HISTORY OF ANIMAL EXPERIMENTS RESEARCH TESTING

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The Unreliability of Animal Models in Research and Testing Experiments

Most people who oppose vivisection do so on moral grounds either through well considered philosophical arguments or by an instinctive revulsion to the suffering and death inseparable from animal research. In fact, the case against animal experiments is strongly reinforced by scientific arguments: animals are different from us both in the way their bodies work and in their reaction to drugs. If animal research were really a valid scientific method, people would surely visit their veterinarians when feeling ill! The truth is that animal experiments tell us about animals, usually under artificial conditions, when in medical research we need to know about people.

The scientific case against animal research was summarized, although perhaps unintentionally, by an article in the *Journal of the American Veterinary Medical Association.* The writer stressed that knowledge of differences between the species is crucial to the rational use of drugs in veterinary practice. For instance, doses of aspirin used in human therapeutics actually poison cats while having no effect on the treatment of horses; unlike dogs and cats, mice, rabbits and horses are physiologically unable to vomit; the body chemical serotonin raises the blood pressure in dogs but reduces it in cats (humans react like dogs in this case); the LD50 of heart drug digitoxin in the rat is 670 times as great as that found in the cat; anticancer drug azauridine is comparatively well

tolerated by people but causes lethal bone marrow depression in dogs after only 7-10 days; phenol-based disinfectants are particularly toxic to cats because they only slowly metabolize the chemical, and, the article might have added, dogs, cats, rats and mice do not need vitamin C added to their diet but, like us, guinea pigs do. The writer concluded that "It is unwise to extrapolate information concerning drugs from one species to another."[1]

Why then have animal experiments become so much a part of scientific practice that any criticism is considered heresy? Much of today's obsession with animal models of human disease can be traced to the 19th century physiologists who transformed vivisection from an occasional method into the scientific fashion we know today. One of the most influential figures was the French physiologist Claude Bernard who, in 1865, published his *Introduction to the Study of Experimental Medicine,* a work specially designed to guide physicians in their research. Bernard regarded the vivisection laboratory as the "true sanctuary of medical science" and considered it much more important than the clinical study of hospital patients. It was Bernard who popularized the artificial production of disease in animals by chemical or physical means, thereby leading the way for today's reliance on animal models in medical research. But by far his most dangerous legacy was the belief that animal experiments are entirely relevant to people:

"Experiments on animals, with deleterious substances or in harmful circumstances, are very useful and entirely conclusive for the toxicology and hygiene of man. Investigations of medicinal or of toxic substances are wholly applicable to man from the therapeutic point of view... ."[2]

► ***Claude Bernard's vivisection 'salon'***

"We sacrificed daily from one to three dogs, besides rabbits and other animals, and after four years' experience I am of the opinion that not one of these experiments on animals was justified or necessary. The idea of the good of humanity was simply out of the question, and would be laughed at, the great aim being to keep up with, or get ahead of, one's contemporaries in science, even at the price of an incalculable amount of torture needlessly and iniquitously inflicted on the poor animals." Dr George Hoggan, Morning Post, February 2,1875.

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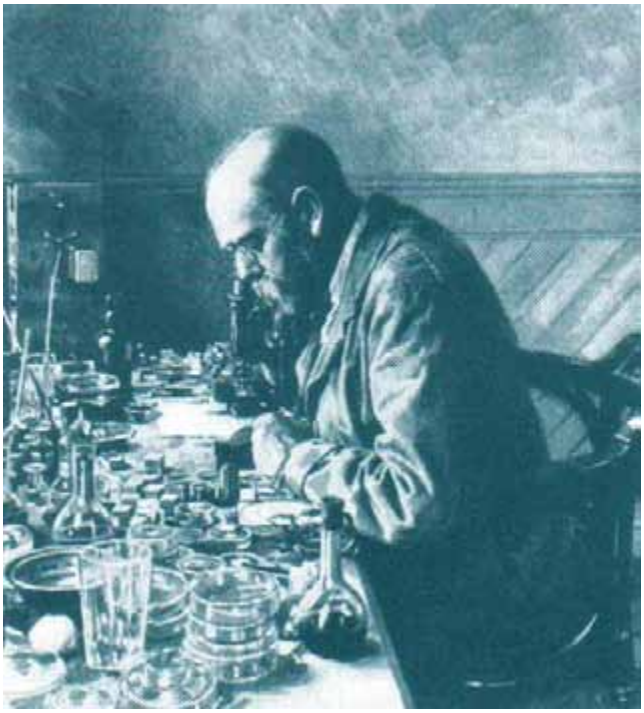
Animal models were further popularized by the German doctor Robert Koch, a rival of Pasteur's in developing the germ theory of disease. Koch produced a set of rules for "proving" that a particular germ caused the disease under investigation and one of these stated that, when inoculated into laboratory animals, the microbe should reproduce the same condition.[3]

Yet Koch's ideas were soon challenged by his own research into cholera when it proved impossible to reproduce the disease in animals. Koch wrote to the *British Medical Journal* of 1884 describing how he had been forced to rely on clinical observation of patients and microscopic analysis of samples of actual cases of human cholera. Using these methods he was able to isolate the microbe, discover its mode of transmission and suggest preventive action.[4]

► ***Robert Koch:*** *Human research isolated the cholera microbe when it proved impossible to reproduce the disease in laboratory animals*



Despite such evidence, medical science came to rely on animal models of human disease perhaps because animals are regarded as disposable species whereas investigation of human patients requires so much more skill and patience in avoiding unnecessary risks. Nevertheless it is acknowledged that animal models are generally poor and in some cases non-existent[5] which explains why many treatments that work on animals fail when given to humans. It also explains why so many useful drug effects are only identified during clinical studies of human patients.

In view of the widespread use of animals to develop and test new medicines, it is surprising that there have been so few attempts to see how well they predict effects in people. An indication of the accuracy of animal tests can be obtained by the failure rate of drugs during clinical trials. For instance, studies reported in the 1960s showed that 97.7% of new drug candidates selected for clinical trial failed to reach the market.[6] Similar findings were reported by Ciba Geigy in 1965 when 95% of chemical

compounds found safe and effective on the basis of animal tests were discarded during clinical trials.[7] A more recent analysis in the United States once again revealed that the majority of new medicines (68% in this case) subjected to clinical trials never reached the market.[8] The survey was carried out between 1963 and 1976 and listed the main reasons for discarding the drugs as lack of efficacy in treating patients, human toxicity and inappropriate action of drugs within the human body (pharmacokinetics).

Other surveys have shown that most of the adverse reactions occurring in people when they take a drug cannot be predicted by animal experiments.[9] Tests to identify cancer-causing chemicals have been particularly suspect. An editorial in the February 1980 edition of the *Journal of Pharmaceutical Sciences* referred to carcinogenicity testing in the United States as "a national catastrophe." Although at the same time costing the National Cancer Institute $65 million a year, no studies had been carried out to validate the results from animal experiments. Subsequently an investigation by the pharmaceutical company Pfizer asked whether rodent tests could have successfully predicted the chemicals already known to cause cancer in people. Animal tests gave the correct answer in less than half the cases and it was concluded we would have been better off to toss a coin![10] Perhaps this is the reason so little credibility is given to the results of carcinogenicity tests. Anticancer drug Farlutal and acne treatment Diane are examples of medicines put onto the market despite causing cancer in animals, the manufacturers stating in their literature that the relevance to humans is unknown or has not been established.[11]

Difficulties are compounded because species are usually chosen not on anticipated similarity to people but on non-scientific grounds such as cost.[12] The most commonly used animals in research are rodents which make up some 85% of the total.[13] One of the most important characteristics is size which largely determines both the cost of the animals and the space needed during the experimental period. Another key factor which can influence costs is the animals' productivity in terms of the number of babies they can produce. Rats and mice can produce far more offspring than cats, dogs and primates.

Species variation in toxicity tests can often be traced to differences in the way people and animals metabolize, or break down drugs in the body. In this respect rats and mice are known to be among the most *unsuitable* models for humans yet they still feature prominently in test procedures. A comparative study of 23 chemicals showed that in only four cases did rats and humans metabolize products along the same biochemical pathway.[14] So great are the differences that American pharmacologist Bernard Brodie argues that[55] "it is often a matter of pure luck that animal experiments lead to clinically useful drugs."

Small rodents are the main species used in acute toxicity tests such as the LD50, so it is fortunate that few take the results seriously. According to their LD50s in rats, aspirin should be safer in overdose than another, similar painkiller, ibuprofen. Yet clinical experience does not tally with this and suggests that ibuprofen is the safer drug.[15] On the basis of its LD50 in rats, the heart drug digitoxin would seem around 100 times safer than it actually is in human subjects.[16] As Dr. G. N. Volans, Director of Britain's National Poisons Center at New Cross Hospital in London, has pointed out, acute toxicity data from animal tests contribute "very little of value" to the prevention and management of drug overdose.[15]

► *"For the recognition of the symptomatology of acute poisoning in man, and for the determination of the human lethal dose, the LD50 in animals is of very little value." Prof. G. Zbinden, Institute of Toxicologv, Zurich.*

Rabbits are the favorite animal for eye irritation tests but once again the reason is not scientific. In fact, the rabbit eye is widely acknowledged to be a poor model for the human *eye.*[17] Nevertheless the Draize test traditionally uses the albino rabbit because it is cheap, readily available, easy to handle and has a large eye for assessing test results.[18] While there may still be species differences, results from primates are considered more relevant but, fortunately for them, drawbacks such as expense, availability and temperament have largely precluded their use for eye irritation tests.[18]

► ***The Draize eye irritancy test:***
"It has not been possible for us to use the results of rabbit studies to predict accurately the actual irritation that might occur in humans after accidental exposure." Procter & Gamble scientists, Toxicology & Applied Pharmacology. 701-710, vol. 6, 1964

Rabbits are one of the two or three species routinely used to test for birth defects. The decision follows the observation that rabbits are one of the few animals to react like humans to thalidomide. But this is no guarantee that they will react like us to every other drug. Indeed, the widely used drug cortisone produces birth defects in rabbits[19] but is considered safe for pregnant women.[20]

Rabbits are also the favorite animal in atherosclerosis research despite substantial differences between the artificially induced condition and the naturally arising disorder in people. Pigs are considered the best model for the human disease but they are regarded as expensive and difficult to work with, so rabbits have become the species of choice. As David Gross points out in his book *Animal Models in Cardiovascular Research*

(1985), this is because they are "easy to feed, care for and handle. They are readily available and inexpensive."

Dogs are described as man's best friend but not when it comes to research. Although they are considered better than rats as predictors of human responses in toxicity tests, they cannot be relied on to give safe results. Oral contraceptives are known to increase the risk of blood clots, causing heart attacks, lung disorders and strokes, and after many deaths, the pill's estrogen content was reduced. Yet animal tests had not only failed to reveal the hazard, but in dogs, oral contraceptives had totally the opposite effect, actually *prolonging* blood clotting times.[19]

Dogs are widely used in physiological experiments, particularly on the heart. They are a convenient size for surgical procedures, react well to anesthesia and are good tempered. But recent findings show that while the body chemical acetylcholine *dilates* the coronary arteries in dogs, it has the opposite effect in people, constricting the arteries and leading to heart spasm.[21]

Even in primates, the animals closest to us in evolutionary terms, subtle differences in physiology mean that disease can take quite a different form. The use of monkeys to investigate malaria led to the suggestion that coma in human patients is caused by an increased concentration of protein in the cerebrospinal fluid and that this leakage could be corrected with steroids. But steroids do not help people and subsequent clinical observation of malaria patients showed that the monkey model may simply not be relevant.[22] Attempts to induce AIDS in non-human primates have proved equally unsuccessful. In 1989 the weekly science magazine *Nature* noted that more than six years after being inoculated with human brain tissue containing HIV-1, chimpanzees still show no sign of the disease.[23] (The latest reports also suggest that the recent and much heralded mouse models of AIDS,

produced by inserting parts of the human immune system into the animals, may not only be biologically irrelevant but could also promote hazardous changes in the AIDS virus.[54])

► *Chimpanzees still show no sign of AIDS after inoculation with HIV*

Although it must be admitted that differences between the species are a handicap to those who rely on animal experiments, there are times when they have been used to commercial advantage, to imply superiority over a competitor's product. On the basis of animal tests the arthritis drug Surgam was promoted as giving "gastric protection", a major advantage over similar drugs which do damage the stomach. But human trials showed that Surgam was just like its rivals and the company - Roussel Laboratories - was found guilty of misleading advertising. According to a report of the case in the medical journal *Lancet,* witnesses for *both* sides of the case "agreed that animal data could not safely be extrapolated to man."[24]

Paradoxically, it is the very uncertainty of animal research, particularly in toxicity tests, which has led to more and more experiments being performed. But more species do not necessarily overcome the problem and can increase confusion. Aspirin is known to cause birth defects in rats, mice, cats, dogs, guinea pigs and monkeys but is considered relatively safe for pregnant women.[25] On the other hand, arthritis drug Fenclozic

acid seemed safe after tests with rats, mice, dogs and monkeys yet caused liver toxicity during clinical trials. Further animal tests, with rabbits, guinea pigs, ferrets, cats, pigs, horses and another strain of rat, still gave no indication of liver damage.[26]

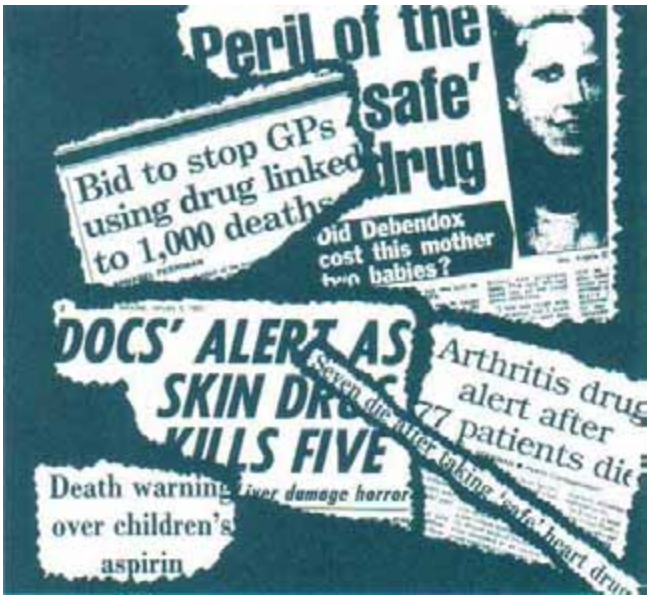
There is no doubt that animal tests have failed to predict many of the dangers of drug therapy. Occasionally, unforeseen side effects lead to a drug's withdrawal from the market. An analysis by scientists at the pharmaceutical companies Pfizer and Rhone-Poulenc revealed that at least 80 products have been withdrawn on safety grounds from one or more of four countries (France, West Germany, UK and the USA) between 1961 and July 1987. The most common adverse reactions which led to withdrawal were liver damage, blood disorders and neurological problems.[27]

Alternatively, unforeseen hazards lead to restrictions in the drug's use or there may be special warnings sent to doctors or published in the medical press. The problem is that drug side effects are thought to be very much under reported so the overall dangers of drug therapy are difficult to assess. For instance, the British system of monitoring drugs once they have reached the market has been established since the 1960s but is known to be inadequate with only 1-10% of side effects being reported.[28] Even very serious reactions, including drug-induced fatalities, are grossly under reported.[29] Nevertheless, the United States General Accounting Office found that 51.5% of drugs had to be relabelled due to "serious" unexpected side effects. The labelling changes either limited the drug's use or added major warnings or precautions.[56]

In the case of ICI's heart drug Eraldin, patients suffered intestinal and eye problems, including blindness, and there were many deaths. Ultimately ICI compensated more than 1000 victims, yet

animal experiments had given no warning of the dangers which took four years to surface.[30] Improved monitoring of patients would surely have identified the problem at an earlier stage. The arthritis drug Oraflex is one of several anti-inflammatory agents recently withdrawn on safety grounds. Deaths occurred mainly through liver damage but in the animals considered closest to us - non-human primates - no evidence of toxicity could be seen at 7 times the maximum tolerated human dose for a year.[30]

► *When disaster strikes, criticism of animal "safety" testing is rarely mentioned.*



During the 1960s thousands of young asthmatics died following use of isoprenaline aerosol inhalers. Isoprenaline is a powerful asthma drug and deaths were recorded in countries using a particularly concentrated form of aerosol. Animal tests once again failed to reveal the hazards and indeed cats could tolerate 175 times the dose found dangerous to asthmatics. Even after the event it proved difficult to reproduce the effects in laboratory animals.[30]

Japan suffered a major epidemic of drug-induced disease in the case of clioquinol, the main ingredient of antidiarrhoea medicine Enterovioform. At least 10,000 people were victims of a new

disease called SMON (subacute myelo-optic neuropathy) whose symptoms included weakness in the legs, paralysis and eye problems including blindness. The effects are caused by nerve damage yet tests by Ciba Geigy with rats, cats, beagles and rabbits revealed no evidence that clioquinol is neurotoxic.[30]

Animal tests have failed to predict many other hazards:[30] the addictive properties of the benzodiazepine minor tranquilizers; the deadly diarrhoea associated with antibiotics such as clindamycin; the fatal blood disorder caused by the antibiotic chloramphenicol; and the liver damage linked to a wide variety of medicines including the antifungal drug Nizoral, the anesthetic halothane, the arthritis drug Ibufenac and the antidepressant Zelmid.

Apart from failing to reveal many of the hazards, animal experiments could also lead to the rejection of potentially valuable medicines on the basis of side effects which never occur in people. This needs to be taken seriously because a comparison between human and animal test data found that, at most, only one out of every four side effects predicted by animal experiments actually occurred in people.[31]

▼ *Penicillin, discovered by Fleming, was thankfully nor tested on guinea pigs. The drug kills them and in other animals causes fetal deformities. Happily, humans react quite differently.*

Many long established drugs exhibit sufficient toxicity in animals to make it unlikely they would be introduced with today's greater emphasis on animal research. Had penicillin been tested during its development on guinea pigs, to whom it is highly toxic, this

important antibiotic might have been discarded.[32] Frusemide is a valuable diuretic but causes severe liver damage in mice because of a metabolite not formed to any serious extent in people;[33] iron sorbitol is used to treat iron deficiency anaemias but causes sarcomas at the site of intramuscular injection in rats and rabbits although clinical experience has revealed no real hazard to patients.[33] Narcotic drugs such as morphine were discovered without animal research and remain invaluable agents in the relief of severe pain but had morphine been tested on cats prior to clinical trial, it could have been rejected. The drug causes hyperexcitement in cats but calms people.[34] And would valuable medicines such as streptomycin, insulin and penicillin be withheld from pregnant women because they cause birth defects in laboratory animals?

Reliance on animal experiments can also have detrimental effects in other areas of medical research, diverting attention and resources from more relevant sources of information based on the study of people. By the early years of the 20th century, human population studies (known scientifically as epidemiology) had identified several causes of cancer but when, in 1918, Japanese researchers produced cancer on a rabbit's ear by painting it with tar, attention swiftly diverted towards animal experiments, and epidemiology lost favor. As British cancer expert Sir Richard Doll has pointed out, human observational data was commonly dismissed and carried little weight compared with that obtained by experiment, since it was confidentially believed that the mechanism by which all cancers are caused would soon be discovered.[35]

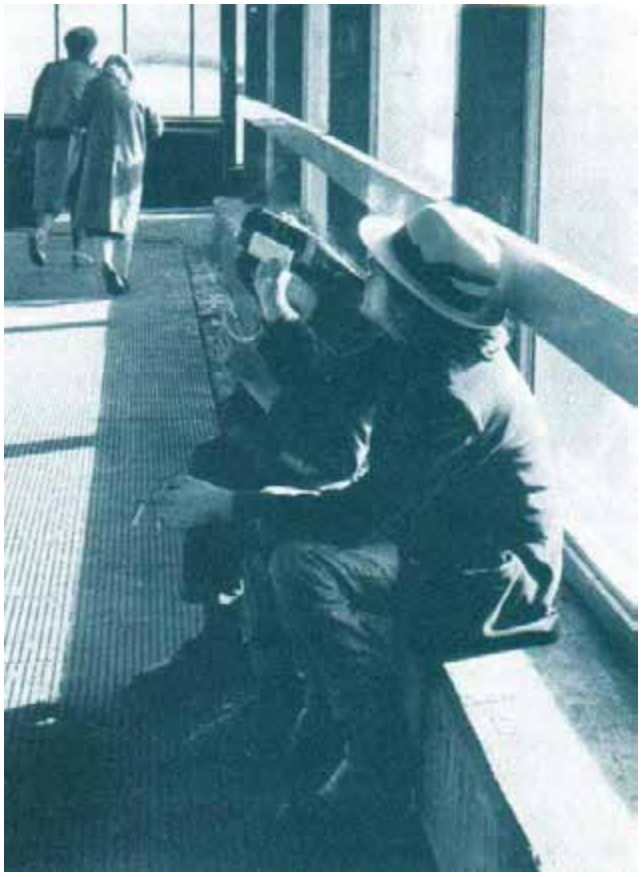
By neglecting epidemiology, doctors were unable to identify the underlying causes of the disease, so there was little solid basis for preventive action. This has been a serious mistake because despite success in treating some rarer forms of the disease, it is clear we are losing the war against cancer.[36] Fortunately, interest

in human observational studies has recently been revived, showing that 80-90% of cancers are preventable.[37]

Over the years doctors have asked why so much attention is devoted to the use of the animals in cancer research. In 1980 an editorial in the medical journal *Clinical Oncology* stated that it is hard to find a single, common human cancer where management and expectation of cure has been markedly affected by the results of laboratory research. Although not opposed to animal research in principle, the editorial warned that most human cancers are different from the artificially induced disease in animals and wondered why so little attention is paid to the *human* condition. The editorial concluded that it is the study of human patients which will eventually produce relevant answers.[38]

The belief that clinical findings must be reproduced in the laboratory before finally being accepted can hold back progress and has often proved a wasteful detour. It was clinical observation which showed that diabetes is often caused by a damaged pancreas[39] but the idea was not accepted for many years partly because physiologists found it difficult to reproduce the effects in laboratory animals.[40] The link between smoking and lung cancer was first discovered through human population studies although attempts to duplicate the effects in laboratory animals by forcing them to inhale the smoke have generally failed.[41]

► ***Smoking and drinking:***
Animal research has produced a mass of confusing and contradictory results which have hampered medical progress.



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One of the most striking examples of wasted resources is the use of animals in alcohol research. Although the damaging effects of alcohol have been known for a long time, further insights can be obtained through clinical studies with alcoholics or with human tissues from biopsy samples and autopsy specimens. Nevertheless animal research continues unabated despite conflicting results. For instance, while alcohol-induced cirrhosis of the liver is a main cause of sickness and death in Western society, scientists have had great difficulty reproducing the effects in laboratory animals. Only in baboons has cirrhosis been induced[42] although even this finding has now been challenged.[43] Alcohol is also known to raise blood pressure but this is not the case in laboratory animals.[44] And while some people react violently after excessive drinking, many animal experiments have failed to show an increase in aggressive behavior.[45]

If animals are often poor models for human illness and an unreliable guide to the safety of medicines, surely it is only common sense to switch our resources to methods of more direct relevance to people? In the investigation of human illness, researchers can employ test tube experiments with human tissues to investigate disease at the cellular level and match their results with clinical and epidemiological findings so an overall picture can be obtained. On some occasions, it might be argued, animal experiments do provide a similar model of human disease. But the accuracy of animal experiments can only be judged *after* clinical research with volunteers and patients has taken place. So why waste resources on experiments which could produce conflicting results?

Test tube studies with human tissues are not only valuable in understanding human disease; they can also be used to test the effectiveness of new medicines, for instance in the development of drugs to treat AIDS.[46] The unreliability of animal models has finally persuaded the National Cancer Institute to change the way it searches for new drugs, with human cancer cells replacing mice, albeit only in preliminary tests at present.[47] Yet it was over 30 years ago, in 1956, that Eagle and Foley showed how human tissue culture could be used to test new anticancer drugs.[48]

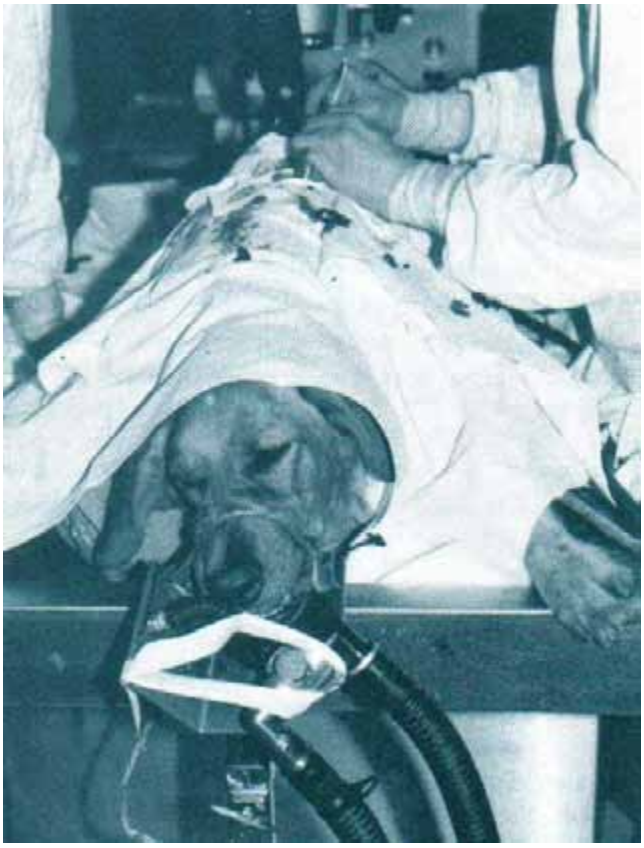
Test tube experiments with human cells could also be used to test the safety of medicines prior to clinical trials. While clinical trials with healthy volunteers and patients are the most reliable test of a new drug, some preliminary assessment is essential to identify the most toxic substances. And while human cell systems have their limitations, they do promise better protection against hazardous drugs. For instance, results from Britain's Lister Hospital show that human bone marrow cells can be used to detect drugs like chloramphenicol which cause deadly blood disorders. The

researchers conclude that test tube methods with human tissues can give a degree of reassurance not provided by animal experiments.[49] Others have shown that human cell tests can identify thalidomide's ability to damage the unborn child.[50] And human lymphocytes are being used as part of a battery of tests to detect mutagens and carcinogens.[51]

Unfortunately, continued reliance on animal "safety" tests has delayed the full development of these systems. An International Workshop on the Application of Tissue Culture in Toxicology reported in 1980 that funds for the development of relevant tissue culture systems must be almost negligible compared with the total costs for toxicity testing.[52] It has been known for decades that human tissue culture offers great promise for the safety evaluation of chemicals[53] yet the emphasis is still overwhelmingly on animal experiments. Perhaps industry is deterred by the fear that human cell tests would be seen as *additional* rather than replacements for animal experiments.

The time has come to challenge Claude Bernard's medieval doctrine that lives can only be saved by sacrificing others, and that animal experimentation is a valid system of research. The very uncertainty of animal experiments shows that it can never be a choice between dogs and babies. The real choice lies between good science and bad science. Vivisection is bad science because it tells us about animals when we need to know about people. If medical science is to achieve its full potential and attain the image of a noble and humanitarian endeavor, then we must relegate animal experiments to the history book where they truly belong.

► *"Before the bar of justice vivisection stands condemned on three main counts - cruelty to animals, uselessness to man and obstruction on the path of real knowledge." Dr M. Beddow Bayly, 1887-1961*



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References:

1) L.E. Davis, ***Journal of the American Veterinary Medical Associations,*** 1979, vol. 175, 1014-1015.
2) ***An Introduction to the Study of Experimental Medicine,*** C. Bernard, 1865 (translation of the original text by H. C. Green) (Dover Publications Inc., 1957).
3) ***Lancet,*** 1909, March 20, 848-849.
4) R. Koch, ***British Medical Journal,*** 1884, September 6, 454.
5) C. T. Dollery in ***Risk-Benefit Analysis in Drug Research,*** Ed. J. F. Cavalla (MTP, 1981).
6) S. Irwin, ***Science,*** 1962, April 13, 123.
7) F. I. McMahon, ***Medical World News,*** 1965, vol. 6, 168.
8) S. R. Walker & J. A. Parish in ***Trends and Changes in Drug Research and Development,*** Eds. B. C. Walker & S. R. Walker (Kluwer Academic Publishers, 1988).
9) J. T. Litchfield Jnr., ***Clinical Pharmacology & Therapeutics,*** 1962, vol. *3,* 665-672.
10) D. Salsburg, ***Fundamental & Applied Toxicology,*** 1983, vol. 3, 63-67.
11) Farlutal promotional literature (Farmitalia Carla Erba); Diane promotional literature (Berlimed Pharmaceuticals).
12) D. M. Davies (Ed.), ***Textbook of Adverse Drug Reactions*** (Oxford University Press, 1977).
13) A. Rowan, ***Of Mice, Models and Men,*** (State University of New York, 1984).
14) D. V. Parke & R. L. Smith (Eds), ***Drug Metabolism -from Microbe to Man*** (Taylor & Francis, 1977).

15) G. N. Volans in ***The Contribution of Acute Toxicity Testing to the Evaluation of Pharmaceuticals,*** Eds. D. Schuppan, A. D. Dayan & F. A. Charlesworth (Springer-Verlag, Berlin, 1986).
16) G. T. Okita, ***Federation Proceedings,*** 1967, vol. 26, 1126.
17) F. Coulston & D. Serrone, ***Annals of the New York Academy of Science,*** 1969, vol. 162, 681-706; see also reference 18.
18) D. W. Swanston in ***Animals and Alternatives in Toxicity Testing,*** Eds. M. Ball, R. J. Riddell & A. N. Worden (Academic Press, 1983).
19) M. H. Briggs in ***Biomedical Research Involving Animals,*** Eds. Z. Bankowski & N. Howard-Jones (Council for International Organisations of Medical Sciences, 1984).
20) R. M. Ward & T. P. Green, ***Pharmacology & Therapeutics,*** 1988, vol. 36, 326.
21) S. Kalsner, ***Journal of Physiology,*** 1985, vol. 358, 509-526.
22) ***Lancet,*** 1987, May 2, 1016.
23) P. Newmark, ***Nature,*** 1989, October 19, 566-567.
24) J. Collier & A. Herxheimer, ***Lancet,*** 1987,January 10, 113-114.
25) R. D. Mann, ***Modern Drug Use, an Enquiry on Historical Principles,*** (MTP, 1984).
26) S. J. Alcock, ***Proceedings of the European Society for the Study of Drug Toxicity,*** 1971, vol. 12, 184-190.
27) C. Spriet-Pourra & M. Auriche, ***Drugs Withdrawn from Sale*** (PJB Publications, 1988).
28) *New Scientist,* 1980, July 17,218.
29) W. H. Inman in ***Monitoring for Drug Safety,*** Ed. W. H. Inman (MTP, 1980).
30) R. Sharpe, ***The Cruel Deception*** (Thorsons, 1988) and references therein.

31) A. P. Fletcher, ***Journal of the Royal Society of Medicine,*** 1978, vol. 71,693-698.

32) T. Koppanyi & M. A. Avery, ***Clinical Pharmacology & Therapeutics,*** 1966, vol. 7, 250-270.

33) M. Weatherall, ***Nature,*** 1982, April 1, 387-390.

34) B. Brodie, ***Clinical Pharmacology & Therapeutics,*** 1962, vol. 3, 374-380.

35) R. Doll, ***Cancer,*** 1980, vol. 45, 2475-2485.

36) J. C. Bailar & E. M. Smith, *New* ***England Journal of Medicine,*** 1986, vol.314, 1226-1232.

37) C. S. Muir & D. M. Parkin, ***British Medical Journal,*** 1985, January 5, 5-6.

38) D. F. N. Harrison, ***Clinical Oncology,*** 1980, vol. 6, 1-2.

39) W. P. U. Jackson & A. I. Vinik, ***Diabetes Mellitus*** (Edward Arnold, 1977).

40) R. Levine, introduction to B. W. Volk & K. F. Welman, ***The Diabetic Pancreas*** (Tindall, 1977).

41) F. T. Gross et al, ***Health Physics,*** 1989, vol. 56, 256.

42) E. Rubin & C. S. Lieber, *New* ***England Journal of Medicine,*** 1974, vol.290, 128-135.

43) C. C. Ainley et al, ***Journal of Hepatology,*** 1988, vol. 7, 85-92.

44) J. V. Jones et al, ***Journal of Hypertension,*** 1988, vol. 6, 419-422.

45) B. Everill & M. S. Berry, ***Physiology & Behaviour,*** 1987. vol. 39, 45-51.

46) ***Science,*** 1985, December 20, 1355-1358.

47) ***Scrip,*** 1987, January 16,30.

48) H. Eagle & G. E. Foley, ***American Journal of Medicine,*** 1956, 739-749.

49) G. M. L. Gyte&J. R.B.Williams, ***ATLA,*** 1985, vol. 13.38-47.

50) J. W. Lash & L. Saxen, ***Nature,*** 1971, August 27, 634-635.

51) **See *Mutagenesis,*** 1989, vol. 4 for several examples.

52) **E. Heilbron, *Toxicology,*** 1980, vol. 17, 269-272.

53) For example, C. N. D. Cruickshank & E. J. L. Lowbury, ***British Medical Journal,*** 1952, November 15, 1070-1072; M. Albrecht, ***Arzneimittel-Forschung,*** 1962, no.3, 282-285; G. Corrssen et al, ***Anesthesiology,*** 1966, vol. 27, 155-162.

54) J. Marx, *Science,* 1990. February 16, 809.

55) B. B. Brodie, Acceptance Speech, Torald Sollaman Award, Meeting of the American Society for Pharmacology & Experimental Therapeutics, Fall 1963.

56) F. D. A. Drug Review: Postapproval Risks 1976-1985 (U.S. General Accounting Office, April 1990).