Book Reviews

SACRED COWS AND GOLDEN GEESE

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This book claims that "Animal experimentation . . . is a gross betrayal of science . . . [and] that reliance on laboratory animals is not necessary. It is expensive. It is inaccurate. And further it is detrimental to the very species it professes to help—humankind."

Unfortunately, the book ". . . is a feat of omission and distortion", to use the words that it uses to describe somebody else's work. It cannot be described as a serious attempt to show the limitations of animal research, because any facts that conflict with the beliefs of the authors have simply been ignored, or history has conveniently been rewritten. As a way of reducing the use of animals in medical research, I think this book will be counter-productive, because even if the authors do have a few good points to make, its numerous inaccuracies and distortions make it impossible to trust anything that they have written.

There have been enormous advances in medicine in the last 75 years. Most bacterial infections can now be cured by one of the many antibiotics discovered following the development of penicillin in the 1940s; a wide range of diseases caused by viruses, such as polio, mumps and measles, can be prevented by vaccination; and many other diseases such as type I diabetes, and some types of heart disease and mental disease can be controlled, if not cured, by medicines or biological preparations. Surgical methods have also advanced with new and better anaesthetics, organ transplants and keyhole surgery. As a result, human life expectancy has increased, with many people now enjoying a life relatively free of serious disease. However, there are still many diseases that we are not yet able to cure or treat effectively, such as most cancers, a range of genetic diseases, diseases of old age (for example, senile dementia), and several viral diseases, including AIDS.

While many improvements in human health can be attributed to better hygiene, diet and working conditions, medical research has also made a substantial contribution. Unfortunately, medical research uses large numbers of animals. Worldwide, the total amounts to tens of millions of animals per year. Although these numbers are large, they are only a small fraction (less than 2%) of the number of animals that are killed for food. However, if it could be shown that the use of animals in research was scientifically unjustified, their use could be banned without detriment to medical research. Unfortunately, this book totally fails to make such a case.

Three specific examples serve to show how the book has rewritten history:

The development of a rabies vaccine by Louis Pasteur, by using dogs and rabbits

In 1880, the microbiologist Louis Pasteur began to study rabies, a terrible disease which is usually passed from animals to humans when they are bitten by a rabid dog, though many other species can become infected and pass on the disease. Once the symptoms appear, the disease is invariably fatal. Pasteur's strategy was to find a reliable way of causing rabies in dogs, and then try to cure them by vaccination. There are many biographies of Pasteur which describe exactly how he did this by using intra-cerebral inoculations of infected neural tissue to induce rabies in dogs and rabbits, with homogenates of dried spinal cords of rabbits as a vaccine. Rabies is a unique viral disease because it has a long incubation period, and the exact time of exposure to the infection is usually known. It took Pasteur five years to develop the vaccine, at which point he had about 50 dogs that were immune to rabies. According to some accounts, he thought that it would take many years to develop a human vaccine. However, ". . . on Monday, 6th July 1885, an Alsatian woman brought her child, Joseph Meister, to the Rue d'Ulm. He had been attacked, two days before, by a dog, thrown down, bitten in fourteen places . . . and found covered with the dog's saliva and his own blood."[1] The dog had been shot, and its body had shown evidence of rabies. Pasteur and his colleagues examined the child and decided that they dare not refuse to treat him. Meister did not develop the disease, and by 1 March 1886, of 350 patients treated, only one had developed rabies, and she had not been treated until 37 days after she had been bitten. It has been estimated that 40–80% of people bitten by rabid dogs developed rabies, so there is not the slightest doubt that Pasteur had in fact developed a highly effective vaccine, which has since saved many thousands of human lives. The vaccine continued to be used for many years, until replaced by a vaccine prepared in cell cultures.

On page 33 of this book, it states that ". . . Pasteur used animals as pseudo-humans as he attempted to craft a rabies vaccine. He took spinal column tissue of infected dogs and made what he thought was a vaccine. Unfortunately, the vaccine did not work seamlessly and actually resulted in deaths. Yet, this gross failure somehow did not detract from the reverence for the animal-lab process." This account is simply not true. The vaccine did not cause any deaths, it failed to cure one person out of the first 350, for a very good reason, and it was highly successful. The book does not even acknowledge that Pasteur did in fact produce a rabies vaccine.

The development of insulin as a treatment for type I diabetes

"The discovery of insulin at the University of Toronto in 1921–1922 was one of the most dramatic events in the history of the treatment of disease. Insulin's impact was so sensational because of the incredible effect it had on diabetic patients. Those who watched the first starved, sometimes comatose, diabetics receive insulin and return to life saw one of the genuine miracles of modern medicine. They were present at the closest approach to the resurrection of the body that our secular society can achieve, and at the discovery of what has become the elixir of life for millions of human beings around the world."[2]

The work that led to these dramatic results was done in dogs and rabbits, and was initiated by Frederick Banting, a young Canadian surgeon who worked in the Physiology Department of the University of Toronto, headed by J.J.R. Macleod. Banting was assisted by Charles Best, and the techniques for isolating the insulin were largely developed by J.B. Collip. By modern standards, the work was done in a haphazard manner, and it was surrounded by considerable controversy. Exactly who "discovered" insulin is still open to debate (see reference 2 for an excellent and detailed account). However, the research was successful, insulin was developed in a sufficiently pure state to be used in humans, and it has since saved many millions of lives.

On page 51 of their book, the Greeks state that "Banting and Best experimented on some dogs and by sheer happenstance persuaded people who had knowledge of *in vitro* research to look for insulin and purify it." They go on to say "The real credit for purifying insulin should have gone to Collip who used chemistry to purify the insulin." It is perfectly true that the purification of insulin posed some severe problems, particularly in scaling up for volume production. What the book fails to mention is that Collip had to have an assay method to determine whether his isolation methods produced active, injectable, insulin. "It was Collip who found that pancreatic extracts were effective in rabbits. And not necessarily diabetic rabbits, perfectly normal ones. Extract lowered their blood sugar from normal to below normal . . ."[2] Collip tried many ways of extracting insulin from the pancreas of farm animals, and used the rabbits to assay the results. The problems in scaling up the methods meant that Ely Lilly, the commercial company chosen for this task, used over a hundred thousand rabbits in the first six months in order to try to get a consistent product[2] (p. 72). Insulin has saved many millions of lives, but its discovery and isolation depended on the use of laboratory animals, which continued to be needed to assay the potency and safety of each batch of commercial insulin until the 1990s, when an *in vitro* method was finally developed.

The discovery and development of penicillin

The development of penicillin has resulted in the saving of more human lives than any other medical advance. The story of the discovery of penicillin by Alexander Fleming in 1929, as a result of the chance contamination of a bacterial Petri dish by a fungus, is well known. An excellent account is given by Hare,[3] who was a friend and colleague of Fleming, working in the same department of St Mary's Hospital. Penicillin is secreted into the medium in which the mould is grown. Unfortunately, Fleming was unable to purify it, so the only material he could work with was "mould juice". According to Hare, "Fleming evidently did think that penicillin might be of value when used locally, even though his attempts to employ it can only be described as feeble." Others did use this crude material on humans, sometimes successfully. Exactly why Fleming was not successful in purifying and developing penicillin is a bit of a mystery. Hare makes several suggestions. There were already several compounds that had anti-bacterial activity *in vitro*, but which turned out to be useless in practice. It had also been shown that some bacteria could become resistant to penicillin after only a short exposure. Also, the methods for the partial purification of small quantities were too clumsy for large-scale production, and in any case the penicillin was extremely unstable. So penicillin remained impure and untested for 11 years until 1939, when Ernst Chain and Howard Florey developed a method to purify and preserve it on a large scale.

The account of how they tested it by using mice is well known. As recorded by Medwar,[4] "At 11 a.m. on Saturday, 25th May 1940, eight white mice received approximately eight times the minimal lethal number of streptococci. Four of these were set aside as controls, but four others received injections of penicillin — either a single injection of 10 milligrams or repeated injections of five milligrams. The mice were watched all night (but of course). All four mice unprotected by penicillin had died by 3.30 a.m. Next morning, Sunday 26th May, Florey came into the department to discover that the results of his experiment were clear-cut indeed . . . They all recognised that this was a momentous occasion . . . Animal experiments on a much larger scale soon made it clear that penicillin was indeed of great potential importance."

On page 73 of their book, the Greeks claim that animal testing delayed the introduction of penicillin, because Fleming used it on a rabbit and it did not work. Given that: he was unable to purify the penicillin; that the use of a rabbit is not mentioned by Hare; that had Fleming had some pure penicillin, there were patients he could have tried it on; that mice would have been the natural choice of test animal, because of their small body size; and that the only references to the use of a rabbit are from antivivisectionist literature, I doubt whether this is true. The Greeks go on to claim that "He later had a very sick patient, and since he had nothing else to try, administered penicillin. The rest is history." In fact, Florey gave Fleming the purified penicillin. The vital part played by Chain and Florey in isolating it, proving it by using mice, and developing it, is largely ignored.

There are numerous other comments that could be made about the Greeks' book. For example, Chapter 4 gives a long list of drugs withdrawn because of adverse reactions in humans that were not predicted by using animal tests. Although it is certainly true that animal tests cannot predict all adverse reactions, the book fails to point out that all drugs undergo extensive clinical trials, so that if they later have to be withdrawn, it is because the clinical trials also failed to detect these adverse effects.

A book like this always has to have a villain. And, true to form, Chapter 5 is a polemic about how vested interests are making money out of animal research. It is true that the supply of animals, cages, diet and sundries for animals is a valuable business. However, money for medical research comes largely from government (for example, the Medical Research Council in the UK, and the National Institutes of Health in the USA), the pharmaceutical industry, research charities such as the Wellcome Foundation, and universities. All these organisations already spend many millions on clinical science and on non-animal alternatives such as research with insects (for example, *Drosophila*) and the nematode *Caenorhabditis elegans*. All of them would be only too pleased to save money by not using animals if they thought real alternatives were available.

FRAME, of course, believes that there is still considerable scope for finding more alternatives. It will continue to press the scientific community to invest more time, effort and money in the search for these. But this book is not going to be of much help, because scientists set great store by the truth.

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References

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NEW MICROBIOTESTS FOR ROUTINE TOXICITY SCREENING AND BIOMONITORING

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This is a substantial volume representing the Proceedings of the International Symposium on New Microbiotests for Routine Toxicity Screening and Biomonitoring, held on 1–3 June 1998 at Brno in the Czech Republic. The initiative for organising the meeting came from the Laboratory for Biological Research in Aquatic Pollution of the University of Ghent, Belgium, which has long been active in this field. In the Preface, emphasis is placed on the problem of cost in ecotoxicity testing, and the need for the development of alternative microbiotests that allow routine testing with basic laboratory equipment and materials. The objective in organising the meeting was to obtain the widest possible representation of laboratories engaged in this type of work internationally. That there are no fewer than 60 contributions on diverse topics, from European, North American, South American, Russian, Australasian and Japanese laboratories, is indicative of the success of the venture. The strong representation of Eastern Europe and countries of the former Soviet Union is particularly encouraging, in view of the very serious legacy of pollution problems following the collapse of communism.

The text is divided into 11 large chapters, each containing a number of individual contributions. The first of these contain five relatively wide-ranging reviews, whereas the remainder deal with more focused topics. In the first contribution, Blaise refers to the development of small-scale aquatic toxicology, which "gave rise to numerous microscale procedures now commonly referred to as microtests". In an accompanying figure, a distinction is made between *bioassays*, which are (sub)cellular systems utilising bacteria, algae, protozoans, microinvertebrates and fish, and *biomarker assays*, which are concerned with the measurement of biochemical and physiological changes in individuals following exposure to chemicals. Bioassays, which are generally cheaper and easier to use than biomarker assays, are the main subject of this book. There are, however, a few references to biomarkers; for example, in a useful early chapter by Coen, Janssen & Giesy entitled *Biomarker Applications in Ecotoxicology: Bridging the Gap Between Toxicology and Ecology*.

Turning to the main part of the text (Chapters 2–11), the topics are as follows: *Toxicity Testing for Regulatory Purposes; New Microbiotests and Specific Test Criteria; Sensitivity Comparisons of Toxicity Tests; Toxicity Testing of Natural Waters; Toxicity Testing of Wastes, Waste Waters and Leachates; Toxicity Testing of*

Soils and Sediments; Toxicity Testing of Air Pollution; Toxicity Testing of Specific Chemicals; Testing for Mutagenicity and Genotoxicity; and *Microbiotests for Toxicity Evaluation of Biotoxins*. There is a brief but useful index at the end, which is divided into two sections: a listing according to major subject class; and an alphabetical listing of subjects.

Taking the text as a whole, many of the tests utilise microorganisms or invertebrates. Only six chapters are concerned with fish. This raises questions about the extent to which such biotests can be used as alternatives to conventional toxicity tests on fish or other vertebrates. In a comparison between conventional assays and alternative microbiotests, Fochtman (contribution 25) finds reasonable correlations between conventional toxicity tests and biotests when conducted upon the same species, but poorer ones when comparing dissimilar species (or example, when comparing results from an algaltoxkit with toxicity to fish). The author goes on to conclude that "the closer the phylogenetic relationship between test biota, the higher the probability of high correlations in dose–effect relationships". This is hardly surprising, because of the very large differences between unrelated species in regard to the mechanism of toxicity. Many of the most toxic compounds to animals act on sites in the nervous system which do not occur in microorganisms or plants.

Many of the assays described here are already proving their value for rapid, cost-effective monitoring and screening or for identifying hot spots which require further investigation. In this regard, they can be much more cost-effective than detailed (and relatively expensive) chemical analysis, the results of which are often difficult to interpret in a toxicological way. There is already good evidence that microbiotests can give reasonable predictions of toxicity as determined by conventional testing, as long as comparisons are of the same or of closely related species. In the quest for alternatives to conventional toxicity tests on vertebrates, there is clearly a case for developing more microtests employing cellular/subcellular systems. In the case of birds and fish, toxicity tests on eggs hold promise.

This book is generally well produced and well illustrated. It contains a wealth of material on microbiotests, and is a must for practitioners in the field. More generally, it is a valuable reference work on the wide range of microbiotests currently being used, which will be of interest to scientists working in related fields.

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