDS, for example, claimed that to set up an advisory body competent to oversee the whole of biological, medical, and veterinary research "to adjudicate the availability of alternatives is an almost impossible task and could be very wasteful of talent, time and money." In any event, the bill did not succeed.[50]

The real push for amendment of the 1876 act began with a document submitted in 1976 to the Home Secretary by a group of animal welfare advocates that included, among others, Lord Houghton, Lord Platt (a past president of the Royal College of Physicians), Clive Hollands (director of the Scottish Society for the Prevention of Vivisection), and Richard Ryder (a leading member of the Council of the Royal Society for the Prevention of Cruelty to Animals). The Houghton-Platt memorandum, as it was widely known, called for a significant tightening of the controls over animal experimentation established by the 1876 act. This group went on to establish the Committee for the Reform of Animal Experimentation (CRAE) in 1978. Largely due to the influence of Houghton, the group of advocates was able to achieve access to ministers through face-to-face meetings. In spite of their lobbying, however, animal protectionists were not able to succeed in their goal of amending the 1876 act until 1986.[51]

In the United States, as discussed in the previous chapter, the Rogers-Javits bill, which attempted to expand protection of animals to their treatment during experimentation, died in committee due in part to a disagreement between HSUS and AWI over whether the administration of the Laboratory Animal Welfare Act should be transferred to the Department of Health and Human Services or remain with the Department of Agriculture (USDA). In 1969, in an effort to resolve the dispute, Representative Rogers rewrote the bill in a way that would not interfere with the existing Laboratory Animal Welfare Act. Then in 1970, representatives William Whitehurst and Thomas Foley introduced a bill that was supported by Christine Stevens of AWI. Although convinced that the Rogers-Javits bill was the stronger one, HSUS threw its support behind the Whitehurst-Foley bill. This bill was passed by both the House and the Senate, and on Christmas Eve, 1970, President Nixon signed it into law. As a

result of this bill, the Laboratory Animal Welfare Act became the Animal Welfare Act (AWA), with USDA still responsible for its administration. In spite of its limitations, it was a significant step forward in improving the welfare of laboratory and other animals. Bernard Unti summarized its major provisions as follows:

> Now the law regulated more dealers, exhibitors, and others who handled live animals and provided enhanced housing, care, sanitation, and veterinary care for animals in laboratories, including the use of pain-killing drugs, tranquilizers, and analgesics. The 1970 law required that institutions provide pain-relieving drugs and analgesics and report their use or lack of use. Another important addition to the law was its requirement for an annual report by the Secretary of Agriculture on the administration of the law, "to include recommendations for legislation to improve the administration of the Act or any provisions thereof."[52]

Of particular interest in connection with alternative methods is the fact that the Rogers-Javits bill included a provision encouraging the development and use of replacements for animals (cell and tissue cultures, computer simulation, etc.), but this provision did not make it into the final legislation. In addition to this omission, the 1970 act still did not provide adequate protection to animals actually undergoing an experimental process or procedure. Animal welfare advocates therefore continue to press for further reforms.[53]

In the midst of continued legislative discussions about animal research, the National Academy of Sciences sponsored a symposium in October 1975 on "The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing," the proceedings of which were published in 1977.[54] It is interesting, and perhaps indicative of the concerns of scientists, that the word "alternatives" was not used in the title of the symposium. In his preface to the published volume, George Harrell, the former vice president for medical sciences at the Hershey Medical Center of Pennsylvania State University, listed among the factors for deciding to hold the symposium the interest of the press in the use of animals in research, the concern of Congress with the progress of research receiving federal funding, and the hopes of groups of citizens concerned with animal welfare that sufficient progress had been made in research project designs to reduce the use of animals in research. He cautioned, however, that "certain types of research always will require whole living animals" and added that the "proposed newer methods will provide data to supplement that obtained by traditional methods proved by time and when properly used can reduce the number of animals required." Harrell clearly did not want to promise too much for alternative techniques.[55]

In addition to scientists who presented papers on various aspects of medical research, animal models, biostatistical methods, in vitro systems, and other topics, the symposium also featured talks by animal welfare advocates Christine Stevens of the Animal Welfare Institute (who, according to Andrew Rowan, helped organize the symposium[56]) and Robert Hummer, veterinary consultant to the American Humane Association. There were also presentations on ethical and legal aspects of animal research, as well as one by Representative Tom Foley of the State of Washington giving a legislator's view on animal legislation affecting biomedical research. Foley reported that Representative G. W. Whitehurst of Virginia had recently introduced a House Concurrent Resolution stating "that it is the sense of Congress that the Federal Government should take appropriate steps to develop new research methods for its research projects where feasible, to complement or eliminate current methods involving the direct or indirect use of animals; and that no Federal funds should be provided for research projects involving the direct or indirect use of animals if other methods, such as but not limited to, computers, tissue culture, chromatography, spectrometry, non-animal models, lower organisms, or dummies can be successfully substituted."[57] This resolution, which if passed would have expressed the sentiments of Congress but would not have enacted a law, was referred to the House Committee on Science and Technology, where it apparently died.

The remarks of those selected to provide the concluding comments to the symposium were cautious and conservative with regard to alternatives. Howard Schneider, director of the Nutrition Institute at the University of North Carolina, Chapel Hill, provided the summary of the proceedings. In various places he emphasized that "alternatives are complementary, but do not displace the need for animals," that the study of animal behavior is "an aspect [of] biology for which there is no imaginable substitute" for the intact animal, and that the replacement of whole animal tests by tissue-culture tests "does not seem imminent in the foreseeable future." He concluded: "Finally, in these many alternative systems that we have discussed in relationship to animal experimentation, I conclude that to varying degrees they have a place in biomedicine: they are complementary and help fulfill our dreams of reductionism, but they will not replace animals, not yet. They have a place, but they will not replace."[58]

In his closing comments, George Harrell reiterated Schneider's point that alternatives could provide supplemental information to complement other data collected (presumably from whole animal studies). In other words, these nonanimal techniques were in general complements rather than alternatives to animal research. He argued that the "unmistakable conclusion that must be reached from the deliberations of this symposium is that these techniques cannot replace experiments with whole animals."[59] Both men also expressed satisfaction with the assurance from Representative Foley in

his presentation that there was no need at present for new laboratory animal legislation. Schneider also expressed his preference for "self-policing by the profession, instead of a smothering layer of regulation and law."[60]

Although further amendments to the AWA were enacted in 1976, these dealt largely with the transportation of animals and animal fighting ventures and did not address animal experimentation.[61] Proponents of animal welfare continued to push for further legislation relating to the use of animals in laboratory research, including the promotion of alternatives. Bernard Unti has noted that in the late 1970s and early 1980s, "bills promoting the investigation and validation of nonanimal alternatives surfaced regularly." These bills were supported by HSUS and other animal protection organizations and opposed by groups such as the National Society for Medical Research (NSMR), which criticized "vocal antivivisectionist groups who continue beating the public over the head with their erroneous claims of available 'alternative methods' and 'useless' research with animals."[62] In 1977, for example, Representative Edward Koch of New York introduced a bill calling for the promotion of methods of research, experimentation, and testing that would minimize the use, pain, and suffering of live animals. When Koch published this alternatives bill in the *Congressional Record*, he included a letter of support from Eleanor Seiling of United Action for Animals. The bill was referred to the House Committee on Science and Technology, and like other similar proposals, it did not make it to the floor for a vote.[63] It was not until the following decade that the act was amended to provide stricter regulation of animals during experimental procedures, and that some attention was finally given to alternatives in legislation.

David Smyth's Book on Alternatives

The 1970s saw the development of a number of significant new alternative methods, which FRAME reported on in its *Progress Reports* and in *ATLA*. Advances in the technology of nonanimal methods certainly played an important role in fostering the adoption of the principles embedded in the Three Rs concept. Although it is not my intention to trace the history of individual alternative methods in the present work, I will mention a particularly significant one that occurred near the beginning of the decade, the development of the Ames test. In 1973, Bruce Ames, professor of biochemistry at the University of California, Berkeley, introduced a new assay for detecting mutagens and potential carcinogens. The test utilized four mutant strains of *Salmonella* and did not involve the employment of any higher organisms. The Ames test was soon widely adopted, with sixty or seventy major companies using it for toxicological screening by

1976. As Angela Creager explained: "Ames showed that his test could identify nearly all known chemical carcinogens and he advocated its utilization in assessing the cancer risks posed by new substances. Companies immediately began adopting the Ames test as a way to undertake routine chemical screening; the new method was both quicker and less expensive than traditional animal testing. Facilitating the adoption of his test method, Ames made his strains freely available."[64]

The increased development and availability of alternative techniques and the growing pressure from animal protection groups to adopt these methods likely played a role in prompting the publication of the first book on alternatives since Russell and Burch's pioneering work (and the first to use "alternatives" in the title) toward the end of the decade. David H. Smyth's *Alternatives to Animal Experiments*, published in 1978, provided a comprehensive overview of alternative methods and their status, as well as addressing questions and issues surrounding their use. The volume, which undoubtedly raised awareness of alternatives in the scientific community, was not sponsored or published by an animal protection society, but rather had the imprimatur of the Research Defence Society in Britain. In his preface, however, Smyth made it clear that the views in the book were entirely his own and were not subjected to approval or censorship by the society. At the time, Smyth was emeritus professor of physiology at the University of Sheffield.[65]

James Gowans, secretary of the Medical Research Council, claimed in a foreword to the book that no one could deny the benefits to medicine that had accrued from the use of animals in research, but he recognized that public esteem for science was balanced by public concern for animal welfare. He noted that there had been a growing demand, especially in Britain, for stricter control over the use of animals in research, and a call in more recent times for the use of alternative techniques. Gowans added that it had been argued that scientists, whether through lack of awareness of alternative methods or lack of imagination or conservatism, were unlikely to employ and develop these methods unless forced to do so by legislation. On the other hand, scientists responded that they also wished to reduce the number of animals used in research and had been responsible for the introduction of alternatives used in research. They countered that they did not need any further incentives from the public or from government to continue the development and use of these methods. Gowans then summarized the objective and scope of the book: "At the suggestion of the Research Defence Society, Professor Smyth has set out with great clarity and objectivity the issues involved in this debate. He explains why living animals are used in medical studies and the legislation which controls and sometimes even demands their use. He gives a detailed account of the various methods which people have in mind when they speak of alternatives. Particularly

important is his discussion of the oversimplification which has resulted from the use of the term 'alternative.'"[66]

In his introductory chapter, Smyth discusses Russell and Burch's *Principles* and their concept of the Three Rs, which he believed "still remain the best approach to alternatives." He went on to state that in his book "the term 'alternatives' includes any procedures which do away with the use of animals altogether, lead to a reduction in the total number of animals used, or lead to less distress to the animals employed." In other words, his definition of alternatives was based on the principle of the Three Rs: replacement, reduction, and refinement. He admitted, however, that the term "alternative" meant different things to different people.[67]

After providing several background chapters on scientific topics such as biomedical research, toxicity testing, and biologicals, Smyth devotes a chapter to discussing alternative techniques such as tissue culture, lower organisms, and models and computers. He also briefly discusses ways to reduce the number of animals used.[68] While Smyth discusses the uses of these techniques to replace animals in some cases, he also devotes significant attention to what he sees as their limitations. In the case of computers, for example, he argues that while they enable us to make more use of data from animal experiments and allow us to better design experiments to reduce the number of animals used, they do "nothing to replace experiments themselves." He concludes his discussion of computers with the following anecdote: "A friend of mine who is an MP interested in alternatives said to me once, 'Why don't you use computers instead of animals in biomedical research?' I replied 'Why don't you use computers instead of general elections in politics?' That really sums up the situation."[69]

In discussing in vitro methods, Smyth argues that they can provide information about how one part of the body works, but not how it fits in with the working of the body as a whole. As an example, he points out that even when we know the effects of a drug on different isolated organs, "we are not sure of its effect on the whole animal without injecting it into a whole animal."[70] Specifically addressing tissue culture studies, Smyth admits that they are useful in biological research and even concedes that they sometimes give us information we could not obtain from whole animal experiments. He goes on to state, however, that for some types of work, "including almost the whole of mammalian physiology, tissue culture would be useless." He concludes that tissue culture and animal experiments "are not alternatives to each other, they are complementary, and each one answers questions which the other could not solve."[71]

Smyth discusses a host of other alternative techniques, in each case describing what he sees as the ways in which these techniques are being used in medical research and their potential for increased use, but also emphasizing their limitations. In discussing

the use of microorganisms, for example, he explains that they can be useful in metabolism and toxicity studies because some of the chemical reactions carried out in these organisms are similar to those in higher animals. However, there are also vast differences between the metabolic processes, cellular structure, and so forth of microorganisms and higher animals. A given chemical, for example, might have a toxic effect on a microorganism but not affect a higher animal, or vice versa. Once again Smyth sees the use of microorganisms as complementary to, rather than as alternatives to, animal experiments. He did single out, however, one particularly useful alternative to animal experiments, the Ames test for mutagenicity or carcinogenicity (discussed above).[72]

Throughout his discussion of alternatives, Smyth continually emphasizes that scientists are already aware of and making use of these methods when they are available and appropriate. It is also scientists, he stresses, who have developed these alternative techniques and will continue to do so. Smyth also comes back several times to the point that these methods are complementary to, rather than alternatives to, animal research.

Smyth's penultimate chapter, just before his summary, is titled "Some Questions about Alternatives." It begins with the question "alternatives to what?" Smyth then enumerates some of the possible answers: alternatives to animal experiments of any kind, to experiments causing pain or distress, to experiments on certain species of animals, and so on. He suggests that it would be useful if those campaigning for alternative methods would make clear which of these meanings they have in mind and expresses his belief that progress would be quicker if all would agree that we should concentrate on experiments that cause pain or distress.[73]

Following up on this last point, Smyth discusses the extent of animal involvement in various types of experiments (no animal is involved, animals have to be killed to obtain biological material, animal is anesthetized, animal is used without anesthesia, etc.). Here again he emphasizes that it would be useful to "focus attention on the procedures which cause pain or distress, instead of putting equal effort into finding alternatives to all animal experiments, whether painful or not."[74] He then addresses various motives that prompt individuals to look for alternatives, such as humanitarian reasons, a belief in the absolute rights of animals, scientific motives, and economic incentives. In this section he examines claims by some that nonanimal methods are more reliable than animal methods. He points out that the question of reliability is complex because the loose term "reliability" includes several different qualities (e.g., sensitivity, accuracy, reproducibility) other than the technical sense of reliability (i.e., the capacity to measure what we think we are measuring). General statements that nonanimal methods are more reliable are meaningless and must be determined for each particular type of procedure or experiment. After discussing some of the problems encountered in

replacing animals with nonanimal alternatives in the case of bioassay, which he considers to be the simplest case, Smyth concludes: "The majority of cases are far more complicated, and in the case of tissue culture the scientist is usually asking a different question than he would ask when using animals. It is therefore meaningless to say that one is more reliable than the other. It is like asking which is more reliable, a fine screwdriver or a sledge hammer. The answer is that a fine screwdriver is more reliable for repairing a delicate piece of machinery but a sledge hammer is more reliable for breaking a rock."[75]

In discussing the reasons why alternatives are not more widely accepted, Smyth counters many of the charges made about scientists by supporters of alternatives (e.g., scientists are too conservative and conventional, there is a lack of knowledge of alternatives, ingrained irrational resistance of the majority of scientists). He argues that scientists are well aware of alternative methods, that it is in their interest and nature to be open to new ideas, and that scientists would not willingly cut themselves off from promising techniques that could advance their careers. He points out some of the practical reasons why alternatives might not be tried in some cases, such as legal and regulatory requirements requiring animal testing of medicine, food additives, and other substances. Smyth concludes that the real reasons why alternatives are not more widely used "are that in cases where they are useful it is difficult to see uses not already being fully exploited, and in very large areas of biomedical research there is no alternative to using animals to obtain the kind of information now used as a background to health and welfare service in the widest sense of these words."[76]

The final chapter of the book provides a summary and conclusions. Smyth agrees that there are some alternative methods available that are useful, and he also makes several suggestions for increasing the use of these methods (e.g., that consideration be given to increasing financial support for *ATLA Abstracts* to make better known developments in alternatives and that a research project should be initiated to find out if there is a useful alternative to the Draize test). On the whole, however, he takes a very cautious approach to alternatives and is critical of some of the claims made for them by animal welfare advocates. For example, he cites tissue culture as a field in which many claims are made about its potential for replacing animals and discusses its limitations. He argues that it has "very little place in studying problems in higher animals where there is interaction between different tissues and organs" and that no tissue culture expert he has spoken to "envisages the likelihood of a dramatic breakthrough in tissue culture techniques in the near future to change the situation." He also repeats his message that all the alternatives that have been put forward are widely known by scientists in a position to use them and that alternative techniques are widely used when they have been found to be better than animal experimentation. He refers again in one place to

these methods as being complementary to rather than alternatives to animal experiments, and he emphasizes that no alternatives to toxicity testing in animals are compatible with the present standards of safety.[77]

Smyth's book provided a fairly comprehensive overview of the alternative techniques known at the time. It undoubtedly increased awareness of and interest in alternative methods among scientists. The work clearly laid out the issues involved with alternatives and encouraged broad discussion of them. It was a landmark in the history of the development of alternatives. Given its cautious, skeptical view of the prospects of alternatives replacing animal experimentation on a large scale in the foreseeable future, however, it probably did not satisfy the hopes of animal advocates who were pressing for a more immediate and widespread adoption of alternatives. Nevertheless, it helped to pave the way for the important advances that helped to establish the field of alternatives on a firm footing in the 1980s, as discussed in the following chapter.

The decade of the 1970s also marked the beginning of a decline in the use of animals in research and testing, as predicted by Peter Medawar in 1972 (see chapter 2). Rowan and Loew estimated that laboratory animal use declined by about 50 percent from 1970 to the early 1990s, peaking in the mid-1970s. They attributed this decrease in animal use to several factors, one of which was the development and improvement of new scientific techniques (i.e., alternatives) that enabled animal use to be greatly reduced or replaced altogether in some cases. They also cited a growing concern for animal welfare, the increasing costs of research (including the purchase and maintenance of animals), and less reliance by pharmaceutical companies on random screening of chemicals in their drug discovery programs. The numbers did begin to rise again substantially in the period 1995–2015 due to the widespread introduction of the use of genetically modified mice, but then began to fall again when that technology did not fulfill its promise. The role of alternative techniques in this overall decline in the use of laboratory animals was probably relatively minor in the 1970s, but was to increase significantly over the ensuing decades.[78]

5

Alternatives Come of Age

The 1980s

As the 1980s opened, supporters of alternatives devoted significant attention in Britain and the United States to the area of toxicity testing. Chemicals have played an increasing role in the lives of consumers in recent decades. In a 2014 workshop, Lynn Goldman, dean of the George Washington University School of Public Health, noted that the volume of synthetic organic chemicals produced in the United States tripled between 1970 and 1995, from about 50 million tons to approximately 150 tons. New chemicals are constantly being discovered or synthesized, and there are tens of thousands of such compounds in commerce. Concerns over the possible toxic effects of these substances led to requirements for toxicity testing of new products (e.g., drugs, cosmetics, cleaning supplies, pesticides) before they are marketed. Traditionally these products were tested for toxicity on live animals. As the introduction of new chemicals increased, so did the demand for animals to be used in testing. Although we do not have good historical data on the number of animals used in testing, the US Office of Technology Assessment estimated in a 1986 report that while the use of animals for such testing did not become common until a few decades ago, in the United States "it now accounts for several million animals per year." That estimate was undoubtedly low due to the incompleteness of the data, as the report itself made clear.[1]

The use of animals in the testing of cosmetics and toiletries drew particular fire from animal protectionists and others as very large numbers of animals were used in connection with these products, which were viewed by many as not being essential. Already

in 1975 Richard Ryder criticized the toxicity testing of new products, calling it an "increasingly huge area, probably already the largest field in which live animals are used for research." Among other tests that he singled out were the Draize test for eye toxicity and the LD50 test (discussed below). In his 1978 book on alternatives, discussed in the previous chapter, Smyth recommended that a research project be initiated to attempt to find a useful alternative to the Draize test and that there should be a discussion of the place of the LD50 test in safety evaluation programs.[2]

Henry Spira and the Campaign Against Toxicity Testing of Cosmetics

After the completion of the American Museum of Natural History campaign, Henry Spira turned his attention to other animal welfare issues. One of the most important of these, especially from the viewpoint of alternatives, involved the toxicity testing of cosmetics and toiletries on animals. Peter Singer later recalled that in his 1974 course, attended by Spira as previously mentioned, he discussed a widely used safety test that he found especially outrageous, namely the Draize test for eye toxicity: "Cosmetics and other substances are tested for eye damage. Here the standard method is the Draize test, named after J. H. Draize. Rabbits are the animals most often used. Concentrated solutions of the product to be tested are dripped into the rabbits' eyes, sometimes repeatedly over a period of several days. The damage is then measured according to the size of the area injured, the degree of swelling and redness, and other types of injury."[3]

In order to prevent the rabbits from possibly dislodging the substance by shutting or clawing at the eye, they were usually immobilized in devices from which only their heads protruded, with their eyes often held open with metal clips which kept the eyelids apart. The test had been introduced in 1944 by John H. Draize, a pharmacologist at the Food and Drug Administration, and soon became the standard for determining eye toxicity. With the development of the animal rights movement, the test increasingly came under attack, especially because of its use on a large scale in the testing of cosmetics for eye toxicity.[4]

As mentioned in the previous chapter, Andrew Rowan and others suggested to Spira that the Draize eye test would be a good target for his next campaign.[5] The procedure was used to test a wide variety of chemicals and household products, even though a study of twenty-five laboratories found extreme variation in evaluating the same chemical.[6] Spira decided to focus on the cosmetics industry as the most vulnerable target. As

he later wrote: "We could pose the issue this way: is another shampoo worth blinding a rabbit? It was so incongruous for the cosmetics industry to be carrying out these tests. The cosmetics industry is trying to sell dreams, but the reality is that they are creating a nightmare for the rabbits. Exposing the reality of what they are doing threatens the whole image of the industry. Blinding rabbits isn't beautiful."[7]

The test was also an especially painful one that was performed on an animal species that most people viewed as cuddly and lovable, so Spira could expect public sympathy for his campaign. He asked the public to imagine having harsh chemicals forced into your eye while being confined in a box with only your head sticking out. "Think of the trauma, the panic and the burning pain."[8]

Spira decided that the best strategy would be to focus initially on a single company. He chose Revlon, a giant in the field that sold a billion dollars' worth of beauty products in 1978. Rather than trying to get them to immediately abandon the Draize test, which would have been impractical because it was the standard test for eye toxicity used in meeting regulatory requirements, he proposed that Revlon fund a research project to develop an alternative test that did not use animals. He hoped that success with Revlon would encourage support from other companies, providing sufficient funds for an accelerated research program to develop a nonanimal substitute for the Draize test, thus replacing it across a range of industries.[9]

An initial approach to Revlon was made in September 1978 via a letter from Spira and Leonard Rack, a psychiatrist and a collaborator of Spira, to the company's vice president for public affairs, Frank Johnson. The letter outlined some ideas for methods that could replace animal testing of cosmetics, providing references to scientific papers that offered promising avenues of research. Spira and Rack did not receive a response to the letter. Spira eventually managed to arrange a meeting with Johnson but concluded after that session that Revlon was not taking the proposal seriously.[10]

After further unsuccessful attempts to engage Revlon, Spira concluded that he needed to take a more aggressive approach. He decided to build a broad Coalition to Stop Draize Rabbit Blinding Test. On August 23, 1979, he issued a blueprint for the campaign. The document was circulated to individuals and organizations interested in supporting the campaign, as well as to the cosmetics industry. Among the steps outlined were the establishment of the coalition, a pressure campaign on the cosmetics trade association to persuade them to tax their members 0.01 percent of their gross earnings to fund research for a nonanimal alternative to the Draize test, and the promotion of a bill "which mandates regulatory agencies to encourage innovation and optimize safety testing by accepting reliable non-animal methods as they are developed." The blueprint closed with a promise: "A victory in the Draize campaign, made possible through the

evolution of science, will have an enormous real impact—a possible beginning of the end of live animal safety testing."[11]

The coalition grew in time to include more than 400 institutional members, with a total membership in the millions. The operational costs were covered by the larger institutional members, such as the Humane Society of the United States (HSUS), the American Society for the Prevention of Cruelty to Animals, and the Anti-Cruelty Society (Chicago). Several HSUS staff members, including Andrew Rowan and President John A. Hoyt, worked closely with Spira on the campaign. Peter Singer noted: "On one occasion the Humane Society sent out a mailing to 250,000 people on behalf of the coalition, and for a time employed a part-time staff member to assist the coalition." The coalition sent letters to federal agencies, lobbied the Cosmetic, Toiletry and Fragrance Association (CTFA), sent Revlon a specific proposal to help with the development of an alternative to the Draize test, and threatened to encourage consumers to boycott the company's products if they did not agree to actively support such a project.[12]

In January 1980, Andrew Rowan, on behalf of the coalition, sent Frank Johnson of Revlon a specific proposal related to alternatives for toxicity testing of cosmetics. On February 13, 1980, Johnson wrote to Spira informing him that the proposal had been referred to CTFA, which established a subcommittee of its Committee on Pharmacology and Toxicology "to review short term testing procedures for the industry." Rowan's proposal was in the hands of that subcommittee, and Johnson stated: "Neither Revlon, nor any other single company, can give any assurances as to what action, if any, this committee, or any other committee of the CTFA, may take on this matter, except to say that it will receive consideration."[13]

Whether or not this response was the last straw, Spira decided that it was time for bolder action. He contacted Mark Graham, an advertising executive who had earlier been outraged at the cat experiments at the American Museum of Natural History, which Graham had learned about through one of Spira's flyers. Graham had given the volunteer handing out the flyers his business card and asked her to pass it on to the organizer of the campaign. Spira had filed the card away but now recalled this earlier contact and asked Graham if he would be interested in helping to design an advertisement against Revlon and the Draize test. Graham agreed. The advertisement that he produced was, in the words of Singer, "unlike most previous advertising done by the animal movement; it had the style and professional look of the advertising of major corporations like Revlon itself." Spira then secured funding from the Millennium Guild to pay for a full-page ad in the *New York Times*. The ad appeared on April 15, 1980, and was headlined "How many rabbits does Revlon blind for beauty's sake?" It prompted a flood of letters of protest to Revlon.[14]

On April 17, Revlon issued a statement calling the ad "false and misleading." They argued that the Draize test was the standard one used by industry and government to determine the toxicity of chemicals on the eyes and that there was no substitute for it. The statement also emphasized that the animals were cared for by trained professional handlers "working under carefully devised federal standards." Revlon also claimed that it and other cosmetic companies were "actively looking for alternatives that would produce acceptable results."[15]

The coalition continued to exert pressure on the industry though letters, publications, and protests. In November 1980, the campaign went international, with simultaneous demonstrations organized in six other countries, including Great Britain (British efforts to promote alternatives in cosmetics testing are discussed in the following section). It is not my purpose here, however, to provide a detailed account of the campaign, and the interested reader is referred to Peter Singer's *Ethics into Action* for such an account.[16] My focus here is on how the campaign eventually convinced the cosmetics industry to provide significant funding for research on developing alternatives to animals in toxicity testing.

Eventually Revlon agreed to provide funds to a university for the purpose of undertaking research to find an alternative to the Draize test. They approached Rockefeller University of New York, which was receptive to the idea, and Revlon gave the university $750,000 over three years to support research into nonanimal safety tests. On December 23, 1980, Revlon issued a press release announcing the grant, which it claimed was "one of the largest grants of its kind made by a cosmetic company." It also called on other manufacturers of personal care products "to join Revlon as full partners in supporting this research." On the same day, the coalition issued its own press release hailing Revlon's initiative and strongly supporting the company's suggestion that other members of the industry provide similar support for the effort.[17]

Other companies soon followed suit. In March 1981, for example, Avon contributed $750,000 to a fund established by the CTFA to support research on nonanimal methods of safety testing for cosmetics and related products (with an initial focus on the Draize test). More firms continued to join the effort, and CTFA announced that it planned to use this growing fund to establish a new Center for Alternatives to Animal Testing, eventually resulting in the creation of such a center at Johns Hopkins University (discussed in the following section).[18]

While continuing his efforts to end the Draize test, Spira expanded his campaign to include another widely used toxicity test, the LD50 test, which by 1980 was performed on four to five million animals each year in the United States alone. The LD in the test name stands for lethal dose, and the LD50 is the amount of a single dose of a substance

that kills half of the test animals. It is a measure of acute toxicity. Peter Singer pointed out that in the process of determining the dose that killed half of the sample, all of the animals would likely become very ill. He added: "The tests commonly last fourteen days, but some take up to six months. Symptoms observed include convulsions, breathlessness, vomiting, internal bleeding, tremors, and paralysis. If the animals will not eat the substance, it will be force-fed to them through a tube down their throat. The same technique will be used if the substance is a relatively harmless one, and enormous quantities have to be given to the animals to make half of them die."[19]

Spira established a Coalition to Abolish the LD50 (his various campaigns were organized under an umbrella Animal Rights Coalition). By this time, in the early 1980s, the LD50 test had not only come under fire by animal welfare groups but had been criticized by some in the scientific community since at least the 1960s. Marked differences were often seen between the LD50 values for different species, and many toxicologists argued that the test had little value in predicting nonlethal toxicity resulting from single or multiple low-level exposure. Others pointed out the number of animals used in a test could be significantly reduced without affecting the precision of the results. These widespread scientific doubts about the value and necessity of the LD50 in the evaluation of the toxicity of cosmetics and household products made it easier for Spira's coalition to achieve success in their campaign to eliminate it or at least dramatically reduce the number of animals used in the test.[20]

The coalition used many of the same tactics that it had employed in the Draize test campaign, including a full-page newspaper ad stating that the LD50 test caused agonizing deaths for millions of laboratory animals. The ad first appeared in the *Trentonian*, a local Trenton, New Jersey, newspaper, on May 3, 1983, because Spira had won free advertising space in the paper at a raffle. It was also run in the *Washington Post* and generated significant media coverage. It led, for example, to an invitation for Spira to appear on the *Today* show, which had seven million viewers.[21]

The coalition's campaign played a significant role in getting industry trade associations such as the Pharmaceutical Manufacturers Association and the CTFA to issue statements that the use of the classical LD50 test lacked justification and that regulatory requirements should accommodate this position. Even the National Society for Medical Research (NSMR), which had traditionally been suspicious of animal welfare groups and of alternatives, supported this position. The Food and Drug Administration (FDA) convened a workshop on November 9, 1983, that included representatives of federal agencies, the cosmetics and drug industry, and animal welfare activists such as Henry Spira and Christine Stevens. Officials of several regulatory agencies admitted that the LD50 test had limited value and that other tests requiring fewer animals would

suffice for safety evaluation. Over the succeeding months, the FDA, the Environmental Protection Agency, and other relevant regulatory agencies made it clear that they no longer required LD50 tests. While the efforts of Spira's coalition, which continued, had not succeeded in completely eliminating tests such as the Draize and the LD50, they had challenged their dominant role in toxicity testing, had substantially reduced the number of animals undergoing such tests, and had stimulated the search for nonanimal alternatives.[22]

Establishment of the Center for Alternatives to Animal Testing (CAAT)

As discussed in the previous section, the pressures brought by Henry Spira and other animal rights activists on the cosmetics industry had prompted CTFA to establish a fund, with contributions from individual cosmetics companies, to support research on nonanimal methods of safety testing for cosmetics and related products. At some point in the latter part of 1980, Robert Worsfold, president of Estée Lauder International and board member of CTFA, had a discussion with D. A. Henderson, dean of the Johns Hopkins University School of Hygiene and Public Health (now the Johns Hopkins Bloomberg School of Public Health), where he asked his advice on the issue of alternatives to animal testing. Worsfold knew Henderson well as he was a member of the School of Public Health's advisory committee. He explained to Henderson that animal activists were giving the cosmetics industry a black eye over animal testing and that the industry was interested in developing nonanimal methods of testing. He added that the industry had created a fund through the CTFA and was prepared to spend one million dollars over three years for this purpose. Henderson recommended that the program be established at a university as developing a new entity would be more time-consuming and possibly less productive, especially given the short three-year time frame.[23]

Henderson recalled that Alan Goldberg, the director of the Division of Toxicology of the Department of Environmental Health Sciences (EHS) at the Johns Hopkins School of Hygiene and Public Health, had published an article on in vitro toxicology using tissue culture methods. He consulted with Gareth Green, chair of EHS, about whether the school should get involved in the effort that CTFA was interested in supporting and whether Goldberg should be brought in on the discussions. Henderson later remembered that the idea seemed somewhat odd to him and that he did not have much hope for it, in part because he was not sure what could be accomplished before

the money ran out. In any case, a meeting between Henderson, Green, and Goldberg to consider the matter was arranged, probably sometime in early 1981.[24]

Alan Goldberg had received his PhD in pharmacology at the University of Minnesota in 1966. After a postdoctoral fellowship and then a faculty appointment at Indiana University, he moved to the Johns Hopkins School of Public Health to join the faculty in the Division of Toxicology in EHS in 1969. While at Hopkins, he was working with organophosphates, one group of which can produce neuropathy weeks after exposure. Goldberg was trying to find the reason for the delayed neuropathy and whole animal studies were not yielding useful results. He then decided to try nerve muscle tissue in culture. Goldberg consulted with Neville Brooks of the University of Maryland and collaborated with him on this research. Their collaboration resulted in the publication in 1979 of a paper using spinal cell cultures, which Goldberg believes was the first to use in vitro tissue culture as the biological matrix in toxicology. Goldberg recalls that they were using the technique because of its scientific value and were not thinking in terms of finding an alternative to animal research. It was, however, his introduction to in vitro toxicology studies. Henderson and Green were aware of Goldberg's research in this area and so he was a logical person to include in their deliberations about a potential CTFA-funded project. Henderson presumably had also mentioned this work to Worsfold because James Merritt and Norman Estrin of CTFA wrote to Goldberg on September 5, 1980, according to Goldberg at Worsfold's suggestion, inviting him to participate in a workshop devoted to a consideration of possible in vitro alternatives to in vivo ocular safety testing methods.[25]

Goldberg later recalled how he had been contacted by Gareth Green concerning the matter raised by Robert Worsfold.

> Gareth called me and asked, "If you had a million dollars how would you eliminate animal testing in the cosmetic industry?" He suggested that we discuss how to address Bob's ideas for creating a less hostile environment between animal rights groups and CTFA and its members. The three of us—D. A. [Henderson], Gareth, and myself—scheduled a meeting to discuss the issue. As I recollect, the issues we labored over were as follows: How would the scientists in the university feel about such a center? What should we name it? How would the grant ($1 million from the CTFA) impact on the school?[26]

Goldberg also remembers that it was agreed at this meeting that the university would accept the grant only if it was driven by a scientific agenda. They did not decide at this meeting on a name for the new unit they envisioned but agreed that "alternatives"

should be a part of it. Discussions about the name continued for several weeks, even after a grant application was submitted. The term "complementary" was rejected because they believed in vitro methods would eventually replace animal testing. In an interview with me, Goldberg said that he was influenced by the encouragement of neuroscientist Richard Hammerschlag of the City of Hope Hospital to use the term "alternatives," so long as it was defined by the Three Rs.[27]

The three Hopkins colleagues also discussed how to develop a proposal for the new center they were considering. Rather than establish a giant laboratory at Hopkins, the center would distribute small grants spread over various laboratories at Hopkins and other institutions to serve as seed money to encourage the development of in vitro toxicological testing methodologies. These cell-based assays would be designed to replace animal tests for regulatory purposes. After the discussion, Goldberg was given the task of drafting the proposal. He recalled later how he completed a first draft of the grant proposal in one evening.[28]

Goldberg was the logical person to serve as the director of the proposed center, and he listed himself as such in his initial draft. At that point, however, he was not certain that he should accept the position and over the next few days he reached out to people at Johns Hopkins and beyond for their input on the question. The majority of those he consulted told him that they thought he would be making a mistake and harming his career, or even be seen as "selling out" to animal activists. He had been warned that he should expect personal rejection from some colleagues, but he was unprepared for how extensive the rejection would be. Goldberg later recalled that the rejection came on two fronts, "the perception of my work on what were understood as 'animal rights' issues and the rejection of applied research." The scientists whom Alan most respected (including Green and Henderson), however, encouraged him to accept the position, and he was identified as the director of the center in the proposal submitted to CTFA.[29]

The proposal requested a total of one million dollars for the period September 1, 1981, to August 31, 1984, and provided a general outline of proposed expenditures. The proposal called for the establishment at the Johns Hopkins School of Public Health of "a highly creative and visible Center for the testing of chemical compounds in biological systems that do not involve whole animals." The specific purposes of the center, which is referred to in the document as the Center for Alternatives to Whole Animal Testing, would be to encourage research in the development of in vitro or other nonanimal test procedures to examine the toxicity of commercial products and other chemicals, to develop methodology that would provide alternatives to whole animal studies for the evaluation of safety, and to disseminate research progress via symposia, workshops, and publications.[30]

The research program would focus initially on finding alternatives to the Draize test and other animal tests that produced inflammation. The research program would involve both intramural grants with Johns Hopkins University and extramural grants to other institutions. In order to shape the research approach, the center would first hold a symposium in Baltimore, to be planned by the center director and advisory board, "to examine the currently available alternatives to whole animal testing." The proposal then discussed the intramural and extramural programs in more detail.[31]

The rest of the proposal was devoted to the discussion of the organization of the center; the qualifications of the proposed director, Alan Goldberg; the composition of the advisory board; the review and management of grants; and facilities and resources. The proposal also indicated that the center would solicit additional funds from other industries, such as the pharmaceutical, chemical, and soap and detergent industries, whose products required toxicity testing and safety evaluation, so that the cosmetics industry was not alone in supporting efforts to develop alternatives.[32] A concluding section emphasized that the "guiding principle of the Center and its programs will be scientific excellence and credibility." In a bow to the potential sponsor of the center, the proposal added that the research program would be developed in part "through a process of familiarization with the needs of CTFA and its members."[33]

The proposal was submitted to CTFA. Alan Goldberg recalls, however, that CTFA also requested a contract proposal from a contract research firm (he believes it was Battelle) because some members of their board wondered whether it would not be advisable to contract out the project, rather than provide a grant, so that the organization could have greater control over the work. CTFA eventually decided, however, to go with the Johns Hopkins group.[34]

An agreement was signed between CTFA and the university on September 21, 1981. The agreement is a remarkably brief (eight pages) and general document for the disbursement of one million dollars. It is similar in its general provisions to those in the grant proposal. The new center, however, was named the Johns Hopkins Center for Alternatives to Animal Testing (CAAT). CTFA had the right to appoint a nonvoting industry liaison representative to the center's advisory board (whereas in the grant proposal CTFA was asked to nominate individuals from among its member companies or other corporations to serve as presumably voting members of the board). The agreement was for three years but could be extended by mutual written agreement.[35]

Hopkins held a press conference on September 21, 1981, the day that the grant proposal was formally approved, to announce the creation of the center. The university had been advised to have security present because of the possibility of protests from

the animal rights community.[36] It was not only portions of the scientific community who were skeptical about and critical of the new center, but also many animal activists. As Deborah Rudacille, who was a writer and communications officer at CAAT from 1992 to 1997, wrote:

> Initial reaction to the formation of the center within both the animal rights and scientific community was outright cynicism. It was a public relations ploy, animal rights activists were convinced, meant to take the pressure off companies who were under attack not only by Spira and his allies but also by more radical animal rights campaigners who demanded not a leisurely search for "alternatives," but immediate abolition of the Draize and other animal tests. Scientists, on the other hand, aware of the international regulatory apparatus mandating testing of products and the legal and moral obligation of companies to establish product safety—a mandate carried out entirely by animal testing for more than forty years—were not sanguine about the prospect of change.[37]

As it turned out, there were no protests at the press conference. James Merritt, president of CTFA, announced the grant, stating that it was "a major initiative of industry in response to both public and industry interest in finding alternatives to product safety tests which involve animals." Goldberg also spoke at the press conference. While he expressed confidence that the efforts of the center would help to significantly reduce the need for animals in testing, he cautioned against overly optimistic expectations. He noted that as a practical matter, "there will be a need to rely on animal tests for some time to come to protect the public, and to advance the frontiers of medical knowledge."[38]

From the beginning, Goldberg tried to rein in any expectation that the use of animals in testing would be totally eliminated within a short time, and he also emphasized that animal use in research, as opposed to testing, would certainly need to continue for the foreseeable future. He was to repeat these two themes on many occasions. In response to a letter from a woman who expressed disappointment that the center was still justifying animal testing, for example, Goldberg wrote that while the center was working to eliminate animal testing as soon as possible, he could not recommend that industry cease animal testing immediately. Companies would need to continue to use animal tests to ensure the safety of their products until nonanimal methods were proven at least as effective as animal tests. In another letter to J. C. J. van Vliet, a Dutch veterinary surgeon, Goldberg expressed his firm belief that alternatives could be developed

in the area of testing methodology but added: "On the other hand I do not believe that animals can be replaced in the development of fundamental and basic knowledge in the advancement of our understanding of biological systems. The name of the Center was very carefully chosen to reflect this."[39]

In a CAAT newsletter in 1985, Goldberg felt the need to clearly define the terms "alternatives" and "testing." He emphasized that the center used the term "alternatives" to refer to all of the Three Rs: replacement, reduction, and refinement. Noting that some in the animal protection movement would like to restrict the word "alternatives" only to replacement, he expressed the concern that such a narrow definition would distract the public from reduction and refinement, which offered real improvements in animal welfare. As for the term "testing," Goldberg stated that when the name of the center had been chosen, he had been "very careful to distinguish between toxicological *testing*, which is routine, and biomedical and behavioral *research* or *experimentation*, which involves the development of new knowledge." He added that while scientists could develop alternatives to animal tests, where there were known end-points, they would need to continue to use animals in research for the foreseeable future.[40] One can understand Goldberg's desire to emphasize these points as part of his efforts to make it clear from the outset that the center was primarily a scientific program, although with animal welfare as a necessary concern.

CAAT held its first full board meeting on February 1, 1982. Plans for a proposed symposium in May to assess the existing state of knowledge about testing requirements and potential alternatives, as well as provide guidance for the center's research programs, were discussed. Grants for the intramural program, that is, grants from laboratories within Johns Hopkins, were reviewed and six were approved. The director also announced the creation of a newsletter and of a sponsorship program that would provide opportunities for other organizations and institutions to support the center. CAAT had already received a substantial grant of $200,000 at the close of 1981 that would allow it to expand its scope.[41]

The planned symposium was held in Baltimore in May 1982. There was broad representation from industry, academia, government, and animal welfare groups among the ninety participants. The proceedings of the symposium were summarized in the *CAAT Newsletter* and published in 1983 in a volume titled *Product Safety Evaluation*. In his remarks, Goldberg stated that the presentations and discussions taking place at the symposium would be taken into account when CAAT's board considered the research grant applications that the center was then soliciting from institutions outside of Hopkins. In his presentation on the interaction between science and animal welfare,

Andrew Rowan expressed the view that "the notion of alternatives to animal testing appears to be an idea whose time has come for a variety of reasons. Whether through dissatisfaction with current tests, visions of advances made possible by the availability of new technologies, ethical concerns over the treatment of animals or other reasons, this was one point upon which all seemed in agreement."[42]

At the end of the first year of funding in September 1982, Goldberg provided CTFA with a report of expenditures and progress. He listed as accomplishments the symposium held in Baltimore and the establishment of the intramural grants program and expressed the belief that with the launch of the extramural grants program in November, "we will have established, in just over one year, the most comprehensive approach to developing alternatives to whole animal testing." He also claimed that the center "has been widely accepted by the scientific community and I believe its acceptance and credibility will continue to grow," while admitting that "we have been attacked by a very limited segment of the Animal Rights Community."[43]

At the end of the initial three-year grant period in 1984, CTFA extended its support of CAAT for an additional three years. It also gave CAAT permission, at the end of this three-year extension, to solicit individual cosmetics, toiletry, and fragrances companies, something that was not permitted under the terms of the CTFA grant. Alan Goldberg has indicated that he and D. A. Henderson had not been overly optimistic that the center would outlast the original CTFA grant and would never have predicted with any confidence that it would still be operating today, more than forty years later, stronger than ever.[44]

The creation of CAAT was significant not just for the grant support and visibility that it provided for alternatives, but also because having such an entity established at a major biomedical research center helped to lend scientific credibility to the field of alternatives. Speaking of CAAT in 1997, Andrew Rowan stated: "Its mere existence validates the concept of alternatives."[45] Johns Hopkins, founded in 1876, was the first American university to be based on the model of the German research-oriented university. The School of Medicine, which opened in 1893, was a model of modern medical education.[46] It continues to be viewed as one of the premiere medical research institutions in the country, and even in the world. The School of Public Health, where CAAT is based, shares the prestige of the university and its rich tradition of excellence in the health field.

As noted above, Goldberg claimed that by a year after its creation, CAAT was already widely accepted by the scientific community, although certainly many scientists still had mixed views about alternatives (as will be seen in the discussion of legislation

below). In spite of the misgivings that some of his colleagues had voiced about his becoming the director of CAAT, however, their fears that his scientific career would be in jeopardy never materialized. From the beginning, Goldberg was able to recruit prominent scientists to serve on the center's advisory board and to participate in symposia and other events sponsored by CAAT. Goldberg emphasized that CAAT's role was "strictly a scientific one" and that "the Center has a responsibility to use its resources carefully and imaginatively in promoting scientific inquiry of the highest caliber."[47]

Animal welfare supporters also began to cooperate with CAAT. Surprisingly, Henry Spira, whose campaign against animal testing of cosmetics helped to stimulate CTFA to provide the funds that supported CAAT, was initially critical of the center. Goldberg discovered at the CAAT symposium in May 1982 that Spira had drafted a letter to him accusing him of using CAAT funds for personal gain. The draft letter had been sent to members of the CAAT board asking their advice on whether it should be sent to Goldberg. Goldberg gave the copy of the letter that he had obtained from a board member to the Hopkins public relations representative for the center, assuring her that none of it was true. They confronted Spira and he backed down. After this incident, Spira became supportive of CAAT and he and Goldberg actually became good friends and worked together on other issues related to animals. HSUS was approached by Goldberg to join CAAT's advisory board and agreed, naming Andrew Rowan as their representative. In June 1983, Goldberg even sent the National Anti-Vivisection Society (US) a progress report on CAAT for their *Bulletin*, apparently at their request. On the other hand, as Goldberg mentioned in a recent interview with the author, People for the Ethical Treatment of Animals (PETA) never showed any support for CAAT until recent years. PETA complained that in their view CAAT did not place enough emphasis on replacement methods for animal tests and focused too much on refinement techniques, which had only minimal impact on laboratory animal usage.[48]

By 1984, the center had already distributed in excess of $750,000 for research to develop alternatives and its newsletter was being distributed to approximately 9,000 individuals. It continued over the rest of the decade and beyond to increase its funding and activities. By 2003, CAAT had funded a cumulative total of nearly 300 grants for a total of about $5.5 million. This support helped to establish the basic scientific knowledge leading to a variety of in vitro methods of testing and to the development of validation processes for alternative methods. CAAT continued to hold symposia, the results of which were published, leading eventually to the establishment of the World Congress on Alternatives and Animal Use in the Life Sciences (discussed in the epilogue). It also sponsored periodic workshops, most of which were published as technical reports.[49]

FRAME and Toxicity Testing in Britain

As mentioned in the previous chapter, the subject of toxicity testing was also viewed as a promising field for alternatives in Britain in the late 1970s. The Fund for Replacement of Animals in Medical Experiments (FRAME) began a campaign at this time to promote in vitro methods to replace animals in the testing of cosmetics and household products. Its leaflet "What Price Vanity?" criticized the Draize and other tests used in evaluating the toxicity of cosmetics. This campaign was followed by the creation of FRAME's Toxicity Committee in 1979. Dorothy Hegarty asked Alistair Worden, founder of the Huntingdon Research Centre, to organize the committee, which eventually consisted of twenty-four members, almost all of them toxicologists.

The committee held its first meeting on October 16, 1979. It was chaired by Michael Balls, who had recently been appointed a FRAME trustee. Balls had received his DPhil in zoology from Oxford in 1964 and at the time he became involved with FRAME he was a senior lecturer in human morphology at the University of Nottingham Medical School. In 1975, Balls was visited at Nottingham by David Smyth, who was at the time in the process of writing his book on alternatives. Smyth knew about the work Balls was doing on organ culture and asked him if he was aware that he was working on alternatives. Balls replied that he did not know the term in the context of animal experimentation. At the suggestion of Smyth, he applied for financial support from organizations campaigning against animal experimentation and received a grant from the Humane Research Trust. He reported on this research at the 1978 symposium on alternatives sponsored by FRAME, discussed in the previous chapter, and through Andrew Rowan was introduced to FRAME.[50]

The purpose of the FRAME Toxicity Committee was to produce a report, "which, it is hoped, will be regarded as authoritative and will assist the recognition, evaluation and more widespread use of alternatives to conventional animal toxicity testing procedures." Deliberations were expected to take a minimum of two years. The members included representatives from academia, industry, and government. The committee established various working groups to consider specific areas, such as neurotoxicity testing and teratology.[51]

One member on the committee, Anthony Dayan of Wellcome Research Laboratories, where he was responsible for preclinical safety testing for the firm, expressed some disappointment in the group after attending his first meeting. In a letter to a colleague who had inquired about the committee, he stated his belief that "in two years time the Committee is in great danger of producing a well-meaning, inoffensive set of

generalities, which will offend no one and will lead nowhere." He saw no good scientific reason for large expenditures in this area and made clear his doubts about using nonanimal alternatives in toxicity testing to any meaningful extent at that time: "My understanding is that in most areas of 'toxicology' (and hence of most animal experimentation) either our basic knowledge is too limited to permit development of in vitro but safe models simpler than intact animals, or that, in the few instances where abandonment of animals may be possible, there is already more money than good experimentation (e.g., genetic toxicology)."[52]

Dayan did see an opportunity, however, for significantly reducing the number of animals used in toxicity testing, providing that one could combat the illusory view that increasing the number of animals used always increased the validity of the results. He noted that it would also be necessary to obtain the official support of regulatory authorities. Interestingly, Dayan's comments were expressed in a letter to Leon Bernstein, who was writing on behalf of the Animal Welfare Institute (AWI), for which he was serving as a consultant in physiology. Dayan advised Bernstein, however, not to "be put off by my despondent view of FRAME."[53]

At the suggestion of Dayan, Bernstein wrote to Alastair Worden, who was serving as scientific secretary to the committee, for more information about the work of the group. Worden was much more positive about the efforts of the committee. Even he, however, stated that he recognized "that it will be a very long time, if ever, before animals can ever be excluded from medical and allied research." He was much more hopeful that in the field of toxicity testing "alternatives may lead to very considerable refinement and reduction" (thus emphasizing these two Rs over replacement).[54]

Contrary to the concerns privately expressed by Dayan, however, the committee, which met twenty-seven times between October 1979 and November 1982, produced a substantive report that was issued as a separate booklet in 1982. It included scores of general and specific recommendations. Going well beyond the report itself, however, the committee sponsored a meeting at the Royal Society of London in November 1982 to present and discuss the report. In addition to the members of the committee, about forty toxicologists and scientists in related fields participated in the meeting. The proceedings of this meeting were published in a substantial volume of 550 pages in 1983.[55]

The format of the proceedings consisted of a contribution by a member of the committee on a specific topic (e.g., acute toxicity, long-term toxicity, mathematical modeling, design of experiments), the comments of several independent discussants, and a summary of the main points made in the discussion. The committee had decided that the meeting "could best serve to highlight the inadequacies and excesses of conventional toxicity testing procedures and to point a way forward." They believed they had

largely achieved this goal, in spite of clear conflicts of ideas and interpretation among participants on some topics. Nevertheless, there was "a concerted attempt to recommend elimination of the unnecessary and to elevate the scientific status of such work, as must, for the time being at least, continue to be carried out with experimental animal models." Examples of their recommendations included the virtual elimination of the LD50 test, the much greater use of humans in dermal toxicity studies, and modification of ocular irritancy procedures (e.g., the Draize test).[56]

With respect to alternatives, "there was enthusiasm for the continuation and inauguration of research programmes and controlled studies that would serve to promote the development, validation and acceptance of non-animal methods." However, the preface to the published proceedings issued a warning that uncritical, blanket attempts to press for the use of alternatives as wholesale replacements for animals before their value had been objectively demonstrated would be a disservice to progress in the field.[57]

The proceedings volume also included a copy of the report of the FRAME Toxicity Committee.[58] The report began with a declaration that FRAME was not an antivivisectionist society "and considers that the immediate and total banning of all live animal experimentation is an unrealistic and unachievable goal." The report emphasized that FRAME believed that "progress toward the material reduction and possible eventual elimination of the need for animal experimentation" would be achieved only by collaboration between those who desired this progress and the scientists who had the training, experience, and imagination to make it possible.[59]

The report summarized the conclusions of the committee and of its fourteen individual working groups (e.g., mathematical modeling, ocular irritancy, dermal toxicity). It also included numerous general recommendations and recommendations in the specific areas covered by the working groups. I will not attempt to summarize here the scores of recommendations presented in the report but will just note a few examples. Some of the alternative methods suggested included the enhanced use of statistics to increase the efficiency of experiments (thus reducing the number of animals required), the testing of skin irritants of low and medium toxicity in humans, the testing of ocular irritants (where possible) on skin or on isolated eyes taken from animals killed for other purposes (e.g., in abattoirs), and the development of better in vitro methods (which already had shown great promise) for screening of chemicals for toxicity and carcinogenicity. Many of the recommendations identified promising lines of research and encouraged further research in these areas.[60]

After the Toxicity Committee published its report, FRAME announced that the committee would begin a new series of meetings in November 1983. Michael Balls, however, did not see any purpose in continuing the committee with the same membership.

He believed that what was needed was a focused discussion on the way forward to replace animal tests with alternative methods. At about this time, however, FRAME became actively involved in other activities, such as a newly established research program and the campaign for new legislation on animal experimentation (as discussed below), and the new committee was not immediately established.[61]

At the suggestion of several members of the original committee, a new Toxicity Committee was established in 1988 with a goal of producing a second report in 1990. FRAME recognized that a follow-up to the original committee was needed to promote the recommendations in the original report on the development and implementation of alternative methods. Interest in reviving the committee may also have been stimulated in part by the fact that its report had been given a favorable reception in a 1986 report on alternatives issued by the US Office of Technology Assessment (this report is discussed below). The new committee had twenty members and was chaired by James Bridges, with Balls serving as scientific secretary. The group met ten times between June 1989 and October 1990. FRAME followed essentially the same procedure that it had used in connection with the earlier report. A conference was held at the Royal College of Physicians in London in November 1990 to discuss the committee's report. The report and the conference proceedings were then published in a volume in 1991.[62]

One of the general conclusions set forth in the report was that the total replacement of animals in toxicity testing "is a morally desirable and scientifically defensible, long-term goal." The report also recommended that greater recognition should be given to the fact that new laws on the protection of laboratory animals (discussed below) required "that non-animal methods must be actively sought and used whenever possible." In addition, it emphasized that there were continued opportunities for significant reduction of the numbers of animals used in toxicity testing.[63] The report also made numerous specific recommendations concerning the use of alternatives in various areas of toxicity testing.

FRAME also initiated a research program in the 1980s. In 1981, Dorothy Hegarty resigned as chair of the board of trustees and was replaced by Michael Balls. As an active scientist, Balls believed that FRAME "needed to change its approach and become actively involved in research on the development of and application of alternative methods, rather than merely preaching about them and passing on second-hand information." He recommended that FRAME move from London to Nottingham, where he was on the faculty of the University of Nottingham Medical School. Balls further proposed that FRAME should establish a working partnership with the Medical School, which would enable the organization to become actively involved in alternatives research. A relocation to Nottingham would also allow Balls to more effectively lead the organization in new directions.[64]

FRAME did move to Nottingham in 1982, and collaboration with the university began. Three young scientists were hired, one to work full-time at the university to help develop plans for collaborative research, one to work part-time at the university and part-time at FRAME, and one to work at FRAME and serve as editor of *ATLA*. Balls established a research group that initially focused on the study of amphibian organ cultures but gradually changed to human cell cultures. FRAME also developed a collaborative research program with three other institutions. Balls described it as follows: "We also established the FRAME Research Programme, in collaboration with St. George's Hospital Medical School, London, the University of Surrey, and Huntingdon Research Centre. Our aim was to develop a human cell culture test for predicting the acute toxicities of chemicals. And we succeeded in developing the kenacid blue (KB) cytotoxicity test."[65]

In anticipation of supporting research in areas of study that FRAME expected the Toxicity Committee to identify, the organization had begun fundraising for this purpose already in 1981. FRAME began campaigning vigorously for industrial and government funding. By September 1981, they had received a contribution of £10,000 from the cosmetics company Rimmel International. The following year FRAME reported that it had received the bulk of the £250,000 needed to fund the first three years of the research program, largely via donations from cosmetics and pharmaceutical companies.[66] The August/September 1984 issue of *FRAME News* announced that the organization had been awarded a substantial grant (expected to be in the range of £160,000) from the British government "to further their research into the use of alternatives to live animals in research." The three projects to be funded by this grant were (1) research into the use of human tissue cultures to replace animals in medical research and toxicity testing; (2) a study of the feasibility of an international validation scheme for in vitro alternatives; and (3) exploration of the possibility of establishing a database of work on tissue culture techniques to bring together information on the subject and make it readily available to scientists. The article proclaimed: "The grant is of great significance to FRAME, not only because of our confidence in the promise of the three new research initiatives which will now be possible, but also because it indicates that the Government recognises and respects FRAME's policy of seeking a reduction in animal experiments through the development and validation of alternative techniques and strategies."[67]

The laboratory made significant contributions to the field of alternatives to animal testing, including the development of the KB assay (mentioned above) and the application of it to thousands of chemicals. The research team also developed other new alternative methods such as the neutral red release assay and the fluorescein leakage test, both of which were internationally applied as alternatives to eye irritancy tests in

rabbits. The FRAME group also created an international test validation scheme that "laid the foundation for the validation process (i.e., the independent evaluation of the reliability and relevance of a test method for a particular purpose) as it is applied today."[68]

Legislative Efforts in the United States

In the late 1970s and early 1980s, several bills were introduced in the US Congress promoting the allocation of funds for the development and validation of alternatives to animals in research and testing.[69] The most far-reaching of these was the Research Modernization Act (H.R. 4805), introduced in the US House of Representatives on July 16, 1979. The bill proposed the establishment of a National Center for Alternatives Research. Funding for the new center would be provided by diverting a minimum of 30 percent and a maximum of 50 percent of all funds allocated to federal agencies for live animal research to the development of alternative methods of research and testing. The bill also directed that no federal funds were to be used to support research and testing involving the use of live animals in cases where alternative methods had been published in the *Federal Register*. The use of federal funds was also prohibited for the purposes of sponsoring or supporting research and testing if it duplicated work performed by an agency.[70]

Not surprisingly, this far-reaching bill was attacked by the scientific community. The National Society for Medical Research (NSMR) protested the diversion of funds designated for animal research to research on alternatives. The organization claimed that if enacted, "the new law would very rapidly halt significant research currently underway which represents the best hope of the public to accomplish advances in medical knowledge that will increase the quality of life for both animals and mankind." The NSMR claimed that the bill was just a strategy of antivivisectionists to further their goal of ending animal research by cutting off funding for it. The society argued that "alternatives" (a term that they always put in quotes) had limited use and that the center was redundant because it would only do what was already being done under existing laws and regulations.[71]

The bill was referred to two House committees, Interstate and Foreign Commerce and Science and Technology. Representative George Brown Jr. of California, chair of the Science, Research and Technology Subcommittee of the latter committee, sent out letters to many scientists seeking input on the bill. According to the NSMR, the responses that came to their attention confirmed their own analysis of the bill. The general feeling was that alternatives were already being used where applicable and that the purpose of developing alternative methods would be better served by providing more

funds for research through existing laws and regulations rather than creating a new National Center for Alternatives. NSMR concluded that the "idea of someone starting out solely for the purpose of developing a new technique to avoid using animals appears to be a very unlikely approach to the goal."[72]

When Congress asked Secretary of Health, Education and Welfare Patricia Roberts Harris for a position on the bill, she responded that the department opposed it. While acknowledging that promoting animal welfare was commendable, she stated that the scope and nature of the proposed legislation was unnecessary and unworkable. She added: "These prohibitions on the use of funds would severely restrict scientific judgement and ultimately would not promote human health and safety because they could prevent much important research from being conducted."[73] The National Institutes of Health (NIH) also carefully expressed concerns about the proposed legislation when consulted by the General Accounting Office, indicating that they believed that alternatives were being used when available and appropriate and that there were already adequate incentives to use them.[74]

Organizations supporting the bill included the American Anti-Vivisection Society and the National Antivivisection Society, as well as United Action for Animals (which, according to the NSMR, had drafted the bill). The HSUS Institute for the Study of Animals and the American Humane Association also endorsed the bill (although strongly supportive of alternatives, HSUS withdrew its support, according to NSMR, when United Action for Animals refused to consider any changes in the bill). FRAME also weighed in on the proposed American legislation, not only H.R. 4805 but also two other bills that dealt with alternatives. Although supporting the goal of promoting alternatives, FRAME clearly had some reservations about these specific bills, commenting: "While all of these Bills might in fact be counter-productive this surge of interest in alternative techniques is clear indication of growing public feeling on the whole subject of animal experimentation, both at home and abroad."[75]

Representative Brown, whose Subcommittee on Science, Research and Technology was considering the proposed legislation, urged Secretary Harris to ask the National Institutes of Health (NIH) to sponsor a national conference on alternatives to determine the current state of the art of the field. Whether on its own or in response to Brown's urging, NIH indicated at about this same time that it was developing plans for a conference later in 1980 to address the advantages and limitations of alternatives, which they believed was a necessary first step in determining whether further research on alternatives was needed and whether greater use of alternatives was warranted.[76]

The NIH-sponsored conference was held on February 18–20, 1981, in Washington, D.C. The title of the symposium, which was organized in collaboration with other

agencies participating in the National Toxicology Program, was "Trends in Bioassay Methodology: *In Vivo*, *In Vitro* and Mathematical Approaches." The scope of the meeting had thus been limited to bioassay methodologies, rather than research and testing more broadly. In addition, there was no specific use of the term "alternatives" in the title of the symposium. Attendees included participants from academic institutions, industrial firms, animal welfare groups, government research agencies, and government regulatory agencies.[77]

The symposium featured three days of scientific papers on topics such as animal methods for toxicity testing, in vitro ocular toxicity testing, and physiological system modeling. The discussion sections, which were recorded in the proceedings, included (in addition to considerations of technical scientific points) lively but polite exchanges between scientists and animal welfare advocates. Attendees from the animal protection movement included Andrew Rowan, Henry Spira, Ingrid Newkirk, and Christine Stevens. Philosopher and animal rights advocate Tom Regan of North Carolina State University commented at the meeting that animal protectionists were not anti-science or antihuman but were counting on scientists to discover the techniques that would reduce reliance on animals in research and testing. He pointed out that none of the animal advocates present had called the scientists names, referred to their work in a derogatory way, disrupted the proceedings, or demanded that animal laboratories be closed today. This was not their style, he claimed.[78]

Similarly, scientists did not attack the animal advocates present or question their sincere motives and convictions. In spite of the relatively cordial tone of the conference and the reporting of some advances in alternatives, however, animal advocates could not have been entirely satisfied with the proceedings. Many of the scientific presentations and comments by scientists in the discussion sessions expressed skepticism about the current state of alternatives and the prospects for significant near-term progress in the field. In discussing toxicity testing, for example, one presenter stated that no satisfactory substitutes for animals existed today and the prospects for short-term development of such methods was not promising. Another argued that mathematical models were not alternatives to animals. Still another claimed that he saw no chance in the foreseeable future that quantitative studies of structure-activity relationships in chemicals would be able to predict biological properties with enough reliability to make animal testing superfluous (although he did see some hope for reducing the number of animals used). Other scientists used the occasion to express opposition to the Research Modernization Act.[79]

The symposium was designed to be informational, with a goal of describing "the state of the art of bioassay from a variety of perspectives." For those assays requiring

the use of live animals, particular attention was also devoted to the feasibility of using in vitro or mathematical methods to reduce the dependency on animals.[80] It was not intended to be an advisory report and did not include any recommendations for action. In discussing possible conference follow-up, however, William Raub of NIH did recommend the formation of a forum to continue the discussion of testing methods, promised distribution of the proceedings to the various federal agencies involved with the use of experimental animals, and urged consideration within the Department of Health and Human Services of the issue of whether the chimpanzee should be accorded protections in research protocols analogous to those accorded human subjects. He also emphasized that the purpose of the meeting was not necessarily to search for consensus but to sharpen distinctions.[81]

The issue of laboratory animal welfare was brought to widespread public attention in September 1981 when a group of monkeys were removed by police from the Institute for Behavioral Research, a small private research center in Silver Spring, Maryland, whose chief research scientist was Edward Taub. In May of that year, college student Alex Pacheco, an animal rights activist, took a volunteer position at the institute with the aim of investigating the treatment of the monkeys. Over a period of months, Pacheco worked undercover taking photographs and collecting information on the laboratory. Taub's research involved severing nerves in the spinal cord that controlled particular limbs in an effort to challenge the theory that limb function was permanently lost in such cases. He wanted to see if he could force recovery, and he used various means to force a crippled monkey to use its bad limb. His studies focused on the disabling of a single arm and his methods involved restraining the animals with straitjackets, using binding and restraining chairs, and giving them electric shocks if they did not move their numbed arms. In addition to his horror at these techniques, Pacheco also found the animal cages to be filthy (smeared with feces, infested with roaches, etc.), rusty, and very small. The survivors of the experiments showed classic stress symptoms. Eventually Pacheco and Ingrid Newkirk, with whom he had co-founded People for the Ethical Treatment of Animals (PETA) in the previous year, took their findings to the police, leading to the raid on the laboratory. Taub was charged with and convicted of animal cruelty, but his conviction was later overturned by the Maryland Court of Appeals.[82]

In the midst of the controversy over the Silver Spring monkeys, the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology held hearings on "The Use of Animals in Medical Research and Testing" on October 13–14, 1981. The chair of the subcommittee, Representative Doug Walgren of Pennsylvania, stated in his introduction that a "number of pieces of legislation have been referred to this subcommittee to protect animals in research settings, as well as

to develop research alternatives that do not use live animals." With respect to this latter issue, he noted that one of the goals of the hearings was to determine "how [we] can distinguish those areas in which animal-based research or testing remains critical to the protection of human health or the advancement of knowledge and training from those in which alternative methods could just as well be used." He added that some encouraging beginnings had been made in this area, specifically mentioning the recent creation of the Johns Hopkins Center for Alternatives to Animal Testing.[83]

Seven proposals concerning various aspects of the use of animals in biomedical research, some including provisions on alternatives, were before the subcommittee at the time. According to subcommittee staff members, information obtained at the hearings would be used to formulate proposed legislation.[84] I will not attempt to summarize here these detailed hearings, which included testimony from various representatives of the scientific and animal protection communities. I will focus instead on one example from each of these communities to illustrate some of the major differences in viewpoints expressed on the question of alternatives. I have chosen Andrew Rowan of HSUS and William Raub of NIH for this purpose as I believe that these two individuals made especially detailed and coherent arguments in their testimony for their positions. Although they do not comprehensively cover all of the views concerning alternatives put forth in the hearings, they illustrate some of the major differences in perspectives between the scientific community and the animal welfare movement.

Rowan began his oral testimony by emphasizing that alternative was a concept, not something that one picked up off a laboratory bench, but an attitude of mind (presumably contrasting it to a typical "method"). One of the problems faced by alternatives, Rowan argued, was the lack of real commitment to the concept by federal granting agencies. He added that as long as there was "no active encouragement, and I stress that it must be active and not a mere paper trail, researchers will continue to pay lip service to the idea without concentrating their minds on the topic." Money, he continued, was an excellent concentrating force, and he encouraged the government to change priorities and devote more funds to alternatives research.[85]

In the written statement that he provided to the subcommittee, Rowan was able to state his argument in more detail. Although conceding that some benefit had been derived from animal research and that HSUS did not oppose legitimate research on animals, he noted that "we do differ with scientists as to what constitutes 'legitimacy,' and we are very concerned at the lack of attention paid to alternatives." Rowan used the Three Rs to define alternatives and expressed the hope that the subcommittee would report out legislation supporting these goals.[86] He went on to critique testing methods such as the LD50 and Draize tests, and pointed out that alternative methods

could greatly reduce the number of animals used and the costs involved. Rowan estimated that approximately 60–80 million laboratory animals were used every year in the United States, but admitted that estimates varied and some put the figure far lower. He provided various tables of the estimates of animals used and cited statements by toxicologists saying that faster and less costly testing procedures were needed and encouraging the development of alternative methods.[87]

Rowan complained that one problem with alternatives was that most members of the scientific community were unenthusiastic about them. He listed three reasons for this lack of enthusiasm.

> First, scientists only hear about alternatives from the animal welfare movement and they have a built-in resistance to any ideas emanating from this source. (Scientists perceive animal welfare groups as accusing them of being cruel and unfeeling.) Second, most scientists misunderstand the concept and its potential in advancing biomedical knowledge. When I can sit down and discuss the issue one-on-one, they will usually agree that more can be done and can even suggest possible avenues for research, but, initially, they see the idea only as a wild claim that computers could replace animals. Third, federal funding sources do not encourage scientists to think in this way, for all their verbal statements to the contrary.[88]

Rowan concluded his statement by recommending four initiatives that he believed would make the concept of alternatives a more pressing matter for interested researchers. His suggestions were that (1) NIH should establish a coordinating committee to review the use of animals and progress made in alternatives; (2) NIH should make funds available specifically for the development of alternatives; (3) an information clearinghouse dealing with all types of research techniques, including alternatives, should be established and should issue critical reviews of methodology; and (4) the National Toxicology Program should establish a new list of priorities that would place the development and validation of new methods at the top.[89]

William Raub began his statement by claiming that it was "almost impossible to exaggerate the importance of laboratory animals in the search for new or improved means to treat, prevent and cure human disease," and that virtually "every major advance in health care stems in whole or in part from research performed with animals." He continued in this vein by emphasizing the important role of animals in the testing of new health care measures before they are tried on humans. Raub argued that there was no way that NIH could fulfill its statutory mission "if the use of laboratory animals were made subject to severe constraints." He conceded, however, that the "social

imperative" for animal experimentation was not a license to take the lives of animals or inflict pain on them needlessly, which would be as inconsistent with good science as it was with good conscience.[90]

Raub stated that progress was being made with new techniques that "may one day" replace animal testing methods. He then went on to caution: "But the promise unfortunately is not uniform across the spectrum of biological science. There is little reason to expect that the use of tumor-bearing animals in cancer drug development could be discontinued responsibly in the foreseeable future to cite but one illustration. . . . Scientists and laypersons who seek nonanimal test methods have to strive continuously to keep their hopes and expectations in tune with biological reality. The extraordinary complexity of living systems and our woefully incomplete understanding of them cannot help but attenuate our ambitions."[91]

For Raub, the prospect of replacing animals in the general area of biological research, as opposed to testing, was even more remote. When dealing with research exploring the integrated functions of intact organisms or the interaction of organ systems, he concluded that "animal experimentation is inevitable." He saw nonanimal methods as adjuncts to animal research, not as replacements. Even if these techniques might someday reduce the need for animal studies, he added, any payoff from them was likely to be long term rather than immediate, although this was not a reason not to make a modest investment in this area.[92]

Rowan thus saw great promise in alternatives and believed that progress in the field was being hindered by lack of enthusiasm on the part of scientists because of their suspicion and misunderstanding of animal welfare advocates. He questioned the legitimacy of some animal research and testing and he decried the lack of funding into research on alternative methods. Raub, on the other hand, argued vigorously that animal research was responsible for much of the advances in medicine and that there was a "social imperative" to conduct such studies. Because of the complexity of living organisms, he believed that animal research was inevitable in many areas of biological science. He thought it unlikely that nonanimal methods, which he tended to view as "adjuncts" to animal experimentation, would be able to replace animal studies in most areas of biological research in the foreseeable future and saw the need for only modest investment in this area.

Various bills and amendments that would have strengthened the animal protection provisions of the Animal Welfare Act continued to be introduced in the House and the Senate, but none of them were enacted into law. As Robert Garner has noted: "The research community opposed all of them and this played a significant part in the decision of a succession of committees to pigeon-hole them." *The Pharmacologist*, the

newsletter of the American Society for Pharmacology and Experimental Therapeutics, for example, charged in 1982 that one "ploy" used by animal welfare groups was "the suggestion of 'alternatives' to the use of animals such as 'molecular toxicology' testing and several non-animal model systems." The article added: "Animal models and *in vivo* studies are a condition *sine qua non* for pharmacology, particularly applied and clinical pharmacology for the development of new and better therapeutic agents." Physiologist Ernst Knobil, representing the American Physiological Society (APS) and other scientific institutions, testified before Congress in 1981 that the Research Modernization Act would "have dire consequences on the health and safety of our people without significant impact on animal welfare." Walter Randall, like Knobil a past president of the APS and representing the society, testified before the Senate in 1983 that the "need for animal models will never be eliminated for the purpose of research and testing" and that "restrictive legislation is not needed." Even Alan Goldberg, director of CAAT, was opposed to the idea of designating federal funding specifically for the development of alternatives.[93]

Meanwhile, another scandal rocked the scientific world and aroused public indignation in 1985 when the Animal Liberation Front (ALF) raided Thomas Gennarelli's head-injury laboratory at the University of Pennsylvania and obtained evidence of mistreatment of baboons. ALF "produced shocking video evidence of researchers mocking injured animals, using unsterilized equipment and even smoking while carrying out procedures." Under pressure from animal rights advocates and a petition from members of Congress, Secretary of Health and Human Services Margaret Heckler ordered the suspension of research funding for the facility, which was also eventually ordered to pay a $4,000 fine.[94]

Provisions to protect laboratory animals were included in the NIH reauthorization bills passed by Congress in 1984 and 1985, but President Reagan vetoed them on both occasions, arguing that they exerted undue political control over decisions regarding scientific research. Animal protectionists finally achieved their goal of amending the Animal Welfare Act in 1985 through the mechanism of an amendment to the farm bill introduced by Senator Robert Dole of Kansas and Representative George Brown of California, who had chaired the 1981 hearings previously discussed. Dole had long been a supporter of animal welfare and had introduced the Improved Standards for Laboratory Animals Act in the Senate in 1983. A similar bill had been introduced in the House by Brown, but neither version had gone anywhere. In 1985, Dole attached the laboratory animal bill to the Senate version of the omnibus farm bill. As Senate majority leader, Dole had controlling influence over the bill. The Dole-Brown amendment survived in the farm bill that was passed by Congress and signed into law by the president.[95]

The strong support of both HSUS and AWI, which had not always agreed on proposed legislation, helped to ensure the passage of the Dole-Brown amendment. The efforts of Bernard Rollin of the Philosophy Department of Colorado State University were also instrumental in the struggle to amend the 1966 act. The legislation amended the AWA in several ways, including mandating institutional animal care and use committees to evaluate research proposals involving the use of animals and to address animal welfare problems within those institutions. It also directed investigators to use the information service provided by the National Agricultural Library (NAL) to ensure that they avoided duplicative research. In addition, the law authorized the assessment of fines for "unchecked violations" and the suspension of funds to facilities that failed to correct identified deficiencies.[96]

With specific reference to alternatives, the legislation required that the principal investigator consider alternatives to any procedure likely to cause pain or distress in an experimental animal and consult a veterinarian in the planning of such procedures. The law also contained some provisions on the use of anesthetics. In addition, it mandated that the NAL information service mentioned above provide information on methods that could reduce or replace animal use or minimize pain and distress to animals. Proposals to create a National Center for Alternatives Research or to divert a portion of federal funds allocated for animal research to research on alternatives, however, did not make it into the final legislation.[97]

The Health Research Extension Act of 1985, which revised and extended the authorities relating to NIH and the National Research Institute, also contained provisions relating to animal care and welfare, including requirements that applicants for NIH grants include assurances that they would provide training to personnel in humane practices of animal care and maintenance and on the availability and use of methods that limit the use of animals or limit animal distress. Applicants were also required to include a statement of the reasons for the use of animals in any research supported by grant funds. The secretary of Health and Human Services was also directed, acting through the director of NIH, to develop guidelines for the proper care and treatment of animals used in research, as well on the organization and operation of animal care committees.[98]

During the course of deliberations on the above legislation, the Office of Technology Assessment (OTA), which had been created by Congress in 1972, was working on a report on alternatives to animal use in research, testing, and education. In March 1983, Senator Orrin Hatch of Utah had asked OTA to undertake a study of the subject. OTA appointed staff and a nineteen-member advisory panel, which included representatives from academia, industry, government, and the animal welfare community, to prepare the report. The advisory panel was chaired by medical ethicist Arthur Caplan of the

Hastings Center. The members included Alan Goldberg, director of the then recently established Johns Hopkins Center for Alternatives to Animal Testing, Andrew Rowan, Henry Spira, and John McArdle of HSUS. Early in the study, OTA contacted 600 institutions and individuals for their input.[99]

The OTA report was published early in 1986, too late for it to be taken into account in the debate over the 1985 legislation. It is an extensive document of 441 pages and I will only briefly summarize its contents here. The report discussed the use of animals in research, testing, and education and alternative methods in each of these areas. It covered ethical and economic, as well as scientific, considerations in addition to federal, state, and institutional regulation of animal use. The report also discussed public and private funding for the development of alternatives. OTA's discussion of policy considerations and options for congressional action, a key component of the document, was included in the report summary.[100]

OTA recognized that the term "alternatives" had "come to mean more than merely a one-to-one substitution of nonanimal methods for each animal technique." They opted to define alternatives using the Three Rs concept, as follows: "For alternatives, OTA has chosen a definition characterized by the three Rs: replacement, reduction, and refinement."[101]

The report raised seven issues for consideration, posing them as questions. The questions covered such matters as whether steps should be taken to stimulate the development of alternatives, whether improvements should be made in information resources to reduce duplicate research involving animals, and whether the AWA should be further amended or its enforcement enhanced. For each issue, the OTA presented several options for possible congressional action, one of which in every case was to take no action. Examples of possible actions included using federal funding for the development of alternatives, creating new databases designed to reduce duplication of animal use, restricting the use of certain kinds of animals or particular protocols, licensing animal users, and increasing funding for enforcement of the AWA. Even some extreme measures were included in the options presented for various issues, such as prohibiting the use of animals in research, testing, and education and eliminating funding for the enforcement of the AWA. The pros and cons of the various options were discussed, but OTA made no effort to recommend one option over another.[102]

After the release of the report, Michael Balls of FRAME, who was one of the persons asked by OTA to review selected chapters in draft form, published a critical appraisal of the report. His assessment of the document was generally favorable, and he noted that he "was particularly pleased to see that OTA decided to adopt the 'Three Rs' definition of alternatives favoured by FRAME."[103] He did, however, voice several criticisms, perhaps the most important of which was his disappointment at the failure of

the report to make specific recommendations rather than just outlining options. With respect to these options, Balls commented that "the authors seem to have been determined not to commit themselves to any of them."[104] In spite of its shortcomings, he saw the report as a major development in advancing the field of alternatives. He characterized it as follows:

> The OTA Report is a document of major political, scientific and animal welfare significance. It is one of a series of developments, such as new national and EEC [European Economic Community] legislation in Europe, which have brought consideration of alternatives to animal experimentation from the well-meaning fringe to the centre stage of thought and action. Though uneven in its coverage and seriously deficient in some areas, the Report is, on the whole, an admirable attempt at a careful and comprehensive coverage of a vast number of topics, ideas and sources of information, and it will provide an excellent starting point for further debate and research planning, not only in the USA, but also in other countries.[105]

Amending the 1876 Act in Britain

As mentioned in the previous chapter, concerted efforts to amend the 1876 Cruelty to Animals Act in Britain intensified in the late 1970s. Parliament at this time was considering two bills, one introduced by Lord Halsbury, which sought to maintain the status quo so far as possible, and one introduced by Peter Fry, which was much more radical in the restrictions that it would have placed on animal experimentation, for example, by prohibiting animal testing for non-health-related products such as cosmetics. No animal welfare group supported the Halsbury bill, which they viewed as too weak. The scientific community vigorously opposed the Fry bill, which also failed to receive the support of the government. Neither measure consequently gained the necessary support in Parliament to be enacted into law.[106]

As Parliament continued to grapple with the issue of amending the 1876 act, moderate elements of the animal protection community began to play a greater role in the development of the legislation that eventually came to pass. The previously mentioned (see chapter 4) Committee for the Reform of Animal Experimentation (CRAE), a group of animal advocates, began collaborating with FRAME and the British Veterinary Association (BVA) in 1981 to promote amendment of the 1876 act. In April 1983, this group, which had come to be known as the Triple Alliance, submitted proposals for new legislation to the Home Office. A Home Office White Paper issued in May 1985 acknowledged that the recommendations of the Triple Alliance had played an important role

in the development of the government proposal for new legislation on animal experimentation developed at the time. Michael Balls of FRAME, who was actively engaged in the process, later recalled that "the Triple Alliance representatives were involved at every stage of the preparation of the new legislation."[107]

The government, as would be expected, had also consulted with the Research Defence Society (RDS) and other representatives of the scientific community in drafting the proposals. As Robert Garner has noted, however, "the RDS had found itself increasingly marginalized, arguably paying the price of failing to reach consensus on a bill which would be accepted by the widest number of participants."[108]

The Animals (Scientific Procedures) Act 1986 was passed by Parliament in May 1986 and took effect on January 1, 1987. Garner has summarized the key differences between the 1986 and 1876 acts as follows:

> . . . in brief, the [1986] Act introduced a dual licensing system whereby researchers would have to apply for a personal licence (reviewed every five years) and a project licence permitting particular procedures [only the former was required in the 1876 act]. In addition, the legislation created a statutory Animal Procedures Committee (APC), previously recommended by Littlewood in the 1960s, with provision for the representation of animal advocates. Finally, as had also been suggested by Littlewood, animal breeders and suppliers were, by 1 January 1990, to register and be subject to inspection under the legislation.[109]

With respect to the subject of this book, alternatives to animal research and testing, the act was disappointing in that it included only a weak token provision on the topic. The relevant section stated that the secretary of state should not issue a license for a project "unless he is satisfied that the applicant has given adequate consideration to the feasibility of achieving the purpose of the programme to be specified in the licence by means not involving the use of protected animals." The legislation did not specify how the secretary of state was to determine that the applicant had given "adequate consideration" to the use of alternatives.[110]

Conclusion

By the end of the 1980s the concepts of alternatives and the Three Rs had become firmly established in the scientific and animal protection communities. This is not to say that there was no longer any skepticism about or resistance to alternatives among researchers and their allies. For example, a National Academy of Sciences publication in 1991

claimed that the present ability to replace animal experiments with alternatives was very limited and that "most researchers generally hold that nonanimal experiments are adjuncts rather than alternatives to animal experiments." In addition, some elements of the animal protection movement were opposed to collaborating with scientists and compromising their goal of an immediate end to animal research or doubted that scientists were seriously interested in finding alternatives. Ingrid Newkirk of People for the Ethical Treatment of Animals (PETA) argued in 1990 "that scientists refuse to investigate alternatives to animals in biomedical research largely out of habit." A move to alternatives, she added, would mean that a lot of people would have to be retrained because they only knew how to work with animals.[111] Nevertheless, alternatives had become widely recognized as a field of scientific research, enshrined in institutions and publications devoted to the topic.

Three journals devoted specifically to alternatives were launched in the 1980s, providing further support for the view that the subject was being recognized as a distinct area of research. The first of these, *ATLA (Alternatives to Laboratory Animals)*, developed out of *ATLA Abstracts*, which had been begun by FRAME in 1973. This publication, as the name indicates, was limited to publishing abstracts of articles in the biomedical literature devoted to alternatives. The journal changed its name officially to *ATLA* in 1980 and appointed an international editorial board in 1982 with the aim of publishing peer-reviewed articles, a goal that was accomplished beginning in 1983. In 1984, the journal *Alternativen zu Tierexperimenten*, which later evolved into *ALTEX: Alternatives to Animal Experimentation* (now the official organ of several organizations including CAAT) was launched. Three years later, *Toxicology in Vitro* was founded as the official journal of the European Society of Toxicology in Vitro and affiliated with the American Association for Cellular and Computational Toxicology.[112]

The first World Congress on Alternatives and Animal Use in the Life Sciences, held in Baltimore in November 1993, planning for which had begun in 1990, provides further evidence that alternatives had become recognized as a legitimate branch of scientific research by the early 1990s. The congress attracted 734 scientists, policy makers, and animal advocates from fifty countries. The headline to the story in the *Johns Hopkins University Gazette* proclaimed: "Hunt for Research Alternatives Called New Branch of Science." Lynette Hart, director of the University of California Center for Animal Alternatives, commented that the congress "carried the field of alternatives into the mainstream." She added: "Clearly this is going to be a major new area of science." Even allowing for some hyperbole, there is no question that this international congress, the first of a series that continues to this day, was a landmark event in the field of alternatives.[113]

Two years later, in 1995, Michael Balls noted that numerous organizations, scientists, and members of the general public were committed to the middle ground in the debate over medical research that alternatives represented, and that the Three Rs approach was by then required by various national and international laws. He went on, however, to add a note of caution: "Nevertheless, as far as the Three Rs are concerned, we are at the end of the beginning—the concept may now be widely accepted, but a great deal more has to be achieved before we can say that the minimum number of animals are being used in procedures which involve the least possible suffering, in meeting the essential needs of man and other animals."[114]

Epilogue

Alternative methods and the three Rs have continued to advance in the decades following the end of the 1980s, but that story is beyond the scope of the present book. I will, however, briefly summarize here some of the major developments that took place near the end of the twentieth century and in the early decades of the twenty-first century, not only in Britain and the United States (the subject of my book), but also in other countries.

The 1990s began with Russell and Burch, who had not been involved with alternatives since the publication of *The Principles of Humane Experimental Technique*, reentering the scene. As Martin Stephens noted, neither of the two men had attended any conferences dealing with alternatives and the Three Rs, and likely were not even aware of such meetings. This situation was to change in 1990 when the Humane Society of the United States (HSUS) decided to establish an award to honor the two individuals who had first advanced the Three Rs. Stephens, who was handling the matter of the award for HSUS, later recalled: "We wanted to name it after Russell and Burch, but first we needed permission to use their names. At the time, my contacts did not know if they were still alive. Eventually, I contacted UFAW [Universities Federation for Animal Welfare], who contacted them on my behalf."[1]

Stephens wrote to Russell, with a copy to Burch, to formally request permission to use his name and that of Burch for the award. After speaking to Burch by phone, Russell responded that they would agree to have the award named after them if the HSUS would work out with UFAW a form of the award that the latter organization would approve. He also requested a change in the description of the award, the draft of which

stated that it was to be given for "an outstanding contribution toward developing or validating methods that can reduce or replace the use of animals in research and testing procedures." Russell asked that the wording be modified to add "refine" to reduce and replace in the criteria for the award, thus covering all Three Rs. These issues were resolved, and the award went forward. On October 11, 1991, the first annual Russell and Burch Award was presented to Alan Goldberg, director of the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), during the HSUS symposium on "Alternatives in Research: Challenging the Status Quo." Unfortunately, health issues prevented both Russell and Burch from attending.[2]

In his correspondence with Stephens concerning the Russell and Burch Award, Roger Ewbank, director of UFAW, revealed in 1990 that UFAW had been considering for some time reprinting *The Principles of Humane Experimental Technique*. A special edition paperback reprint of the book, dedicated to the late Major Hume, was published in 1992. The foreword noted that the book could serve as a memorial to Hume and a "long overdue tribute" to Russell and Burch, as well as a "timely recognition" of the Russell and Burch Award recently established by HSUS.[3]

The award and the reprinting of *Principles* drew new attention to Russell and Burch and caused the alternatives community to invite their participation in various events. Russell, for example, attended the first World Congress on Alternatives and Animal Use in the Life Sciences in Baltimore in 1993 and spoke at the awards luncheon. He also attended the next two World Congresses in 1996 and 1999. Michael Balls recalled that at these meetings Russell "gave characteristic and memorable performances, which included singing and dancing." Russell was also present at the opening of the Fund for the Replacement of Animals in Medical Experiments' (FRAME) new office building, named Russell and Burch House, in Nottingham in 1995. Burch was unable to travel to meetings due to his failing health, but Michael Balls arranged in 1995 for a workshop sponsored by the European Center for the Validation of Alternative Methods (ECVAM), discussed below, to be held in Sheringham, England, where Burch lived. Russell also attended the workshop, and this was the only scientific meeting at which both he and Burch were present together since the publication of their 1959 book. Burch died the following year, and Russell died in 2006.[4]

One sign of the increasing interest in alternatives was the establishment of centers devoted to alternatives, akin to the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), in various countries, such as Germany (1989), Switzerland (1990), the Netherlands (1994), Britain (2004), Finland (2008), Brazil (2013), and Canada (2017). CAAT also collaborated with the University of Konstanz in Germany to establish CAAT-Europe in 2010. Organizations devoted to alternatives or in vitro toxicology

were also created in a number of countries, for example, Japan (1988), Britain (1988), and Italy (1991).[5]

In the United States, a Center for Animal Alternatives was established in 1990 at the University of California, Davis, although it had a system-wide mission for all ten University of California campuses. The center, headed by Lynette Hart, was focused on animal use in education, as opposed to research and testing. Unfortunately, the center was closed in 2006 when its funding ended. The only other alternatives center that I am aware of at an American university is the Center for Animal Alternatives in Testing at Brown University, founded in 2017, with a mission (according to its current website) to develop replacements for the use of animals in research and testing.[6]

Both industry and government became more interested in the use of nonanimal methods, especially for the testing of drugs and other chemical and biological products, leading to the development of more alternative methods. Even when nonanimal testing techniques were developed, however, they required changes in government regulations before they could be implemented. Political and societal pressure led governments to begin to enact such changes. For example, in September 2021, "members of the European Parliament overwhelmingly voted in favor of a European Union–wide plan for phasing out the use of animals in research and testing." The plan demanded "that the European Commission set 'ambitious and achievable' objectives and timelines for transitioning to a research system that does not use animals."[7]

In the United States, the National Institutes of Health (NIH) Revitalization Act of 1993 directed the National Institute of Environmental Health Sciences (NIEHS) to establish an interagency committee to develop recommendations for the validation and acceptance of new and revised testing methods that could replace, reduce, or refine the use of animals in research and testing. In response to this legislation, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was created in 1994, at first as an ad hoc and eventually as a permanent committee. The 1993 NIH legislation also directed the NIEHS to establish a center "to develop and validate assays and protocols, including alternative methods that can reduce the use of animals in acute or chronic safety testing." In 1998, the National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) was established within the NIEHS.[8]

In 2019, the US Environmental Protection Agency (EPA) approved a plan to reduce and eventually eliminate the use of mammals to test the toxicity of chemicals. EPA administrator Andrew Wheeler said that scientific advances in fields such as computer modeling and in vitro studies would permit the agency to better predict potential haz-

ards of products to humans while reducing or eliminating animal testing. The agency announced that it would stop conducting or funding studies on mammals by 2035. The Food and Drug Administration (FDA) Modernization Act of 2022 ended the FDA's mandate that required experimental drugs be tested on animals before human clinical trials, and the agency committed to expand its use of alternatives in its regulatory activities. Animals are still used to a significant extent in testing of products, although as Andrew Rowan stated in the title of a recent article: "Slowly but Steadily, Animals Are Being Replaced in Safety Testing."[9]

Although farm animal welfare is beyond the scope of this book, it is worth briefly noting that some animal protectionists have even made efforts to apply the Three Rs concept to this subject. Factory farming is seen by many animal welfare advocates as a leading cause of animal suffering. One example of an organization that has promoted the Three Rs in the animal welfare area is Four Paws. In order to promote an animal-friendly diet, the group recommended its own version of the Three Rs as follows: "Reducing the consumption of meat and other animal based products, Refining one's diet by choosing products from certified high animal welfare standards and, ultimately, Replacing animal-based products with plant-based alternatives."[10]

Over the past three decades, international cooperation on alternatives has also significantly increased. For example, the European Center for the Validation of Alternative Methods (ECVAM) was created as a unit of the Environmental Institute of the European Commission's Joint Research Centre in 1991. The purpose of ECVAM was to coordinate the validation of alternatives at the European Union level, to stimulate the exchange of information on alternatives, and to set up and manage a database on alternative procedures. Michael Balls left FRAME in 1993 to become the first head of ECVAM. Another example of international action was the establishment of the International Cooperation on Alternative Test Methods (ICATM) in 2009 to foster development among national validation organizations. The initial organizations involved in ICATM were ECVAM, ICCVAM (and NICEATM), the Japanese Center for the Validation of Alternative Methods, and the Environmental Health Science and Research Bureau of Canada.[11]

Other efforts at international cooperation emerged in this period. In 1999, for example, Belgium, the Netherlands, and Germany created the European Consensus Platform (ECOPA), a not-for-profit organization dedicated to promoting the Three Rs and the development of alternatives. Eventually other European nations joined, expanding ECOPA's membership to fourteen by 2005. The North American 3Rs Collaborative, a nonprofit organization that developed partnerships with academics, industry,

government, and other stakeholders, was established in 2017 to facilitate collaborative opportunities to refine, reduce, and replace animals in research. The organization's name was changed in 2023 to simply the 3Rs Collaborative to reflect its increasingly global scope.[12]

In this same period, cooperation on an international basis was also fostered through the World Congress on Alternatives and Animal Use in the Life Sciences, held for the first time in Baltimore in 1993 and then in various locations every two to three years thereafter. As the editors of the published proceedings of this first World Congress noted: "This Congress provided concrete evidence that alternatives research is now mainstream, closely monitored (and in most cases encouraged) by governments and industry worldwide."[13] The 1999 World Congress in Bologna, Italy, was especially significant because of the adoption of the Three Rs Declaration of Bologna. The declaration stated that the participants endorsed and reaffirmed the principles of the Three Rs put forth by Russell and Burch in 1959. The document declared that the only acceptable animal experiment was one that had been approved by an ethical review committee, used the smallest number of animals possible, and caused the least possible suffering consistent with the achievement of its scientific purpose. The Three Rs, it added, should be seen as a unifying concept and as a challenge and opportunity for reaping scientific, economic, and humanitarian benefits.[14]

Alternatives have thus become firmly established as a recognized field of research. The discipline, born to a large extent out of animal welfare concerns, now has its own momentum. Animal welfare groups will continue to push the agenda forward, but even without this public pressure the field would continue to develop and move forward. As we have seen, there are new organizations, academic and government institutions, and journals devoted to the subject. Nonanimal procedures and humane techniques have become embedded in government regulation and industry practices.

In fact, the alternatives paradigm has opened up and fortified an entire expanding area of scientific research, as exemplified by the organ-on-a-chip technology, which even has its own journal. The basic premise of this technology is to artificially create the cellular microenvironment and effectively mimic human physiology and disease processes. These tissue chips "contain engineered or natural miniature tissues derived from various organs that are grown inside miniaturized fluid channels molded into glass, silicon, or polymer." Organ-on-a-chip allows researchers to replicate certain functions of tissues and organs. One example of its use is as an in vitro alternative to assess the safety and efficacy of drugs.[15]

Let me close by returning to the Three Rs paradigm and its future. At least since the 1980s, the concept of alternatives has been almost synonymous with the Three Rs.

Although definitions of the Three Rs varied somewhat over time and place, the basic themes of reduction, refinement, and replacement have dominated thinking about alternatives to animals in research, education, and testing. Even those who had never read *Principles*, which almost certainly included the vast majority of animal researchers and animal activists, were influenced by the concept of the Three Rs first enunciated by Russell and Burch.

In recent years, however, several supporters of alternatives have begun to ask whether we need to reassess, or perhaps even abandon, the Three Rs. It is not my purpose here to present a detailed analysis of this complex and controversial subject, but just to point out that questions have been raised about the role of the Three Rs going forward.

In 2018, for example, Jan Lauwereyns published *Rethinking the Three Rs in Animal Research*, a book in which he called for a reassessment of these principles with the aim of improving the ways in which animal research is conducted. He spoke of "concept fatigue" with respect to the Three Rs, suggesting that examination of the original definition and aims show that they were a product of their times and no longer in line with the needs of today.[16]

In a 2019 article and a 2020 book on *Principles of Animal Research Ethics*, David DeGrazia and Tom Beauchamp affirmed that the Three Rs represent a landmark advance in the promotion of animal welfare, but argued for the need "to add complementary content for animal research ethics that the 3 Rs framework fails to provide." They claimed that Russell and Burch's principles "neglect several important aspects of animal welfare as well some important considerations pertaining to the human social benefits that justify animal research." For example, they pointed out that the Three Rs did not take the costs and benefits of animal research into account. Their new framework of principles for animal research ethics included six principles, three relating to social benefit and three to animal welfare. An example of one of these principles is that one can only use animals if they are the most ethically acceptable way to address the question. In an interview with David Grimm of *Science* in 2020, DeGrazia and Beauchamp explained that this principle went beyond the replacement part of the Three Rs "in that scientists must not just *consider* alternatives to using animals, they must *prove* that there are no viable alternatives."[17]

Melanie Challenger called in 2020 for a reassessment of the Three Rs, noting that the paradigm was under scrutiny. She pointed out that a crucial weakness is uncertainty about how these principles should be prioritized and saw the potential for establishing a new set of protocols for animal research. She argued that the COVID-19 pandemic had revealed the need for an urgent review of the efficacy of the Three Rs in protecting animals, arguing that essential threats to human life can raise perceptions

of social benefits and lower concerns about animal welfare, in addition to promoting a rush to develop new research models that could undermine progress in reducing or replacing animal models.[18]

Even Michael Balls, a longtime admirer of Russell and Burch and strong advocate for the Three Rs, proposed in 2020 that it was time to reconsider *The Principles of Humane Experimental Technique*. In fact, he stated that he believed that "we should now abandon the Three Rs concept in the form that it was originally put forward 60 years ago, as the issue is not just about animal welfare and inhumanity to animals." Balls argued that what he considered to be "unscientific, unnecessary, mindless animal experimentation involved human as well as animal suffering." He pointed out the limits of animal experimentation, which often led to adverse effects of therapies in humans that animal studies could not predict, and possible loss of valuable therapies because of toxic effects in animals that might not have occurred in humans. He called for replacing replacement, claiming that the principal focus should not be on replacing animal tests with methods that give precisely the same kind of information or the same outcome. It is a mistake, for example, to use established animal tests as the gold standard to be matched. He added that "it is a question of taking advantage of developments in cell and molecular biology and in computer science, to devise new, different, appropriate, specific and intelligent preclinical testing strategies which are applicable to particular situations." This testing "should precede ethically approvable and sufficiently safe human volunteer studies."[19]

Some individuals have suggested that the Three Rs need to be supplemented by other mechanisms, sometimes also using alphabetical designations. In 2016, Adrian Smith and Penny Hawkins published a paper in which they put forward the principle of the Three Ss: good science, good sense, and good sensibilities as a complement to the Three Rs. They traced the concept back to a symposium paper delivered by Carol Newton, then chair of the Department of Biomathematics at the University of California, Los Angeles in 1975. Newton never published the concept, however, and Smith and Hawkins published their paper "to increase awareness of the Three Ss, which are a useful supplement to the Three Rs, improving animal welfare and leading to better science." Three years later, Daniel Strech and Ulrich Dirnagi published a paper offering their own idea to complement the Three Rs, namely an additional Three Rs: robustness, registration, and reporting.[20]

Neither of these above proposals has gained acceptance, but another terminology has been gaining increasing acceptance in recent years. The term NAMs, or new approach methodologies, is often used in place of alternatives and the Three Rs, at least in the area of safety testing and risk assessment. In 2018, ICCVAM defined NAMs as

follows: "More recently, the term 'new approach methodologies' (NAMs) has been adopted as a broadly descriptive reference to any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment. These new approaches include integrated approaches to testing and assessment (IATAs), defined approaches for data interpretation, and performance-based evaluation of test methods."[21]

Some see NAMs as a broader concept that includes nonanimal methods that are not directly aimed at replacing existing laboratory animal use.[22] As Andrew Rowan has noted, NAMS has been used to stand for new approach methods, novel alternative methods, or nonanimal methods (in addition to the above-mentioned new approach methodologies).[23] Whatever terminology is employed, however, it seems likely that the use of alternative (nonanimal) methods will continue to increase in research and testing. And whether or not the specific Three Rs terminology plays a significant part in the future of alternatives, the general principle of humanity in animal experimentation that Russell and Burch so elegantly expressed in their classic book in 1959 can still serve as a valuable guide to humane laboratory animal research and as a means of substantially reducing animal suffering.

Notes

Chapter 1

1. Andreas-Holger Maehle and Ulrich Tröhler, "Animal Experimentation from Antiquity to the End of the Eighteenth Century: Attitudes and Arguments," in *Vivisection in Historical Perspective*, ed. Nicolaas A. Rupke (London and New York: Routledge, 1990), 14–47 (quotation on 15). On the history of animal experimentation, see Richard J. Miller, *The Rise and Fall of Animal Experimentation: Empathy, Science, and the Future of Research* (New York: Oxford University Press, 2023) and Anita Guerrini, *Experimenting with Humans and Animals: From Aristotle to CRISPR* (Baltimore: Johns Hopkins University Press, 2022).
2. Nicolaas A. Rupke, "Introduction," in Rupke, *Vivisection*, 1–13 (quotation on 1–2).
3. Richard D. French, *Antivivisection and Medical Science in Victorian Society* (Princeton, NJ: Princeton University Press, 1975), 18–23.
4. Diana Manuel, "Marshall Hall (1790–1857): Vivisection and the Development of Experimental Physiology," in Rupke, *Vivisection*, 78–104 (quotations on 97).
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Chapter 4

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17. Balls, "Eye on the Prize," 772.
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Chapter 5

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Original CAAT Proposal and Agreement folder, see especially 2, 7; "Proposal for Professional Services," 6, 9.

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