A CRITICAL LOOK AT

ANIMAL EXPERIMENTATION

Medical Research Modernization Committee

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Information:

The *Medical Research Modernization Committee (MRMC)* is a non-profit health advocacy organization composed of medical professionals and scientists who identify and promote efficient, reliable and cost-effective research methods. The MRMC focuses exclusively on the scientific merits of different research approaches, even though some undoubtedly raise serious and important ethical concerns. MRMC-sponsored activities include research, publishing and student education.

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Increasing numbers of scientists and clinicians are challenging animal experimentation on medical and scientific grounds.[1-3] In the United Kingdom, for example, 82% of general practitioners said they were «concerned that animal data can be misleading when applied to humans», according to a 2004 survey commissioned by Europeans for Medical Progress.[4] Considerable evidence demonstrates that animal experimentation is inefficient and unreliable, while newly developed methodologies are more valid and less expensive than animal studies.

Historical Impact of Animal Experimentation

Proponents of animal experimentation (tests, experiments and «educational» exercises involving harm to animals) claim that it has played a crucial role in virtually all medical advances.[5,6] However, several medical historians argue that key discoveries in such areas as heart disease, cancer, immunology, anesthesia and psychiatry were in fact achieved through clinical research, observation of patients and human autopsy.[7-16]

Human data has historically been interpreted in light of laboratory data derived from nonhuman animals. This has resulted in unfortunate medical consequences. For instance, by 1963 prospective and retrospective studies of human patients had already shown a strong correlation between cigarette smoking and lung cancer.[17,18] In contrast, almost all experimental efforts to produce lung cancer in animals had failed. As a result, Clarence Little, a leading cancer animal experimenter, wrote: «The failure of many investigators to induce experimental cancers, except in a handful of cases, during fifty years of trying, casts serious doubt on the validity of the cigarette-lung cancer theory.»[19] Because the human and animal data failed to agree, this researcher and others distrusted the more reliable human data. As a result, health warnings were delayed for years, while thousands of people died of lung cancer.

By the early 1940s, human clinical investigation strongly indicated that asbestos causes cancer. However, animal studies repeatedly failed to demonstrate this, and proper workplace precautions were not instituted in the U.S. until decades later.[20] Similarly, human population studies have shown a clear risk from exposure to low-level ionizing radiation from diagnostic X-rays and nuclear

Polio victim in the U.S. in 1948. The monkey model of polio misled researchers about polio's mechanism of infection and clinical course, delaying progress against the disease.

wastes,[21-24] but contradictory animal studies have stalled proper warnings and regulations.[25] Likewise, while the connection between alcohol consumption and cirrhosis is indisputable in humans, repeated efforts to produce cirrhosis by excessive alcohol ingestion have failed in all nonhuman animals except baboons, and even the baboon data is inconsistent.[26]

Many other important medical advances have been delayed because of misleading information derived from animal «models». The animal model of polio, for example, resulted in a misunderstanding of the mechanism of infection. Studies on monkeys falsely indicated that the polio virus was transmitted via a respiratory, rather than a digestive route.[27,28] This erroneous assumption resulted in misdirected preventive measures and delayed the development of tissue culture methodologies critical to the discovery of a vaccine.[29,30] While monkey cell cultures were later used for vaccine production, it was research with human cell cultures which first showed that the polio virus could be cultivated on non-neural tissue.[31] Similarly, development of surgery to replace clogged arteries with the patient's own veins was impeded by dog experiments which falsely indicated that veins could not be used.[32] Likewise, kidney transplants, quickly rejected in healthy dogs, were accepted for a much longer time in human patients.[33] We now know that kidney failure suppresses the immune system, which increases tolerance of foreign tissues.

Nevertheless, society continues to support animal experimentation, primarily because many people believe that it has been vital for most medical advances.[34] However, few question whether such research has been necessary or even beneficial to medical progress.

Contemporary Animal Experimentation

A. Selected Diseases

1. Cancer

In 1971 the National Cancer Act initiated a «War on Cancer» that many sponsors predicted would cure cancer by 1976. Instead, this multibillion dollar research program has proven to be a failure. The age-adjusted total cancer mortality rate climbed steadily for decades until the early 1990s,[35,36] when this rate started to fall slowly, due largely to reduced smoking.[37]

In order to encourage continued support for cancer research – now exceeding two billion dollars annually in the U.S. alone – researchers and administrators have misled the public. In 1987 the U.S. General Accounting Office (GAO) found that the statistics of the National Cancer Institute (NCI) «artificially inflate the amount of ‹true› progress», concluding that even simple five-year survival statistics were manipulated.[38] For one thing, the NCI termed five-year survival a «cure» even if the patient died of the cancer after the five-year period. Also, by ignoring well known statistical biases, the NCI falsely suggested advances had been made in the therapy of certain cancers.[38]

Commenting on the research program's discouraging results after 15 years, epidemiologist and program administrator John C. Bailar III stated in 1986: «[We] are losing the war against cancer. A shift in research emphasis, from research on treatment to research on prevention, seems necessary if substantial progress against cancer is to be forthcoming.»[39] In a review of cancer mortality more than a decade later, Bailar reiterated in 1997: «The more promising areas are in cancer prevention.»[35]

Why hasn't progress against cancer been commensurate with the effort (and money) invested? One explanation is the unwarranted preoccupation with animal research. Crucial genetic,[40] molecular,[41] immunologic[42] and cellular[43] differences between humans and other animals have prevented animal models from serving as effective means by which to seek a cancer cure. Mice are most commonly used, even though the industry's own *Lab Animal* magazine admits: «Mice are actually poor models of the

majority of human cancers.»[44] Leading cancer researcher Robert Weinberg has commented: «The preclinical [animal] models of human cancer, in large part, stink… Hundreds of millions of dollars are being wasted every year by drug companies using these models.»[45] According to Clifton Leaf, a cancer survivor himself: «If you want to understand where the War on Cancer has gone wrong, the mouse is a pretty good place to start.»[45]

2. AIDS

Despite their extensive use since the early 1980s, animal models have not contributed significantly to AIDS research. While mice, rabbits and monkeys born with severe combined immunodeficiency can be infected with the AIDS Virus (HIV), none develops the human AIDS syndrome.[46] Of over 150 chimpanzees infected with HIV since 1984, only one allegedly developed symptoms resembling those of AIDS.[47,48] Even AIDS researchers acknowledge that chimpanzees, as members of an endangered species who rarely develop an AIDS-like syndrome, are unlikely to prove useful as animal models for understanding the mechanism of infection or means of treatment.[49]

Other virus-induced immunodeficiency syndromes in nonhuman animals have been touted as valuable models of AIDS, but they differ markedly from AIDS in viral structure, disease symptoms and disease progression.[50] Animal experimenter Michael Wyand, discussing anti-AIDS therapy, has acknowledged: «Candidate antivirals have been screened using *in vitro* systems and those with acceptable safety profiles have gone directly into humans with little supportive efficacy data in any *in vivo* [animal] system. The reasons for this are complex but certainly include … the persistent view held by many that there is no predictive animal model for HIV infection in humans.»[51]

AIDS researcher Margaret Johnston has concurred: «HIV/AIDS [animal] models have not yielded a clear correlate of immunity nor given consistent results on the potential efficacy of various vaccine approaches.»[52] Indeed, since the first HIV vaccine clinical trial in humans in 1987, more than 100 clinical trials have been funded by the U.S. National Institute of Allergy and Infectious Diseases through mid-2006. Yet every one of the more than 50 preventive vaccines and more than 30 therapeutic vaccines that were successful against HIV/AIDS in primate studies has failed in human clinical trials.[53]

Human clinical investigation has isolated HIV, defined the disease's natural course and identified risk factors.[54] *In vitro* (cell and tissue culture) research using human white blood cells has identified both the efficacy and toxicity of anti-AIDS medicines, including AZT,[55] 3TC[56] and protease inhibitors.[57] Federal law, however, still mandates misleading and unreliable animal toxicity testing.

3. Psychology and Drug Abuse

Animal «models» in experimental psychology, which researchers traditionally subject to painful stimuli in order to study their behavior, have been strongly criticized in part because human psychological problems reflect familial, social and cultural factors that cannot be modeled in nonhumans.[58-63] Indeed, most psychologists disapprove of psychological animal experiments which cause animal suffering.[64]

Harry Harlow's «maternal deprivation» experiments in the 1950s and 1960s involved separating infant monkeys from their mothers at birth and rearing them in total isolation or with «surrogate» mothers made of wire and cloth. Their terror and subsequent psychopathology, Harlow claimed, demonstrated the importance of maternal contact. However, this had been shown conclusively in previous human studies.[65-68]

Despite their conceptual shallowness, numerous maternal deprivation studies continue, claiming relevance to human developmental psychology, psychopathology and even immune and hormone function.[67-69]

Experimental psychology continues to rely on painful research on animals, despite clinical psychologists' disregard for animal research literature. A review of two clinical psychology journals revealed that only 33 out of 4,425 citations (0.75 %) referred to animal-research studies.[70]

Animal models of alcohol and other drug addictions are similarly ill-conceived, failing to reflect crucial social, hereditary and mental factors. Pharmacologist Vincent Dole has acknowledged: «Some 60 years of offering alcohol to animals has produced no fun-

damental insights into the causes of this self-destructive behavior or even a convincing analogue of pathological drinking.»[71]

4. Genetic Diseases

Scientists have located the genetic defects of many inherited diseases, including cystic fibrosis and familial breast cancer. Trying to «model» these diseases in animals, researchers widely use animals – mostly mice – with spontaneous or laboratory-induced genetic defects. However, genetic diseases reflect interactions between the defective gene and other genes and the environment. Consequently, nearly all such models have failed to reproduce the essential features of the analogous human conditions.[72] For example, transgenic mice carrying the same defective gene as people with cystic fibrosis do not show the pancreatic blockages or lung infections that plague humans with the disease,[72] because mice and humans have different metabolic pathways.[73]

B. Toxicity Tests

Numerous standard animal toxicity tests have been widely criticized by clinicians and toxicologists. The lethal dose 50 (LD_{50}) test – which determines how much of a drug, chemical or household product is needed to kill 50 % of a group of test animals – requires 60 to 100 animals (usually rats and mice), most of whom endure great suffering. Because of difficulties extrapolating the results to humans, the test is highly unreliable.[74] Also, since such variables as an animal's age, sex, weight and strain can have a substantial effect on the results, laboratories often obtain widely disparate data with the same test substances.[75,76] *In vitro* tests have been validated to replace the LD_{50} test,[76-78] which was deleted from the test guidelines of the Organisation for Economic Cooperation and Development (OECD) in 2002.[79]

Results of the LD_{50} test are highly unreliable.

The Draize eye irritancy test, in which unanesthetized rabbits have irritant substances applied to their eyes, yields results that are inherently unreliable in predicting human toxicity.[80] Humans and rabbits differ in the structure of their eyelids and corneas, as well as in their ability to produce tears. Indeed, when comparing rabbit to human data on duration of eye inflammation after exposure to 14 household products, they differed by a factor of 18 to 250.[81] A battery of *in vitro* tests would be less expensive and likely far more accurate than the Draize test.[75,82]

Animal tests for cancer-causing substances, generally involving rodents, are also notoriously unreliable. When applied to human cancer causation, Lester Lave et al. found the false positive rate of rodent testing to be as high as 95 %.[83] The authors stated: «Tests for human carcinogens using lifetime rodent bioassays are expensive, time-consuming and give uncertain results.» The tremendous economic costs of such research have recently been reported in a study which examined over 500 rodent carcinogenicity studies and concluded that rodent cancer assays are scientifically invalid and fiscally indefensible.[84]

A combination of *in vitro* tests provides data that compares favorably with existing carcinogenicity databases and costs far less than animal tests.[85] In the late 1980s, the U.S. National Cancer Institute (NCI) developed a panel of 59 human cancer cell lines to screen compounds for anti-cancer activity, due to its «dissatisfaction with the performance of prior *in vivo* primary screens [animal cancer assays].»[86] This panel replaced animal testing at the NCI in 1990, by which time the agency had also adopted a panel of about 100 human cell lines to screen compounds for carcinogenicity.[87]

Animal tests for teratogens (drugs and chemicals that cause birth defects) are equally misleading and unreliable. Jarrod Bailey et al. conducted a comprehensive review of animal tests of 1,396 different substances and found that of those substances known to cause birth defects in humans, animal tests indicated that almost half were safe. Conversely, of those substances known to be safe in humans, animal tests indicated that almost half were danger-

ous. And almost one-third of all substances tested yielded varying results, depending on the species used.[88] In pregnant animals, differences in the physiological structure, function and biochemistry of the placenta aggravate the usual differences in the absorption, distribution, metabolism and excretion of drugs and chemicals that exist between species, thus making reliable predictions in pregnant women impossible.[88]

In vitro tests, such as the embryonic stem-cell test, the whole embryo culture, and the micromass test, provide data that are considerably more reliable and predictive and far less costly than animal teratogenicity tests. While such *in vitro* tests currently utilize cells and embryos derived from animals (thus rendering their extrapolation to humans difficult), advances in human cell culture technology should, in the future, permit a much closer *in vitro* approximation of teratogenesis in humans.[88]

C. Medical Education

Animal laboratories are not necessary for teaching biological and medical principles and skills to medical students, and 85 % of U.S. and Canadian medical schools have eliminated animal labs from their educational curricula.[89] Effective alternative teaching methods include lectures and written course materials, videos and interactive virtual reality programs, mentored patient care encounters and surgery participation, and lifelike programmable interactive patient simulators. Comparative studies of simulation technologies for many aspects of medical education (e.g. anatomy, physiology, pharmacology, surgical skills, trauma management and invasive procedures) have repeatedly demonstrated superior training outcomes, fewer patient complications, greater trainee acceptance, and more efficient use of educational time and resources.[90-99]

Further evidence of the emerging primacy of simulation-based medical education is the American College of Surgeons' (ACS) endorsement and implementation of the TraumaMan® simulator to replace the use of animals and human cadavers for its Advanced Trauma Life Support (ATLS) program. Furthermore, in 2006 the ACS implemented a sweeping educational reform that incorporated a wide variety of simulators to eliminate animal use in its own conferences and educational programs, in addition to establishing the Accredited Education Institutes program to achieve the same goal in surgery training programs.[100]

Scientific Limitations of Animal Models

Animal studies can neither confirm nor refute hypotheses about human physiology or pathology; human clinical investigation is the only way such hypotheses can be tested. At best, animal experiments can suggest new hypotheses that might be relevant to humans.[101,102] However, there are countless other, far superior ways to derive new hypotheses.[2,101]

How valuable is animal experimentation? The Medical Research Modernization Committee's review of ten randomly chosen animal models of human diseases did not reveal any important contributions to human health.[103] Although the artificially induced conditions in animals were given names analogous to the human diseases they were intended to simulate, they differed substantially from their human «counterparts» in both cause and clinical course. Also, the study found that treatments effective in animals tended to have poor efficacy or excessive side effects in human patients.[103] Indeed, when MRMC physicians evaluate specific animal-research projects, they consistently find them to be of little, if any, relevance to the understanding or treatment of human diseases.[104-110]

MRMC's reviews have revealed that, because animal models differ from human diseases, researchers tend to investigate those aspects of the animal's condition that resemble features of the human disease, generally ignoring or discounting fundamental anatomical, physiological and pathological differences. Because most disease processes have system-wide effects and involve many interacting factors, focusing on only one aspect of a disease belies the actual complexity of biological organisms.

In contrast to human clinical investigation, animal experimentation involves manipulations of artificially induced conditions. Furthermore, the highly unnatural laboratory environment invariably stresses the animals, and stress affects the entire organism by altering pulse, blood pressure, hormone levels, immunological activities and a myriad of other functions.[111,112] Indeed, many laboratory «discoveries» reflect mere laboratory artifact.[10,113-119]

For example, artifact from unnaturally induced strokes in animals has repeatedly misled researchers.[117,120] Macleod et al. reported on over 4,000 studies demonstrating efficacy for more than 700 drugs in animal models of stroke.[121] About 150 drugs subsequently tested in human clinical trials failed to show any benefit.[122] Only recombinant human tissue plasminogen activator (rt-PA) administered within three hours of stroke onset has proven beneficial in reducing symptoms, but it was associated with ten times as many intracerebral hemorrhages and did not increase survival.[123] David Wiebers et al. have concluded: «Ultimately, the answers to many of our questions regarding the underlying pathophysiology and treatment of stroke do not lie with continued attempts to model the human situation more perfectly in animals, but rather with the development of techniques to enable the study of more basic metabolism, pathophysiology and anatomical imaging detail in living humans.»[117]

Since 1990, several hundred gene therapies that were successful in animal studies have been tested on thousands of patients worldwide. Yet only one gene therapy, for children with the severe immune system disorder X-SCID, appears to have succeeded. Of the ten successfully treated children, however, three developed leukemia and one of them died of it – a side effect that animal experiments failed to predict and that prompted the U.S. Food and Drug Administration (FDA) to halt several gene therapy trials in 2005.[124,125] Similarly, a highly touted gene therapy that cured dogs of hemophilia was discontinued in 2004 due to «safety problems … in the human trial that weren't predicted in animal studies», including liver damage.[126,127]

Animal tests are frequently misleading.[128] Milrinone increased survival of rats with artificially induced heart failure, but humans taking this drug experienced a 30 % increase in mortality.[129] Fialuridine appeared safe in animal tests, but it caused liver failure in 7 out of 15 humans taking the drug, five of whom died and two of whom required a liver transplantation.[130] Animal studies failed to predict the dangerous heart valve abnormalities in humans caused by the diet drugs fenfluramine and dexfenfluramine.[131]

Hormone replacement therapy increased women's risk of heart disease, breast cancer and stroke, but experiments with mice, rabbits, pigs and monkeys had predicted the opposite effect.[132] The widely prescribed arthritis painkiller Vioxx appeared safe and even beneficial to the heart in animal tests, but was withdrawn from the global market in 2004 after causing an estimated 320,000 heart attacks, strokes and cases of heart failure worldwide – 140,000 of them fatal.[133] David Graham, the Associate Director for Science and Medicine in the Office of Drug Safety at the FDA, described Vioxx as the «single greatest drug safety catastrophe in the history of this country or the history of the world».[134] Animal tests also failed to predict the cases of partial or total blindness suffered by some men taking the popular impotence drug Viagra.[135,136] Despite mandatory, extensive animal testing, adverse drug reactions remain the fifth leading cause of mortality in the United States, accounting for more than 100,000 deaths per year.[137]

In London in March 2006, a new anti-inflammatory drug called TGN1412 caused devastating reactions including multiple organ failure in all six volunteers in phase 1 clinical trials, despite «proof of safety» established by tests on monkeys who were given 500 times the human dose. Many commentators noted that the animal tests provided a false sense of security. The incident prompted calls for an overhaul of drug safety testing requirements and clinical trial design.[138]

In animal tests to evaluate the carcinogenicity of the artificial sweetener saccharin, the weight-adjusted daily saccharin dose given to rats was equivalent to a human consuming about 1,100 cans of soda containing saccharin. Such massive dosing alone can result in cancers, regardless of a compound's actual carcinogenicity at typical human exposure levels.[116] Extrapolating such data to humans is further complicated by the observation that saccharin-induced bladder cancers occurred only in male rats. It was later found that male rats possess a protein in greater quantity than female rats (and lacking in humans) that interacted with saccharin to form irritating crystals in the male rats' bladders, causing cancer. The fact that some rats developed cancers did not (and cannot) clarify whether or not saccharin causes cancer in humans.[139]

Similarly, despite almost 40 years of human consumption, its use in more than 9,000 food and beverage products worldwide, and the irrelevance of animal tests to humans, the artificial sweetener

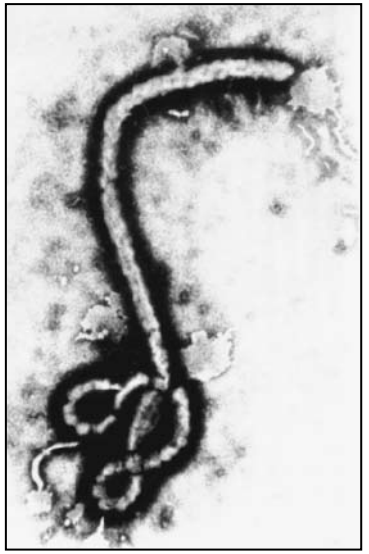
aspartame is still being tested on animals, and regulatory authorities continue to evaluate the results of such studies. Most recently, an Italian study carried out in 2005 on 1,800 rats demonstrated an increased risk for lymphomas and leukemias in rats fed aspartame – but only in females.[140] A subsequent NCI epidemiological study involving 340,045 men and 226,945 women and reported on at the 2006 meeting of the American Association for Cancer Research refuted the findings in rats.[141] So, despite male rats getting bladder cancers from saccharin and female rats getting lymphomas and leukemias from aspartame, no cancer risk from either sweetener has been found for humans of either sex.

Scientists recognize that, even between humans, gender, ethnicity, age and health can profoundly influence drug effects.[142,143] Perhaps the most striking example of the specificity of drug effects comes from the demonstration that even human monozygotic twins display different drug responses and that these become more disparate as the twins age.[144] Obviously, extrapolating data between species is much more hazardous than within a species. Indeed, according to the FDA, a staggering 92 % of all drugs found safe and therapeutically effective in animal tests fail during human clinical trials due to their toxicity and/or inefficacy, and are therefore not approved.[145-147] Furthermore, over half of the mere 8 % of drugs which do gain FDA approval must later be withdrawn or relabeled due to severe, unexpected side effects.[148]

Risks of Animal Experimentation

In addition to squandering scarce resources and providing misleading results, animal experimentation poses real risks to humans. The mind-set that scientific knowledge justifies and requires harming innocent individuals endangers all who are vulnerable. Even after Nazi and Japanese experiments on prisoners horrified the world, American researchers denied African-American men syphilis treatment in order to assess the disease's natural progression,[149] they deliberately exposed students and minorities to toxic chemicals in order to determine safe levels of exposure to pesticides,[150] they intentionally exposed thousands of unsuspecting civilians to lethal bacteria in order to test biological warfare,[151] they injected cancer cells into nursing home patients,[149] subjected unwitting patients to dangerous radiation experiments,[152] and, despite no chance of success, transplanted nonhuman primate and pig organs into children, as well as chronically ill and impoverished people.[153] Psychiatrist Robert Jay Lifton argues that this «science at any cost» mentality may have provided medical justification for the Holocaust.[154]

Furthermore, through animal research, humans have been exposed to a wide variety of deadly nonhuman primate viruses. About 16 laboratory workers have been killed by the Marburg virus and other monkey viruses, and two outbreaks of Ebola have occurred in American monkey colonies.[155-157] Polio vaccines grown on monkey kidney cells exposed millions of Americans to the simian virus 40, which causes human cells to undergo malignant transformation *in vitro* and has been found in several human cancers.[158] Ignoring the obvious public health hazards, researchers transplanted baboon bone marrow cells into an AIDS patient. The experiment was unsuccessful;[159] moreover, a large number of baboon viruses, which the patient could have spread to other people, may have accompanied the bone marrow. Indeed, animal experimentation may have started the AIDS epidemic. HIV-1, the principal AIDS virus, differs markedly from all other viruses found in nature, and there is evidence that it originated either through polio vaccine production using monkey tissues[160,161] or through manufacture in American laboratories, where HIV-like viruses were being produced by cancer and biological weapons researchers in the early 1970s.[162]



Human exposure to animal tissues from xenotransplants could unleash epidemics from deadly viruses like Ebola.

Failing to learn from the AIDS epidemic, many policy makers and industrial interest groups support animal-to-human organ transplants (from pigs and primates) known as xenotransplants. These have failed in the past and will most likely continue to fail because of tissue rejection, the impossibility of testing animal tissues for unknown pathogens, and the prohibitive expense.[163-165]

Similarly, the rapidly expanding field of genetic engineering includes adding genetic material to animals' cells to change the animals' growth patterns or induce the animals to produce human proteins in their milk, meat or urine. Harvesting such proteins poses serious human health risks, such as exposure to pathogens (viruses, prions and other microorganisms)[166,167] or the development of malignancies,[168,169] allergic reactions[170] or antibiotic resistance.[171] These concerns contributed to the European Union's ban on rBGH, a genetically engineered bovine growth hormone that increases cows' milk production.[172]

The Importance of Clinical Research

Typically, medical discovery begins with a clinical observation,[9,10] which animal experimenters then try to mimic with artificially induced conditions in laboratory animals.[7] These researchers tend to highlight animal data that agrees with the previous clinical finding, while discounting or ignoring conflicting animal data (which is usually voluminous). Although animal experimentation advocates routinely take credit for discoveries that actually occurred in a clinical context,[7] many clinicians have recognized the primary role of human-based clinical research. Reviewing the history of hepatitis, physician Paul Beeson concluded: «Progress in the understanding and management of human disease must begin, and end, with studies of man… Hepatitis, although an almost ‹pure› example of progress by the study of man, is by no means unusual; in fact, it is more nearly the rule. To cite other examples: appendicitis, rheumatic fever, typhoid fever, ulcerative colitis and hyperparathyroidism.»[11]

Similarly, key discoveries in immunology,[12] anesthesiology,[13] first aid,[173] alcoholism[71,174] and psychopharmacology[175,176] were based primarily on human clinical research and investigation.

Furthermore, clinical research is the only means by which effective public health education and prevention programs can be developed and evaluated.

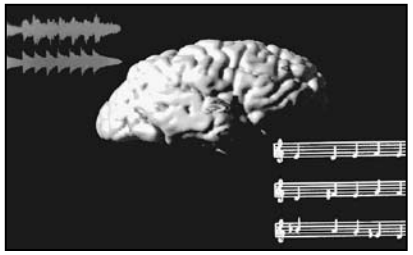
Nonanimal Methods

In science, there are always many ways to address a given question. Animal experimentation is generally less efficient and reliable than many nonanimal methods, which include:

1. Epidemiology (Human Population Studies)
Medical research has always sought to identify the underlying causes of human disease in order to develop effective preventive and therapeutic measures. In contrast to artificial animal model conditions that generally differ in causes and mechanisms from human conditions, human population studies have been very fruitful. For example, the identification of the major risk factors for coronary heart disease, such as smoking, elevated cholesterol and high blood pressure, which are so important for prevention techniques, derives from epidemiological studies.[177] Similarly, population studies have shown that prolonged cigarette smoking from early adult life triples age-specific mortality rates, but cessation at the age of 50 reduces the danger by half, and cessation at the age of 30 eliminates the danger almost completely.[178]

Epidemiology's potential is illustrated by the growing field of molecular epidemiology. Researchers can analyze cellular and molecular characteristics of those suffering from cancer or birth defects, thereby elucidating the mechanisms and causes of DNA damage and yielding effective prevention and treatment approaches.[179]

2. Studies on Patients
The main source of medical knowledge has always been the direct study of human disease by closely monitoring human patients. For example, cardiologist Dean Ornish has demonstrated that a low-fat vegetarian diet, regular exercise, smoking cessation and stress management can reverse heart disease.[180] Similarly, Caldwell Esselstyn has shown that lowering cholesterol levels with plant-



Positron emission tomography (PET) scans can identify areas of the brain functioning under different circumstances, in this case when the subject hears familiar music.

based diets and medicines as needed arrests and often reverses heart disease.[181] Henry Heimlich has relied exclusively on human clinical investigation to develop techniques and operations that have saved thousands of lives, including the Heimlich maneuver for choking and drowning victims, the Heimlich operation to replace the esophagus (throat tube), and the Heimlich chest drainage valve.[173,182]

Modern noninvasive imaging devices such as CAT, MRI, PET and SPECT scans have revolutionized clinical investigation.[183-186] These devices permit the ongoing evaluation of human disease in living human patients and have contributed greatly to medical knowledge.

3. Autopsies and Biopsies

The autopsy rate in the United States and Europe has been falling steadily, much to the dismay of clinical investigators who recognize the value of this traditional research tool.[187,188] Autopsies have been crucial to our current understanding of many diseases, e.g. heart disease,[187] appendicitis,[187] diabetes[189,190] and Alzheimer's disease.[104] Although the usefulness of autopsies is generally limited to the disease's lethal stage, biopsies can provide information about other disease stages. Diagnostic needle and endoscopic biopsies often permit safe procurement of human tissues from living patients. For example, endoscopic biopsies have demonstrated that colon cancers derive from benign tumors called adenomas. In contrast, colon cancers in a leading animal model appear to lack this adenoma-to-carcinoma sequence.[191,192] Small skin biopsies (with intact capillaries) can be used as a tool before or during clinical trials of new drugs and could have revealed the cardiovascular risks of Vioxx, for example, before it was marketed.[193]

4. Post-Marketing Surveillance

Thanks to advances in computer techniques, it is now possible to keep detailed and comprehensive records of drug side effects.[194] A central database with such information, derived from post-marketing surveillance, enables rapid identification of dangerous drugs.[195] Such a data system would also increase the likelihood that unexpected beneficial side effects of drugs would be recognized. Indeed, the anti-cancer properties of such medications as prednisone,[196] nitrogen mustard[197] and actinomycin D;[198] chlorpromazine's tranquilizing effect;[199] and the mood-elevating effect of MAO-inhibitors[200] and tricyclic antidepressants[201] were all discovered through clinical observation of side effects.

5. Other Nonanimal Methods

Between the mid-1950s and mid-1980s, the NCI screened 400,000 chemicals as possible anti-cancer agents, mostly on mice who had been infected with mouse leukemia.[202] The few compounds that were effective against mouse leukemia had little effect on the major human cancer killers.[203] More recently, researchers have favored grafting human cancers onto animals with impaired immune systems that do not reject grafts. However, few drugs found promising in these models have been clinically effective, and drugs with known effectiveness in humans often fail to show efficacy in these models.[204]

By contrast, *in vitro* cell and tissue cultures have proven to be powerful investigative tools. The NCI has now switched to 60 *in vitro* human cancer cell lines, a more reliable and much less costly alternative.[205] Similarly, *in vitro* tests using cells with human DNA can detect DNA damage much more readily than animal tests.[206]

New drugs can be tested in human tissues. This could have predicted the catastrophic reaction to the drug TGN1412 in the clinical trial in London in 2006.[138] Companies such as Biopta and Asterand work exclusively with human tissue because, contrary to animal tissue, the results obtained can be directly extrapolated to humans.[207]

Regarding vaccines, researchers discovered already in 1949 that vaccines made from human tissue cultures not only were

more effective, safer and less expensive than vaccines produced from monkey tissue,[208,209] but also completely eliminated the serious danger of contamination with animal viruses.[210] Likewise, many animal tests for viral vaccine safety have been replaced by far more sensitive and reliable cell culture techniques.[211,212]

Microfluidic circuits provide the nearest thing to a human body on a chip. They comprise tiny channels with cells from various human organs and are linked by a circulating blood substitute. Using these circuits, new drugs can be tested on a «whole system», where they encounter human cells in the same order as they would encounter them in the human body. Sensors in the chip then feed back information for computer analysis. Microfluidic circuits promise to deliver, early in the preclinical phase, data of dramatically improved predictive relevancy to the human organism.[213]

Computer modeling is now so sophisticated that scientists can simulate *in silico* in minutes or hours experiments that would take months or years to perform in animals. Drugs can be rationally designed on computers and then tested on virtual organs or in virtual clinical trials. Research teams around the world are working on a «virtual human» which will predict human responses more accurately than would ever be possible with any animal model.[214]

Microdosing is a tremendously exciting breakthrough in drug development based on the principle that the best model for man is man. Human microdosing relies on ultra-sensitive analytical techniques and permits the safe introduction of miniscule doses (amounting to only 1 % of the normal full dose) of new drugs into subjects in order to evaluate drug activity in the human body. The technique has proven quite accurate, with the results from microdosing studies showing a 70 % correspondence with those from full-dose studies.[215] Microdosing should replace misleading, unreliable animal testing and become part of phase 0 preclinical trials for every drug. Both the FDA and the European Agency for the Evaluation of Medicinal Products have endorsed the use of microdosing to accelerate and improve the safety of drug development.[216]

Why Animal Experimentation Persists

If animal experimentation is so flawed, why does it persist? There are several likely explanations.

1. For the chemical and pharmaceutical industries, animal experiments provide an important legal sanctuary. In cases of death or disability caused by chemical products or adverse drug reactions, the responsible companies claim due diligence by pointing out that they performed the legally prescribed «safety tests» on animals and are therefore not accountable. As a result, the victims or their families most often come away empty-handed after suing for damages.[14]

2. Animal experimentation is easily published. In the «publish or perish» world of academic science, it requires little originality or insight to take an already well-defined animal model, change a variable or the species being used, and obtain «new» and «interesting» findings within a short period of time. In contrast, clinical research, while directly applicable to humans, is more difficult, expensive and time-consuming. In addition, the many species available and the nearly infinite possible manipulations offer researchers the opportunity to «prove» almost any theory that serves their economic, professional or political needs. For example, researchers have «proven» in animals that cigarettes both do and do not cause cancer – depending on the funding source.[217,218]

3. Animal experimentation is self-perpetuating. Scientists' salaries and professional status are often tied to grants, and a critical element of success in grant applications is proof of prior experience and expertise. Researchers trained in animal experimentation techniques find it difficult or inconvenient to adopt new methods such as tissue cultures.

4. Animal experimentation is lucrative. Its traditionally respected place in modern medicine results in secure financial support, which is often an integral component of a university's budget. Many medical centers receive several hundred million dollars annually in direct grants for animal research, and an average of over 40 % more for overhead costs that are supposedly related to that research. Since many medical centers faced with declin-

ing clinical revenues depend on this financial windfall for much of their administrative costs, construction and building maintenance, they perpetuate animal experimentation by praising it in the media and to legislators.

5. Animal experimentation appears more «scientific» than clinical research. Researchers often assert that laboratory experiments are «controlled» because they can change one variable at a time. This control, however, is illusory. Any animal model differs in myriad ways from human physiology and pathology. In addition, the laboratory setting itself creates confounding variables – for example, stress and undesired or unrecognized pathology in the animals. Such variables can have system-wide effects, skew experimental results, and undermine extrapolation of findings to humans.

6. The morality of animal experimentation is rarely questioned by researchers, who generally choose to defend the practice dogmatically, rather than confront the obvious moral issues it raises.[219-222] Animal experimenters' language betrays their efforts to avoid morality. For example, they «sacrifice» animals rather than kill them, and they may note animal «distress», but they rarely acknowledge pain or other suffering.[223] Young scientists quickly learn to adopt such a mind-set from their superiors, as sociologist Arnold Arluke explains: «One message – almost a warning – that newcomers got was that it was controversial or risky to admit to having ethical concerns, because to do so was tantamount to admitting that there really was something morally wrong with animal experimentation, thereby giving ‹ammunition to the enemy›.»[223] Physician E. J. Moore also observes: «Sadly, young doctors must say nothing, at least in public, about the abuse of laboratory animals, for fear of jeopardizing their career prospects.»[224]

Evidence indicates that many animal experimenters fail to acknowledge – or even perceive – animal pain and suffering. For example, sociologist Mary Phillips observed animal experimenters kill rats in acute toxicity tests, induce cancer in rodents, subject animals to major surgery with no postoperative analgesia, and perform numerous other painful procedures without administering anesthesia or analgesia to the animals. Nevertheless, in their annual reports to the U.S. Department of Agriculture (USDA), none of the researchers acknowledged that any animals had experienced unrelieved pain or distress.[225] Phillips reported: «Over and over, researchers assured me that in their laboratories, animals were never hurt… ‹Pain› meant the acute pain of surgery on conscious animals, and almost nothing else… [When I asked] about psychological or emotional suffering, many researchers were at a loss to answer.»[225]

Similarly, a study published in the *British Medical Journal* found that Canadian neurologists who spent a year of their training experimenting on animals «had so hardened themselves to animal suffering that they were no longer capable of recognizing suffering in their patients for quite a while after returning to clinical work».[226]

Animal experimenters' ethical defense of the practice has been superficial and self-serving. Usually, they simply point to the supposed human benefits and argue that the ends justify the means,[227,228] though they rarely substantiate their claims with scientific evidence.[229] Often, they add that nonhuman animals are «inferior», lacking certain attributes compared to humans, such as intelligence, family structure, social bonding, communication skills and altruism. However, numerous nonhuman animals – among them rats, pigs, dogs, monkeys and great apes – reason and/or display altruism. There is accumulating evidence that many animals ex-

Many nonhuman animals demonstrate that their emotions and thoughts closely resemble those of humans.

perience the same range of emotions as humans.[230-232] For example, mice have been shown to exhibit empathy with cage mates suffering pain.[233] Chimpanzees and gorillas can be taught human sign language and to communicate with one another using signs even without humans being present.[234,235]

The general public, which cares about animal welfare, has been led to believe that animals rarely suffer in laboratories. Animal experimenters often cite USDA statistics (derived from researchers themselves) which claim that only 6-8 % of animals used in animal experimentation experience pain unrelieved by anesthesia or analgesia.[236] However, mice, rats and birds, who in the United States constitute over 90 % of all animals used in animal experimentation, receive absolutely no protection from the Animal Welfare Act.[237]

The general public is clearly uneasy about animal experimentation. In a 2006 poll in the United Kingdom, for example, 51 % of nearly one million voters said they are not in favor of animal testing.[238] Since medical research is conducted for the benefit of the public and is financed largely with their taxes and charitable donations, their concerns should be respected and addressed.

The tens of millions of animals used and killed each year in American laboratories generally suffer enormously, often from fear and physical pain, and nearly always from the deprivation inflicted by their confinement which denies their most basic psychological and physical needs.

Conclusion

The value of animal experimentation has been grossly exaggerated by those with a vested economic interest in its preservation. Because animal experimentation focuses on artificially created pathology, involves confounding variables, and is undermined by differences between human and nonhuman anatomy, physiology and pathology, it is an inherently unsound method to investigate human disease processes. The billions of dollars invested annually in animal experimentation would be put to much more efficient, effective and humane use if redirected to clinical and epidemiological research and public health programs.

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