PLANNING APPEAL
BY UNIVERSITY OF CAMBRIDGE

PROPOSED PRIMATE RESEARCH FACILITY

307 Huntingdon Road, Girton, Cambridge

PLANNING INSPECTORATE REFERENCE

APP/WO530/A/02/1090108

PROOF OF EVIDENCE

By Dr Ray Greek MD
On Behalf of Animal Aid,
National Anti-Vivisection Society,
Naturewatch, PeTA,
Uncaged & X-CAPE

LOCAL INQUIRY

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Biography

Dr. Ray Greek is a physician who is board certified in anaesthesiology and sub-specialty certified in pain management. He is a graduate of the University of Alabama School of Medicine and completed his residency at the University of Wisconsin at Madison. He has taught anaesthesiology at the University of Wisconsin and Thomas Jefferson University in Philadelphia. He has published in the lay and medical literature and performed experiments on animals and research with humans.

Dr. Greek has co-written, with his wife - veterinarian Dr Jean Greek DVM* - two books on the scientific fallacy of attempting to extrapolate the results of animal experiments to humans. Jane Goodall wrote the foreword to the first, Sacred Cows and Golden Geese: The Human Cost of Experiments on Animals (Continuum 2000). Their interest in the subject arose from a series of discussions in which it became clear to them that a course of treatment that cured one of Dr Jean Greek's animal patients would often fail in humans, and vice-versa.

This led the Drs. Greek to spend a decade studying comparative anatomy and physiology, reviewing treatment notes, and perusing scientific literature as well as medical history books. Jean's expertise in animal anatomy, physiology and biochemistry, combined with Ray's expertise in the same for humans, allowed this husband/wife team to examine the similarities and differences between the species with greater depth. The publication of Sacred Cows and Golden Geese was followed by Specious Science:How Genetics and Evolution Reveal Why Medical Research on Animals Harms Humans, (Continuum International Pub 2002). Both books focus solely on the science of this hotly debated topic.

Drs. Greek have shown not only that animal experiments are unnecessary, but also that they have resulted in both direct and indirect harm to humans. Thus these expensive and unreliable animal models have been harmful and have produced nothing that could not have been accomplished via other methods. Drs. Greek effectively argue that the money currently going to fund animal experiments should be designated for other historically more productive and scientific means of health/biomedical research.

Dr. Ray Greek is president of Americans For Medical Advancement, a not-for-profit organisation dedicated to educating the public about the hazards of extrapolating the results of experiments on animal models to humans. He is also Medical Director, Europeans For Medical Advancement. Dr Greek lectures frequently and has testified before regulatory bodies in the US and abroad.

(*Dr Jean Greek completed veterinary school at the University of Wisconsin-Madison, an internship at the University Tennessee, and a dermatology residency at the University Pennsylvania, then taught at the University of Missouri as a boarded veterinary dermatologist, one of less than 200 in the world.)

Introduction

1. Experimenting on nonhuman primates in the hope of curing human neurological diseases is an exercise in futility. At first glance, this may seem counter-intuitive, as we all know how closely related we are to our nonhuman primate "cousins". That we share 98.5% of our genes with chimpanzees has been known for years, though the original author of that figure has now revised his estimate to approximately 94.5%. Even so, that is an awful lot of similarity and has led us to believe that laboratory experiments on chimpanzees, monkeys and other nonhuman primates provide results reliable enough to be extrapolated to humans. So let's compare the track record of research on primates with what actually happens in humans.

2. Heart disease is the leading killer in the western world, but while monkeys, chimpanzees and gorillas have all been studied, none has been found to form atherosclerotic plaques like humans. Primate research on cancer, the second leading cause of death in humans, and stroke, the third, has failed to yield insights about the human diseases or drugs to treat them.

3. Primates have been very disappointing with regard to their ability to predict dangerous side effects of medications, especially pertaining to the induction of birth defects. Aspirin produces birth defects in primates, but not babies. Almost all currently used medications cause birth defects in some animal species. PCP, better known as angel dust, sedates chimpanzees but causes humans to have severe experiences including paranoia. Nitrobenzene is toxic to humans but not monkeys. Isoprenaline (isoproterenol) doses were worked out on animals, but proved too high for humans. People died as a result. Even when the researchers knew what to look for they were unable to reproduce this effect in monkeys. Carbenoxalone caused people to retain water to the point of heart failure. Scientists retrospectively tested it on monkeys, but could not reproduce this effect. Flosint, an arthritis medication, was tested on monkeys, who tolerated the medication well. In humans, however, it caused deaths. Amrinone, a medication used for heart failure, was tested on numerous nonhuman primates. Humans haemorrhaged, as the drug caused their blood cells

responsible for clotting to fail. This side effect occurred in a startling 20% of patients taking the medication on a long-term basis. Opren killed 61 people. Over 3,500 cases of severe reactions have been documented. Opren was tested on monkeys without problems.

4. What about infectious diseases? Are we able to draw results from primates about viruses? Chimpanzees harbour Hepatitis B asymptomatically. Humans die from it. Vaccines for polio and rabies were tested safe in primates but killed humans. Even the inventor of the polio vaccine, Dr. Sabin, stated under oath that the polio vaccine was long delayed because of misleading results in primates. AIDS researchers have fared no better. The huge number of differences between the immune system of humans and nonhuman primates invalidates any experimental results. Dr. Mark Feinberg, a leading HIV/AIDS researcher stated: *"What good does it do you to test something [a vaccine] in a monkey? You find five or six years from now that it works in the monkey, and then you test it in humans and you realise that humans behave totally differently from monkeys, so you've wasted five years."* Monkeys do not die of AIDS. Humans do.

5. Our blood typing system bears testament to the fallacy of extrapolating monkey research to man. The Rh factor in human blood was named after rhesus monkeys. Later research in humans showed that the factors in man and monkey were quite different. The mistake was so ingrained in medical lore by that time, that it was decided not to bother to change the name!

6. But perhaps the most ridiculous research is that of drug addiction. To take nonhuman primates out of their natural environment, addict them to a substance they would never have otherwise come in contact with and expect to learn the psychological and physiological reasons why a human abuses crack cocaine is ludicrous. The Committee on Animals in Biomedical Research has stated "It is impossible to reproduce human cocaine abuse in the laboratory - nonhuman primate or human - because drug use reflects psychological factors that do not have laboratory correlates, such as drug cost, drug purity, drug availability, drug mixtures, the setting, users' physical health, and others." State University of New York scientist Diana Dow-Edwards states, "Of course, due to the complex nature of cocaine's

pharmacology, there is no perfect animal model. It is virtually impossible to perfectly model human development in anything other than a human being…Within the animal literature, all in all, there is a low level of demonstrated reproducibility…no two studies have found the same effects." Perhaps we should take the money out of the laboratory and use it to study the many humans who are addicted.

7. Recent experiments in squirrel monkeys and baboons led to headline pronouncements that "ecstasy" (3,4-Methylenedioxymethamphetamine (MDMA)) can cause Parkinson's disease. Yet only two imaging studies of human ecstasy users have been conducted, and no corresponding damage was found. Incredibly, only one neuroscientist has analysed the brain of a chronic ecstasy user after death – again, there was no correlation with the primate research. This is yet another clear illustration of the misdirection of research priorities into animal studies at the expense of proper clinical investigation.

8. Before we explain why research on primates is not in the best interest of humans suffering from diseases of the brain, we need to explain the theory that supports our more general position that animal models of human disease are archaic and dangerous to humans.

Theory

9. In the old days, animal models appeared to be viable for two reasons: First, when so little was known about human physiology and disease, discovering something in a dog or monkey did, at times, translate to humans. (Of course animal models were not adequate even back then when so little was known. In the first half of the twentieth century, animal models led to the notions that smoking was safe and cholesterol good for the heart. Probably no two mistakes have cost as many lives.)

10. Second, some scientists believed doing something to combat disease, such as experimenting on animals, was preferable to doing nothing. Epidemiology, statistics, cell cultures, indeed all of science, was in its infancy. Clinical research was limited due to the lack of basic scientific knowledge about human disease. Artificial

neural nets (a technology involving computer programmes that "learn" is being used to, among other things, read mammograms and pap smears, analyze data, aid in basic and clinical research) were not even thought of. The art of statistical analysis was just emerging. Technology was rudimentary. Mathematical modelling was unheard of, as was the human genome project, MRI and PET scanners, computer-aided drug design, and pharmacogenomics. We acknowledge that many discoveries of the 1600s to early 1900s involved animals. However, even in retrospect, there are doubts as to whether animal experimentation did more good than harm. History has revealed that time could have been better used by studying the basic sciences, by perfecting *in vitro* research, and by discovering and advancing the technology and methods that have proven so beneficial today. But hindsight is 20/20.

11. Today, thanks to those technologies, we are beyond the level of superficial similarities and are now studying disease at the genetic or molecular level. It is at this level that a monkey becomes a monkey and a human, a human. Does the practice of using primates or other animals as models, *today*, do more harm than good? Consider the following:

- Countless treatments for stroke have been developed in primates and other animals – yet all of them have failed or even harmed patients in clinical trials.[1]
- Of twenty-two drugs developed on animals as therapeutic in spinal cord injuries, none has worked in humans.
- Parkinson's Disease becomes progressively worse in patients, while the artificially induced primate version demonstrates gradual recovery.
- There is no successful animal model of Alzheimer's Disease.
- Human stroke patients often take years to recover *any* use of their affected limbs, while marmosets were able to run, climb, swing and jump almost as normal just three weeks following induced stroke during experiments at Cambridge University.
- To give just two quantitative examples, and to demonstrate our theory that small differences on the genetic level mean we can no longer use animals of *any* species to model humans, we turn to cancer research: Of 20 compounds known *not* to cause cancer in humans, 19 *did* cause cancer in animals[2] while

of 19 compounds known to cause oral cancer in humans only 7 caused cancer in mice and rats using a standard National Cancer Institute (NCI) protocol.[3]

- The National Cancer Institute (NCI) tested 12 anti-cancer drugs, currently used successfully in humans, on mice. The scientists took mice that were growing 48 different kinds of *human* cancers and treated them with the 12 drugs. They found that 30 out of 48 times the drugs were ineffective in the mice. In other words, 63% of the time the mouse models, even with human tumours were wrong.[4]

12. Clearly the empirical data for the animal model is not promising. The theory of evolutionary biology lies at the core of our argument that animal models – the primate model included - of human disease are scientifically untenable. Although animal models may appear feasible when first viewed, closer examination of the differences between animals and humans reveals the shortcomings in the concept.

13. One way of speaking about the results of evolutionary biology is to categorize life forms into groups known as species. *Homo sapiens* will have characteristics that are unique to it, but it will also have characteristics that it shares with other species, like *Drosophila melanogaster* (fruit flies) or *Pan troglodytes* (chimpanzees). With the advent of molecular biology, we have learned that what each member of the species in question will have in common with the others is, in part, a collection of genes. However, while different species may have many of the same genes, the way the genes are regulated and interact will be different. All mammals are derived from a common ancestor, and so it is not surprising that we all share certain characteristics; neither is it surprising that each species is unique. The questions modern-day researchers must ask are ‘do the similarities outweigh the differences?’ and ‘Can we extrapolate the results of an experiment on one species to a different species?’ There is evidence that we can. For instance, all mammals have hearts, lungs and immune systems. We all share the same cell types and tissues. But there is also evidence to the contrary. We have examined some of the empirical data that reveals that the results obtained from the use of primate models are not applicable to humans, so now we will examine the theory that predicts that such *should be* the case.

14. Living organisms share biochemical systems and are subject to the same laws of physics, therefore it should not be surprising that they share common structures and biochemical reactions. However, out of all this commonality has evolved very different life forms: bacteria, humans, yeasts and so forth. One reason for the differences between species lies within the genes. Genes can be divided into *structural* and *regulatory* genes. The structural genes are responsible for the similarities. They are responsible for building the proteins of which an organism is made. The regulatory genes turn the structural genes on and off thus affecting the development of the embryo and the physiology of the organism. They account for most of the differences between species. Hugh LaFollette and Niall Shanks state that understanding the role of regulatory genes in evolution is "crucial to a proper understanding of biological phenomena. First, they focus our attention not merely on structural similarities and differences between organisms but also on the similarities and differences in regulatory mechanisms. Second, they illustrate an important fact about complex, evolved animal systems: *very small differences between them can be of enormous biological significance. Profound differences between species need not indicate any large quantitative genetic differences between them. Instead, even very small differences, allowed to propagate in developmental time, can have dramatic morphological and physiological consequences*." (Emphasis added)

15. Lewis Wolpert continues this theme in *The Triumph of the Embryo*:

> Compare one's body to that of a chimpanzee—there are many similarities. Look, for example, at its arms or legs, which have rather different proportion to our own, but are basically the same. If we look at the internal organs, there is not much to distinguish a chimpanzee's heart or liver from our own. Even if we examined the cells in these organs, we will again find that they are very similar to ours. Yet we are different, very different from chimpanzees. Perhaps you may wish to argue, the differences lie within the brain. Perhaps there are special brain cells which we possess that chimpanzees do not. This is not so. We possess no cell types that the chimpanzee does not, nor does the chimpanzee have any cells that we do not have.
>
> …The key changes in the evolution of form are in those genes that control the developmental programme for the spatial disposition of cells. The difference

> between chimpanzees and humans lies much less in the changes in the particular cell types—muscle, cartilage, skin, and so on—than in their spatial organization. Direct confirmation of this comes from studies which compare the proteins of humans and apes. If we look at the genes that code for the average 'housekeeping' proteins—proteins that function as enzymes or provide basic cell structure and movement—the similarity between chimpanzees and humans is greater than ninety-nine percent. The difference must reside not in the building blocks but in how they are arranged, and these are controlled by regulatory genes controlling pattern and growth.

16. A more concise way of explaining this would be to say that biological organisms are non-linear complex systems and thus small differences between them negate extrapolation. There are biochemical reasons for questioning the extrapolation of the results of experiments on animals to humans. Evolutionary biology supports and explains these reasons. Small differences between species' genes lead to huge differences at the molecular level, which is where we focus when treating disease. **This is the crux of our argument; that small variations on the genetic level not only define a species but also confound the ability of one species to 'model' another in aspects such as disease mechanisms and drug effects.**

17. Mark Ptashne and Alexander Gann write in *Genes & Signals*:

> …it is generally believed that mammals—humans and mice, for example—contain to a large extent the same genes; it is the differences in how these genes are expressed that account for the distinctive features of the animals… a relatively small number of genes and signals have generated an astounding panoply of organisms. Thus, the regulatory machinery must be such that it readily throws up variations—new patterns of gene expression—for selection to work on.

18. Same genes, but slightly different regulation. More complex organisms were built from the pieces of older organisms. Evolution took advantage of pre-existing materials and constructed new organisms to fill a niche. Humans were not made *ex nihilo,* but rather evolution took a piece of an enzyme from a predecessor and

combined it with another piece to make the enzyme needed for the organisms that eventually became *Homo sapiens*. Evolution used pre-existing molecular devices much as a brick mason uses the same bricks to make different structures. If one examines bacteria, yeast, and humans one sees the same essential material used as one advances in evolutionary time. "Add-ons" account for many other functions seen in the more complex organisms.

19. All cells of the same species contain the same DNA, but clearly, all cells are not alike. Nerve cells function very differently from muscle cells, which function very differently from liver cells. Likewise, all mammals are comprised of essentially the same genes. But a man is not a mouse. This is true because it is the *products* of the genes, not the genes themselves, that determine a cell's architecture (e.g., a liver cell or a heart cell). Because the DNA in each cell or species is regulated differently, and thus expressed differently, a cell becomes a liver or heart cell and an organism, a mouse or a human. The genes that make the hands are basically the same ones that make the feet, but those genes are expressed at different times and places and in different combinations.

20. What all this means is that even though humans may share 100% of their structural genes with another organism, say monkeys, these two organisms can be as different as a monkey and a man. By studying monkeys it is obvious that we can see only a piece of the puzzle, a monkey piece not a human piece, and the rest of the pieces are usually ignored – to the detriment of humans suffering from illness. By starting with humans, scientists could study human-relevant pieces from the outset, thus eliminating the risk of species differences.

21. John Maynard Keynes, said: "The difficulty lies, not in the new ideas, but in escaping the old ones; which ramify, for those brought up as most of us have been, into every corner of our minds." Animal models were effective when gross observations of similarities and differences between species were still heralded as discovery. But because of the knowledge of evolutionary biology that we have today, vis-à-vis regulatory genes, it should come as no surprise that our level of knowledge has outstripped the animal models' scope. Ptashne and Gann close *Genes & Signals* by stating: "…we realise that these systems evolved, stepwise. And so it should

hardly be surprising that underlying all the complexities are certain rather simple mechanisms that, by being reiterated and constantly added to, can produce living systems."

22. Add-ons produce a system that is nonlinear. Nonlinearity means that the output of the system is not proportional to the input. The complex way genes are regulated is reminiscent of complexity or chaos theory, where very small differences in initial conditions lead to large and unpredictable changes in results over time. There is positive and negative feedback in a complex system, whose behaviour amounts to more than the sum of its parts. Tamas Vicsek states in *Nature*:

> In the past, mankind has learned to understand reality through simplification and analysis. Some important simple systems are successful idealizations or primitive models of particular real situations…in other cases reductionism may lead to incorrect conclusions. In complex systems, we accept that processes that occur simultaneously on different scales or levels are important, and the intricate behaviour of the whole system depends on its units in a non-trivial way. Here, the description of the entire system's behaviour requires a qualitatively new theory, because the laws that describe its behaviour are qualitatively different from those that govern its individual units.

23. Hochachka and Somero write about complexity in living systems:

> …The complexity of physiological systems in multicellular organisms requires ever more complex sensing, signal transduction, and communication, as body plans attain higher levels of complexity. The control networks that have evolved are hugely complex by comparison with single-celled eukaryotes such as yeasts …Several thousand or so genes in unicellular and multicellular organisms seem to be involved in so-called "core processes" central to cell level survival and representative of the "unity" of biochemical design. So-called "non-core" functions, such as those listed immediately above, are what a substantial fraction of the remainder of the protein-encoding regions of the large genomes of complex eukaryotes represents – these are the genes that account for physiological diversity.

> …The problem (and in some senses the paradox) is that protein and gene sequences in the common chimpanzee and in humans are remarkably similar. In fact, human and chimpanzee proteins appear to be nearly 99% identical at the amino acid level, and it is widely assumed that the same percentage similarity prevails at the DNA level. Yet no one could mistake the two species as one. What these examples suggests is that only exceedingly minimal changes in genome sequences may be necessary to specify separate species, possibly with larger percentage changes in gene expression patterns. Of course, the longer any two such related lineages evolve separately from each other, the greater the genetic differences between them may become. However, in terms of the origins of unity and diversity, it is as humbling as it is surprising to realize how very small the differences in the overall genome may be between two lineages as they separate from each other and thus extend our planet's biodiversity.

24. Living systems such as chimpanzees, monkeys, and humans are obviously examples of complex systems. It should be equally obvious, therefore, why extrapolation between species is problematic: small changes on the genetic level can lead to very large differences between species. Indeed, that is what evolution is all about. The claim that humans and monkeys are the same animal dressed up differently *at the biochemical level* just isn't true. Moreover, it is irrelevant to point to observed similarities in genetic makeup between species, since the details of the differences are in the interactions between conserved genes, not in the genes themselves—it is as though humans and monkeys have a common genetic keyboard on which different phenotypic tunes are being played—what matters is not similarity with respect to the key board but differences with respect to the order and timing of the pressing of the keys (keys = structural genes, keys pressed on or off by regulator genes).

Predictability

25. A theory, or in this case a model, when used in biomedical research in an attempt to predict drug response or find cures for human disease, is reliable or *scientific* if it has predictive value. The validity of using animals as models to study human disease depends on their viability as *causal analogical models* (CAMs).

LaFollette and Shanks provide a detailed explanation of CAMs and causal analogical reasoning in *Brute Science*.[5] Early AIDS research provides a good illustration of the misapplication of causal analogical reasoning. Based on the knowledge that chimpanzees and humans a) share much of their DNA, b) can be infected by viruses, c) both have immune systems, etc. animal experimenters reasoned *by analogy* that because HIV replicates slowly in chimpanzees, it would do the same in humans. Unfortunately, their assumptions were based on inadequate knowledge and, in fact, HIV reproduces comparatively quickly in humans. Thousands died in France when blood recipients were infected with HIV because the blood had been tested on nonhuman primates and no adverse affects observed.

26. Only by comparing the results from testing each given substance or procedure in an animal species with human-based data can we determine whether the animal is sufficiently similar to humans to allow extrapolation. We can only know which animals mimic humans *after* we study the human data. Clearly, the *predictive* value of such models is nil.

27. There are areas of research – which do not resort to the use of the animal model – that are scientifically tenable and do offer reliability and predictability. Such methodologies include: pharmacogenomics; human stem cells; epidemiology; *in vitro* research; clinical research; autopsies; mathematical modeling (including artificial neural networks); computer modelling; post-marketing drug surveillance; research with human tissue; basic science research in the fields of physics and chemistry and other human-based and technology-based research methods such as the dazzling array of new brain imaging techniques: positron emission tomography; functional magnetic resonance imaging; magnetoencephalography; magnetic resonance imaging; transcranial magnetic stimulation and single photon emission computed tomography.

28. Animal experimenters will insist that animals are still necessary because without animals, researchers could not evaluate the drug or procedure in an intact system. We agree that life processes are interdependent, that the liver influences the heart, which in turn influences the brain, which in turn influences the kidneys, and so on. Thus, the response of an isolated heart cell to a medication does not confirm that the intact human heart will respond as predicted by the isolated heart cell. The liver

may metabolise a drug to a new chemical that is toxic to the heart whereas the original chemical was not toxic. We also concede that cell cultures, computer modelling, in vitro research etc., cannot replace the living intact system of a human being. But the question is: does the intact animal model – the non-human primate model included – do better than the non-animal scientific methodologies mentioned above? The evidence suggests that it does not. Animal models may be intact but they fail as causal analogical models, and this failure is predicted by evolutionary biology and confirmed and explained by molecular biology.

29. The section that follows (modified from *Specious Science* by Greek, C. Ray and Jean Swingle Greek. Continuum International Publishing 2002) is a critique of animal-based versus human-based research into neurological disorders. It will become abundantly clear which has made the greater contribution to our understanding of these diseases and our progress in treating them.

Diseases of the Brain

30. Dr. J. F. Dunne stated in *Textbook of Adverse Drug Reactions:*

> Notably in the identification of central nervous system activity, animal models are unreliable indicators…some drugs of proven value in man have negligible or paradoxical activity in laboratory animals… inconsistencies are an inevitable outcome of fundamental species-determined differences: and doubtless a number of compounds of potential therapeutic value are lost to medicine, having demonstrated little activity in an array of inappropriate animal models.

31. Nothing is more devastating than a diagnosis of a progressive neurologic disease, since, whatever the condition is, it will worsen. The few treatments available usually treat the symptoms but not the disease. The tragedy of neurologic disease is compounded by the fact that it attacks the very characteristics that make us who we are: our ability to think, remember, and move, and our personality. The nervous system's complexity and our still rudimentary knowledge of its function challenge

scientists daily. As a result, we have few means to deal with neurologic deterioration as more and more people are affected by it. That number will continue to increase because science has arrested so many other diseases, to which people would have succumbed in previous years.

32. Disorders of the nervous system have many origins – birth defects, poisoning, infection, metabolic defects, vascular disorders, inflammations, tumours, degeneration and injury. As is true in other medical disciplines, researchers continue to induce the symptoms of these disorders in animals, and then scrutinize animal brains and nervous systems in an attempt to fathom treatments and cures. Unfortunately, animal studies have done little to elucidate the underlying neurological mechanisms in humans. Human research however, has.

33. Logically, the practice of carefully scrutinizing the human who died from the actual disease is straightforward, informative, and reliable. Autopsy makes sense. Early autopsies characterized the anatomy of the brain and how that anatomy related to function. Documentation exists on many hundreds of thousands of human brain injuries that affected mobility, function, and behaviour. Until PET, MRI, and CAT scans, these copious data provided our most accurate picture of brain-activity regions. Even in the early fervour of animal models precipitated by Claude Bernard, *The Lancet* pointed out in 1883, "It is an interesting and noteworthy fact that pathological observation is doing more to advance our knowledge of cerebral localization than physiological [animal] experiment." In 1958, Dr. Hugh Jarvie reviewed the way in which science had since garnered knowledge concerning the location of various brain functions. He concluded,

> I cannot help feeling that the answers to our questions about the functions of the human brain will not be found in that way [animal experiments], but as they always have been found - in the careful collection of clinical facts and their pathological correlations.

34. Microscopes of ever-greater magnification enhanced the value of autopsy. Researchers were able to catalogue symptoms and explain them in light of the pathologic changes seen in the nervous system. Scientists can now identify the causes of afflictions of an infinitesimal size such as the newly discovered prions that bring on

variant Creutzfeldt-Jakob disease. German neuropathologist Alois Alzheimer, who first described the disease that bears his name, contributed significantly to the process of neurology because he standardized the way autopsies on the nervous system are conducted and developed dyes for staining nervous-system tissue.

35. Also of tremendous significance were autopsies of individuals with supposed neurologic diseases in which no pathologic abnormalities could be identified. Personality disorders were characterized by the lack of pathologic changes found at autopsy. Prior to that, they had been thought to be due to pathological changes in the brain. Despite the predilection for animal models, neurology still depends heavily on the autopsy. Note what pathologists R. B. Hill and R. E. Anderson say about this:

> In recent years, participants in meetings of the American Association of Neuropathologists have heard criticism about the increasing use of animal models to study human neurologic disease…. A strong cadre of diagnostic and research neuropathologists believe that only human material can provide relevant answers to many problems about human central nervous system disease. In fact, examination of the data bears out this contention. Of the 185 abstracts presented at the 1985 meeting of the American Association of Neuropathologists, 115 (62%) were presentations of human neuropathology, and an astounding 81 (43%) were based on investigations of human brains at autopsy. Among these autopsy studies were seven presentations of either the first complete description of a newly recognized human disorder, or one of the first complete descriptions of an uncommon human neurologic disease.

36. Today, *in vitro* analysis of autopsied human tissue is supplying even more detail. And with modern imaging technology, we need no longer even wait for human autopsy to find out what is wrong and where. Among the technologies used to map brain function and to identify brain damage while the patient is still alive are: magnetoencephalography (MEG), magnetic resonance imaging (MRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), positron emission topography (PET), single-photon emission computed tomography (SPECT), event-related optical

signals (EROS), transcranial magnetic stimulation (TMS). These and many other modalities aid us in addition to our clinical observations and autopsies.

MULTIPLE SCLEROSIS

37. Multiple sclerosis (MS) is the most widespread neurological disease affecting young adults. MS is actually a spectrum of diseases ranging from relatively benign to totally devastating. All forms are autoimmune, meaning that the body's immune system attacks itself. This we know from studies of MS patients who had lymphocytes and macrophages (cells of the immune system) in the lesions of the myelin sheaths. It appears that immune cells mistake myelin (a fatty substance which insulates nerve axons) as a dangerous foreign substance and attack it. Animal models suggested that the damage stopped with the myelin, but in humans the underlying nerve tissue, the axons, is also compromised. This knowledge affects how scientists approach not only the study of MS but also the treatment. Having developed two immunotherapy treatments for multiple sclerosis after years of using animal models, researchers at Stanford and the National Institutes of Health were forced to curtail trials because human patients symptoms worsened or they developed allergic reactions.

38. Most studies of humans have been done via clinical research and *in vitro* research using T-cell lines and cells cloned from diseased individuals. Millions of people worldwide have MS so naturally, this nightmarish problem attracts a lot of research funding. Still, though scientists have described types of MS, the exact cause of the disease has not been elucidated, nor has a cure been found. As usual, large percentages of the available resources have been directed to animal models. Many years and many millions of dollars in the animal lab have not helped MS victims. The animal "model" of MS is called *experimental autoimmune encephalomyelitis* (EAE). First induced in monkeys in 1933, EAE has since been induced in guinea pigs, rats, mice, and rabbits. Whereas the animals do have some of the same symptoms, the cause of the symptoms is different and, just as important, imposed. Further, there have been real problems getting EAE pathology to progress even so far as

demyelination. As scientists cannot induce sickness in the animals in the same way, naturally, they haven't even begun to cure multiple sclerosis itself. Note what scientists say about the model:

> In EAE, however, the inducing antigen is known, whereas the antigen specificity of the immune reaction in MS has not been identified. Furthermore, many models of EAE are characterized by perivascular inflammation without significant CNS demyelination, in contradistinction with MS in which demyelination is the primary feature. Furthermore, EAE is not a naturally occurring autoimmune disease.[6]

39. Those are major differences. There are numerous animal models of MS. The shaking canine pup. The shiverer mouse. The myelin-deficient rat. None replicate the human disease. Dr. Gibbs, writing in *Scientific American* in 1993, had this to say about animal models of MS,

> To the 2.6 million people around the world afflicted with multiple sclerosis, medicine has offered more frustration than comfort. Time after time, researchers have discovered new ways to cure laboratory rats of experimental induced encephalomyelitis, the murine model of MS, only to face obstacles in bringing the treatment to humans.

40. Why administer chemicals and viruses to animals that happen to result in loss of myelin? They do not get MS. It is like cutting out an animal's heart to simulate heart failure. These studies are supposed to show MS's causes. The end results may be the same – heart failure, loss of nerve conduction and so forth. But since the mechanisms are not the same, the efforts are unwarranted. While MS research on animals continues to baffle, human clinical and epidemiological studies have linked MS to environmental factors. Epidemiologists have also confirmed that MS has a hereditary component. Not just one gene introduces susceptibility, but multiple genes contribute.

41. On the therapeutic side, pharmaceuticals developed using animal models never cease to disappoint. Copaxone (Glutiramer acetate) was effective in EAE animals but has shown mixed success in humans. Also there are many side effects.

Tumour necrosis factor was given to EAE animals and worked well, but it did just the opposite in humans. Scientists found that one treatment that showed promise in animal models – intravenously injected immunoglobulins – does not remyelinate multiple sclerosis lesions any more than placebos in humans. Two other MS drugs – altered peptide ligand formulas known as CGP77116 and NBI 5788 that constituted an immunotherapeutic approach – worked well in animals. However, clinical trials came to an abrupt halt after several people almost died. Speaking of animal models of autoimmune diseases in a reputable immunology journal, Veena Taneja and Chella S. David stated, "Of course, it is not possible to reproduce a complete human disease in an animal."[7]

ALZHEIMER'S DISEASE AND DEMENTIA

42. Dementia is gradual loss of memory that eventually erodes the ability to conduct everyday activity. Alzheimer's disease (AD) – first described in 1906 by Dr. Alois Alzheimer – is dementia's most prevalent form. Although ageing does not necessarily cause this central nervous system affliction, Alzheimer's symptoms can increase with age. Because many neurological diseases mimic Alzheimer's symptoms, it has always been difficult to diagnose. Until recently, the only way to determine the disease's presence definitively was at autopsy. Scientists gathered much initial understanding of Alzheimer's in this way, by looking directly at patients' brains. They found that neurons in the brain – primarily in the hippocampus and neocortex regions, had deteriorated. There were little lint-like wads called *neurofibrillary tangles* within the cells, hardened protein deposits called *neuritic plaques* outside the cells, and general pockets of degeneration called *granulovacuolar degeneration bodies*. It was evident that proteins running amok had something to do with the aberrations.

43. Research efforts first plumbed to determine the nature of the neurofibrillary tangles, brought about by a protein called *tau*. Scientists located the tau gene on chromosome 17. Concurrently, the lab-animal researchers launched into an unproductive investigation of a made-to-order transgenic mouse, a mouse that had a mutated tau protein gene inserted. However, the mouse's tau did not result in any Alzheimer's-like symptoms or even a neurological change. This implied that tau was

unimportant. Years passed and tau research was largely remanded to the back burner. Scientists, now knowing better, admit that the response to tau is "highly species-specific."[8] There is no successful animal model of Alzheimer's disease.[9]

44. Surprisingly, several clinical studies and autopsies showed that the brain changes commonly associated with Alzheimer's – the *neurofibrillary tangles* and *neuritic plaques* – do not always result in dementia. The first big breakthrough in AD came in Liverpool in 1976. Autopsying the brains of AD patients, Dr. David Bowen found depleted supplies of the neurotransmitter acetylcholine. Acetylcholine would normally help neurons communicate. Bowen's finding and subsequent clinical observation suggested what is known as the "cholinergic hypothesis" to explain AD. This postulates the idea that neurons secreting acetylcholine (Ach), or being stimulated by Ach, are damaged, and AD ensues. That nondemented humans suffered from cognitive deficits after taking anticholinergic medications such as scopolamine reinforced this hypothesis. These results were then duplicated in nonhuman primates. Again, the animal model merely reproduced finding in humans. Further, autopsies and clinical observation showed that the brains of patients with AD demonstrated less choline acetyl transferase (ChAT) activity. Again, these findings were duplicated in animals. R. Bartus stated in 1986 about animal models for AD, the "…value of any model or approach will depend not on the inherent logic of the principle that guided its development, but on its ability to make meaningful predictions about the clinical condition it was designed to study."[10] Studies that merely duplicate known human conditions are not predictive.

45. While the animal model community continued to try and induce AD in animals, epidemiology and *in vitro* research pushed ahead, establishing the genetic basis for Alzheimer's. The disease can be either hereditary or not. When Alzheimer's is hereditary, it is "familial." When not, it is "sporadic." The greatest clues to the etiology or cause of Alzheimer's have come from linkage studies of familial Alzheimer's disease. While epidemiologists continued defining subsets of Alzheimer's victims, *in vitro* research scientists went to work analyzing the neuritic plaque in humans, Alzheimer's second characteristic. Interesting developments took place under the microscope where researchers observed human brain cells. In the autumn of 1999 four separate companies confirmed the involvement of two genes –

presenilin 1 and presenilin 2, on chromosomes 14 and 1 respectively. Each used a different method for finding the gene. None relied on animal models.

46. As it happens, about fifty percent of people with familial Alzheimer's disease have a mutation in the presenilin genes that predisposes them to the accumulation of characteristic amyloid plaques between neurons in their brains. To "validate" this finding, research with mice was immediately under way. But it had already been established so why were animal models employed at all? Here, an interesting lack of congruity between animals and humans again bungled the stream of revelation. Man-made mutations in mice can cause them not to produce presenilin 1. And as a result, the mice produce no amyloid-β. But in humans with presenilin 1 and 2 mutations, it does the reverse. James M. Conner and Mark H. Tuszynski of the University of California, San Diego, summarized the frustration of animal models of AD in 2000, in *Central Nervous System Diseases: Innovative Animal Models from Lab to Clinic,*

> In the case of AD, good animal models have been difficult to come by. The full spectrum of the biochemical and pathological abnormalities characterized by AD have not been found to occur spontaneously in any animal species other than the human, and the complexity of the disease has made it difficult to generate animals with a full range of experimentally induced AD pathological alterations.[11]

47. Researchers have isolated additional genes believed to contribute to AD. The apolipoprotein E, or *APOE-e4*, plays a part in determining when familial Alzheimer's will manifest. Another Alzheimer's-related mutation has been found by studying afflicted Icelandic patients and their relatives. Although identifying the genetic basis for young age-onset AD was fairly easy, finding the genes involved in old age-onset was more difficult. Again, clinical research gave the answer. By studying humans, scientists were able to find a gene on chromosome 10 that contributes to the later onset version of AD.

48. No question, the path to a cure for Alzheimer's disease is very complex and varied, and researchers have a challenging task of unravelling its mysteries either

to avert it or cure it. AD presents a dizzying array of anomalies, which science is revealing in ever-greater detail. Considering the microcosmic detail, it certainly does not make sense to waste money on animal models, when much more accurate and comprehensive information is available *in vitro*, studying humans, or on computers. In the meantime, we need no longer wait until death to determine whether a patient has Alzheimer's. Biotech has spawned new diagnostic techniques. German scientists created a method for confirming the presence of Alzheimer's using fluorescence correlation spectroscopy to find the amyloid deposits in cerebral spinal fluid. In autopsy of Alzheimer's victims, deficits of two neurochemicals – somatostatin and corticotropin-releasing factor – are well recognized. Efforts are under way to diagnose their deficiency as an early marker of the disorder.

49. Another very exciting diagnostic technique is in development. The noninvasive functional MRI (fMRI) determines dysfunction in the entorhinal region of the hippocampus, the brain's key structure for controlling memory and the prime area affected with Alzheimer's. This will be especially beneficial in detecting the disease early, when symptoms are not so pronounced. The lower the blood flow in the posterior regions of the brain, the more rapid the deterioration. A new noninvasive brain perfusion imaging called SPECT can predict survival rates and increase the likelihood of a correct diagnosis.

50. As for cures or vaccines, there still are none. Labs continue to try out therapies on assorted animals even though many knowledgeable scientists feel as does Dr. D. Lindholm of Uppsala University in Sweden who stated, "There is no…good animal model for the [Alzheimer's] disease process characterized by a loss of cognitive functions and memory decline."[12] Last year Dale Schenk and his colleagues buoyed the families of Alzheimer's patients with news of a suggested anti-Alzheimer's vaccine. They worked with mice that overexpress a mutant form of the human amyloid precursor protein, amyloid-β, which in mice brings on an Alzheimer's-like condition called cerebral amyloidosis. Their prevention of this cerebral amyloidosis with vaccination was first published *Nature* and appeared in news media throughout the world. In an accompanying editorial in *Nature*, David Westaway and Peter St. George-Hyslop stated,

> …all of the current animal models provide only a partial model of the human condition. So, although these animals accumulate increased levels of amyloid-β, and have many amyloid plaque deposits, they have only subtle behavioural and electrophysiological deficits. More problematically, these animals do not develop neurofibrillary tangles or show significant neurodegeneration.[13]

51. Optimism over the Schenk group's findings is entirely premature and misleading for this and other reasons, and because translating these results to humans is going to be very difficult and possibly dangerous. The protein used in the study may result in antibodies that damage healthy human tissue. One of the proteins that the vaccine attacks is found in human platelets. Moreover, the underlying premise of the study – that amyloid is responsible for Alzheimer's - may be wrong. This is still controversial. Tau may be the most important factor. As mentioned, not all people with amyloid plaque have Alzheimer's. Autopsies indicated that many elderly have substantial amounts of amyloid in their brains without having been demented or even mentally slower than normal before their death. Whereas amyloid is present in Alzheimer's patients, it is not necessarily the *cause* of their condition.

52. Other human-based data inform the picture. Approximately one-third of all stroke patients are left with some degree of dementia. Stroke prevention could, therefore, lead to the prevention of Alzheimer's-associated dementia. So, clinical trials are under way to see whether antioxidants such as vitamin E or nonsteroidal anti-inflammatory drugs such as ibuprofen alleviate the toxic effect of β-amyloid. Clinical studies revealed that women suffering from Alzheimer's disease improve their memories by wearing an oestrogen patch. Oestrogen replacement therapy has been shown to reduce women's risk of suffering from the disease. Clinical research found that inadequate supplies of B12 and folates increase the likelihood of developing Alzheimer's. Studies confirmed a correlation between aluminium sulphate exposure and memory loss. However, it does not necessarily bring on Alzheimer's. Epidemiological studies linked dementia to a high fat/high cholesterol diet. They also led to the discovery that individuals who smoke are twice as likely to develop dementia as those who do not. *In vitro*, epidemiology and clinical research continues

to inform discoveries of this nature, rendering animal-modelled re-creations a complete mockery.[14]

PARKINSON'S DISEASE

53. Parkinson's is a ruinous illness, which mostly affects middle-aged adults. Parkinson's musculoskeletal symptoms include a tremor, or shaking motion, in the hand and arm and stiffness of the joints, causing jerky, mechanical motion. Body rigidity, addled movement, smaller handwriting, weakness, and imbalance are indicators. Unfortunately, the symptoms are not just confined to the musculoskeletal system. Psychiatric problems, such as depression and psychosis, may also accompany the disease. These and muscular symptoms usually worsen with time.

54. Autopsies of Parkinson's patients exposed degeneration in the midbrain region called the *substantia nigra*, a deeply pigmented portion in the basal ganglia. In 1960, researchers Oleh Hornykiewicz and his colleagues at the University of Vienna performed autopsies on patients who had died with PD and found the nigrostriatal pathway had degenerated and had very little dopamine. The neurotransmitter dopamine (DA), which regulates movement and emotion, is the chief carrier of nerve signals to this region, and *in vitro* research on brain tissue of Parkinson's victims indicated dopamine deficiency. Levels of the substance that dopamine is metabolized to, homovanillic acid, were also subnormal. Researchers determined that nerves containing dopamine die in Parkinson's patients, leaving the brain without enough dopamine to function normally. Hornykiewicz and his colleagues administered a dopamine precursor and saw immediate impressive results. This changed the way PD was treated as well as opened the way for new research on schizophrenia, epilepsy and other neurological diseases. John Hardy of the Mayo Clinic stated that Hornykiewicz's research, "fundamentally changed how neuropharmacology is practiced."

55. No animal, aside from humans, suffers from Parkinson's. Researchers have reproduced the symptoms in animals and this has resulted in their receiving grant money to study them. These Parkinson's models include: the reserpine model, neuroleptic-induced catalepsy model, tremor model, models with degeneration of

nigrostriatal dopaminergic neurons induced by using the chemicals 6-OHDA, methamphetamine, tetrahydroisoquinolines, β-carbolines and iron, and most recently the "parkinsonian baboon." Timothy Schallert and Jennifer L. Tillerson of the University of Texas state in *Central Nervous System Diseases: Innovative Animal Models from Lab to Clinic*

> Many types of animal models of Parkinson's disease are available. Selecting a clinically predictive one is crucial, but has always been difficult…Although some researchers have argued that only primate models… [are useful], there is no consensus or current bias to suggest that one species is more predictive than another in the transition from research to patient.[15]

56. In 1983, researchers learned from clinical observation that the chemical MPTP (a by-product of synthetic heroin) could cause Parkinson's-like damage. The fact that MPTP causes PD-like symptoms was found accidentally after drug addicts injected themselves with MPTP-contaminated chemicals. The MPTP destroyed the dopamine-producing cells in the substantia nigra. So, researchers treated mice and other lab animals to infusions of MPTP. The data was merely demonstrative. Jay S. Schneider, who has worked at both Thomas Jefferson University and Drexel University, received public funds to inject MPTP into cats' brains and into two varieties of macaques. In 1997 Schneider wrote:

> Some monkeys [injected with MPTP] had cognitive deficits and no motor deficits. Other monkeys had full parkinsonism that was produced after short-term high dose MPTP exposure, and some monkeys had full parkinsonism after long-term low dose MPTP exposure.

57. Inconsistent, *coerced* rather than *acquired* symptoms, which in aggregate Schneider calls "parkinsonism," are hardly a true model of this still little understood human disease. Simranjit Kaur and Ian Creese of the Centre for Molecular and Behavioural Neuroscience, Rutgers stated in *Central Nervous System Diseases: Innovative Animal Models from Lab to Clinic,*

> The best model of PD to date, is the 1-meth-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset. The neurotoxicity produced by 1-methyl-4-phenylpyridinium ion (MPP^+), a metabolite of MPTP, is thought to mimic human PD. MPTP reduces the levels of dopamine and its metabolites in the striatum. However, this model is far from ideal owing to the high cost of using primates (MPTP is ineffective in rats) and unlike human PD, which is progressive, the neurotoxic damage produced by MPTP is reversible…In these models, it is difficult to ascertain the roles played by individual dopamine receptors in the pathology as well as the therapy of PD.

58. And is the ability to give animals the Parkinson's-like agitated movement in any way helping real Parkinson's victims? These animal models can only reproduce data already gleaned from humans. Their predictive value is negligible. The problem is, that while it is relatively easy to kill the substantia nigra with these substances and make animals shake, the reason the cells in the substantia nigra die in the animal is not the same as in Parkinson's. Furthermore, none of the models reflects the *progression* of Parkinson's symptoms as it occurs in humans. Philippe Hantraye of Service Hospitalier, France, wrote:

> However, it is essential to understand that animal models only represent an imperfect replica of human disorders [of PD], and this is so for several reasons. First, animal models are generally developed in beings (rodents, nonhuman primates) that are subjects with behavioural repertoires and anatomical characteristics very different from humans. These species differences are known to play a role in the clinical expression as well as in the cellular specificity of the lesions. For example, striatal degeneration in humans is frequently associated with dyskinesia, whereas in rat or nonhuman primates, striatal excitotoxic lesions alone are not sufficient to induce dyskinesia or chorea. Second, in addition to these species differences, the time course evolution of the nerve cell degeneration, which normally evolves over several years in neurodegenerative diseases in humans is for practical reasons, being replaced over a much shorter period of time in animal models.[16]

59. Echoing these views is James A. Temlett, of the neurology unit of the University of the Witwatersrand Medical School in South Africa, who stated,

> Acute parkinsonism models [animal models] have limitations when compared with chronic disease states, and caution should be present when comparing parkinsonism data with human disease… Animal models, including the MPTP-lesioned nonhuman primate data, but especially rodent models, are 'acute parkinsonian models' that provide more controlled conditions, preservation of tissue biochemical or molecular estimates. However, these do not reflect the complexities of the human basal ganglion.[17]

60. Physicians serendipitously discovered that the nightshade plant partially relieves some Parkinson's symptoms. The only therapy for many years, it decreases acetylcholine, the chemical that is in relative excess due to the decrease of the chemical dopamine. The truth is that we will not make real progress in treating Parkinson's until we know *why* the substantia nigra dies. Once the cause is arrested, the symptoms will stop. The obvious interim solution is to replace the dopamine; however, a built-in condition called the blood-brain barrier stands in the way. This protective layer inhibits many substances, such as toxins, from entering the brain from the bloodstream. In this case, it also prevents medications from reaching their destination. Dopamine cannot cross the barrier. Through clinical studies, scientists learned that levodopa, which is a precursor of dopamine, can cross the blood-brain barrier. The levodopa then converts into dopamine in the brain. Although the drug ameliorates Parkinson's symptoms, it does not prevent the substantia nigra nerves from dying, nor does it lead to the restoration of dopamine. It also loses effectiveness with time.

61. Recently, researchers discovered through autopsies that the progressive degeneration of the dopamine-3 (D3) receptor in Parkinson's disease is what causes the gradual loss of efficacy of levodopa. Levodopa therapy is strengthened when patients concurrently take dopamine agonists, such as ropinirole. These stimulate dopamine receptors. Added to this, scientists found a substance that slows dopamine metabolism, making more available to control Parkinson's symptoms. A monoamine

oxidase B inhibitor, a medication developed to treat depression called Selegiline (deprenyl) had this effect.

62. Epidemiology, *in vitro* research and clinical studies are, as always, invaluable in identifying the susceptible population and the plausible causes of Parkinson's. The disease seems to have both genetic and environmental causes. Some people are genetically disposed to Parkinson's. The higher occurrence of Parkinson's in rural areas suggests that pesticides and other contaminants that increase free radicals could activate Parkinson's. Yet, the ultimate cause of Parkinson's remains unknown. As in Alzheimer's, both familial and sporadic forms exist. Researchers identified a discrepancy in the α-synuclein gene on chromosome 4q, responsible for the adult-onset familial form of Parkinson's. There is an overabundance of the α-synuclein protein in these patients. Missense mutations, where the genetic code has additions or deletions that do not translate into a functional protein in the number 17 chromosome, have some responsibility for the defect in the α-synuclein gene. The discovery of the α-synuclein has been called "the first major breakthrough in the understanding of the disease in thirty years." The same combination of human-based research mapped juvenile-onset Parkinson's to chromosome 6q. Another epidemiology and *in vitro* discovery found that genes on chromosome 2p13 may be responsible for the sporadic form of the disease. Scientists hope to elucidate exactly how the disease affects neurons but have not yet done so. The reason neurology is such a frustrating field is that we cannot answer what appear to be simple questions. *In vitro* research enhanced by computers and electron microscopy seems to lead in a promising direction, but it will take time. Early diagnosis of Parkinson's helps physicians treat symptoms more thoroughly. With the advent of the PET scanner, TMS, fMRI and other scanners, almost all components of the dopamine synapses can now be imaged in living humans. SPECT technology mentioned in reference to Alzheimer's, is similarly useful.

63. Until the 1960s, neurosurgeons simply removed one or both of the thalami, the two-part regions of the brain through which sensory impulses travel. Thalamotomies were not that effective. The procedure, designed to mitigate trembling, is being replaced by high-frequency deep brain stimulation, using a wire

inserted into part of the thalamus subthalamic nucleus or globus pallidus. Pallidotomy - the lesioning of the globus pallidus, another nearby brain sector, seems to improve function in Parkinson's patients, however there are risks. Neurosurgeons are now evaluating transplantation and implantation procedures. Ten years after implantation, a graft of embryonic nigral cells in a man with Parkinson's survives and continues to release dopamine. Stem cell research is also promising.

EPILEPSY

64. Epilepsy, from the Greek word *epilambanein* meaning to attack or to seize, was first described in ancient times. Julius Caesar, Napoleon, and Van Gogh are among history's famous epileptics. Epileptic seizures are brief, recurrent attacks of altered consciousness and motor activity. During a seizure, epileptics' extremities often jerk violently, and sometimes victims lose consciousness.

65. John Hughlings Jackson was one of the first moderns to describe epilepsy accurately. Where did he get his insight? From clinical observation. Long before EEGs (electroencephalograms), Jackson deduced that abnormal electrical discharges in the brain caused the seizures. During a seizure, brain waves register on EEGs with abnormal rhythm. Today, MRIs can often distinguish the seat of the disease and its underlying mechanisms. Researchers have identified many different types of epilepsy, all characterized by uncontrollable activity in the brain caused by excessive and synchronous nerve-cell discharges. Computers help scientists chronicle epilepsy types. Some cases of epilepsy are inherited, but most are not. Defects in single genes or a combination of genes, exacerbated by environmental factors can lead to epilepsy. This we know from a combination of epidemiology and *in vitro* research. There is such variety in the causes of human epilepsy that the frequent use of nonhuman brains in research is just ridiculous. Why gather data about animal seizures when the human spectrum is so diverse *and* accessible?

66. As an example, take a look at one cause of epilepsy, cortical dysplasia, which is a result of brain damage that occurs *in utero.* (Cortical means "brain-related," and dysplasia has to do with abnormal cell growth.) The connection between this brain malformation and epilepsy was known in the 1800s, however no one could

act on the knowledge until recently. Cortical dysplasia researcher N. Chevassus-au-Louis and his colleagues are in favour of the animal model. Yet, when they summarized the three most meaningful contributions to our understanding of epilepsy in the 1990s, they made no mention of animal models:

- Development and widespread use of modern brain-imaging techniques, specifically magnetic resonance imaging (MRI).
- The ability to detect malformations during life has opened the door for surgical resection of the malformed areas. Indeed surgery can reduce or abolish seizures or both in most patients, suggesting the existence of at least a causal link between malformation and epilepsy. Moreover, neuropathologic analysis of resected tissue has frequently demonstrated the presence of more subtle malformations that were not identified *in vivo*.
- Recent progress in human molecular genetics has allowed the identification of several genes whose mutation leads to both malformations and epilepsy.[18]

67. This is not to say that they or their colleagues refrain from using animal models. The link and the therapy having been established in humans, researchers sought to copy the cortical dysplasia pathology in animals. They genetically altered animals while *in utero,* administering chemicals such as cocaine and alcohol to pregnant animals to create cortical malformations and seizures in their offspring. All of this was for naught. Certainly, plenty of babies born of substance-abused mothers demonstrate a problem. Nevertheless, scientist E. F. Sperber and colleagues stated in 1999 that the experimental animal models of cortical dysplasia did not mimic the clinical pathology seen in humans.[19] Clinical studies found that infants' seizures are different from adults'. Infants have lower seizure thresholds than adults and respond differently than adults to antiepileptic drugs. Also, when seizures occur in infants they may create a predisposition to seizures or cognitive defects later in life. Animal models have reproduced these clinical observations. Various chemicals isolated in animal models may explain the phenomenon – but only in the animals studied. These findings have not influenced the treatment of humans whatsoever.[20]

68. Since many animals suffer naturally from seizures or can be made to seize from artificial causes, one can see why early experimenters thought they would divine something from animal models. But the long history of ineffectiveness has not borne out the logic of their decision. All told, animal models of epilepsy have many drawbacks, first in the inaccuracies of the way they mimic the disease, and second in their response to medications. Take human epilepsy caused by single gene defects. There are six mouse models of single gene spike-wave epilepsy: tottering, lethargic, slow-wave epilepsy, stargazer, mocha, and ducky. Each rodent has seizures secondary to an absent gene. The problem is that, in each case, the absent gene also contributes to disorders that do not include epilepsy in humans. Also, the mice exhibit symptoms such as ataxia (uncontrolled movement) that humans suffering from single-gene epilepsy do not. Thus, the humans missing the gene are very different from the mice missing the same gene. Thomas N. Seyfried and his colleagues wrote, "The reason for the difference between man and mouse in seizure-associated neuronal loss is not clear, but it may reflect a species difference in either neuronal or glial response to seizures."[21] Yes, these mice seize. But the reason they seize and the impact of the seizure on the brain are nothing like the human experience. Models this disparate cannot be expected to yield useful data.

69. On the treatment side, we find much the same story: Human-based models generate useful drugs; animal models do not. Even though most sufferers can control their seizures with antiepileptic drugs (AEDs), about thirty percent complain of severe side effects. One good reason for this is the predilection for developing drugs around animal models. Once a drug has been shown to be effective against epilepsy in humans by means of serendipitous observation, an animal can usually be found in which that same drug will inhibit seizures. Other similar drugs are then tested on the animal to find what appears to be the optimal solution. This information can also be obtained from studying the structure of the drug instead. How many successful AEDs were lost because they did not effectively treat rats but would have been effective in humans? How many mediocre AEDs are on the market because they worked better on animals?

70. Felbamate was one of the first modern AEDs to be approved in the US. It was thoroughly tested on animals and subsequently underwent an aggressive marketing campaign. *Time* magazine even ran an article titled "Taming the Brainstorms." Within months after its launch, in the early 1990s, reports of aplastic anaemia began surfacing. Cases of liver failure and death ensued. Commenting on the side effects, physicians John Pellock and Martin Brodie stressed the exigency for more patient evaluations prior to giving drugs to the general public and thorough post-marketing drug surveillance after drugs are on the market. They did not call for more animal studies. Tragedies due to animal models are far bigger news than putative successes, but they get very little press. Meijer and colleagues stated in 1983,

> Unfortunately many AEDs [antiepileptic drugs] show marked pharmacological differences between animals and man… [22]

71. An important neurotransmitter of the central nervous system, GABA (gamma-amino-butyric acid), is known to inhibit excitatory responses. GABA was discovered in animal brains, but human brains from cadavers could have been used. Thanks to MRI spectroscopy, one of the more important epilepsy studies revealed that GABA levels are lower in human patients with seizures than in non-epileptics. Many newer anticonvulsants are designed to raise GABA levels. Gabapentin, which researchers realized would inhibit the central nervous system in the 1950s, was initially developed to treat spasticity and then found to be effective against some seizures.

72. Nowhere has new technology influenced drug discovery as much as it has for AEDs. The investigation of specific molecular targets and subsequent development of drugs that interact with those targets has revolutionized AED discovery. Marvellously, *in vitro* techniques allow drugs to be evaluated by displacement of radioligands from a binding site or the inhibition of enzyme activity or neurotransmitter uptake. Computers conduct mass screening of large databases of chemicals looking for specific molecular configurations. Combinatorial chemistry generates a pool of likely chemicals with the same basic structure for testing. Alternatively, a known effective drug undergoes chemical modification and then computers and *in vitro* research evaluate its efficacy compared with the first drug.

Even side effects and efficacy are apparent in this analysis. Drug discovery using this process is called *structure-activity analysis* or *structure-function analysis*.

73. The National Institutes of Health is using human brain tissue of epileptic patients, obtained during palliative surgeries for this disorder, to study why seizures occur and what medications can be used to treat them. The director of a leading epilepsy research facility in Europe said,

> As a scientist, I am of the opinion that animal experiments bring no progress in the diagnosis and therapy of epilepsies. I have a well-founded suspicion that similar facts apply in other areas of medicine.

PSYCHIATRIC MEDICATIONS

74. Psychiatric diseases are especially difficult to reproduce in animals. In any species, physical manifestations of emotions can signal any number of pathologies. For instance, hypoxic (short of oxygen) patients will experience palpitations. So do those who are having heart attacks or heart rhythm disorders or numerous other diseases. A higher pulse and respiratory rate indicate fearfulness, but they also augur fever, viral and bacterial infections, pain, and multiple other illnesses. All told, most psychiatric disorders can only be qualified and quantified through the patient's expression.

75. Without language, we can only conjecture about the source and extent of an animal's mental discomfort, not draw viable conclusions. *Agoraphobia* is anxiety about or avoidance of a place. Is an animal sick because it has an aversion to a veterinary clinic? *Anxiety disorder* is persistent and excessive worry, something hard to distinguish in an animal (especially in the canine toy breeds). *Dementia* involves impaired memory. How can you tell if a rat running around his cage is demented? *Schizophrenia* manifests as speech disturbances, delusions and hallucinations. How can we diagnose an animal as having these problems? How about *manic disorder*? Note that most Labradors suffer from persistently elevated and expansive moods. And certainly we have all seen our dogs look "depressed." It does not necessarily follow

that they have a psychiatric condition caused by an imbalance of neurotransmitters in the brain.

76. We know from studies of people with mental illness that overactivity in the nerve cells employing the neurotransmitter dopamine tends to induce psychosis. Chlorpromazine, an antihistamine serendipitously discovered to have calming qualities by French anaesthetist Henri Laborit in 1949, became known as the "drug that emptied the state mental hospitals." Chlorpromazine blocks dopamine receptors and keeps patients from experiencing severe hallucinations, panic and delusions, so effectively that it is still in use. Obviously, no animal tests predicted chlorpromazine's antipsychotic effect, just clinical observation, clear and simple. The medication was tested in animals after the clinical discovery and animals were found that would duplicate the knowledge already obtained from humans. As so often happens when a physician makes and reports a clinical discovery, animal experimenters repeated it and called it theirs. In this case, the historical reports speak for themselves.

77. The entire history of psychopharmaceutical development is one of refashioning chemicals around events discovered serendipitously. Enthusiasm for conjuring new drugs grew to a fever pitch around mid-twentieth century as scientists and pharmaceutical companies eagerly looked for "new" psychiatric drugs. Their investigation was random, not directed toward a particular substance; they were just trying to increase the number of weapons in the psychiatrist's arsenal. Meprobamate was introduced in 1955 as a centrally acting muscle relaxant, and subsequently found to have anti-anxiety properties. Remarketed, meprobamate became the first medication to be called an anxiolytic (providing anxiety relief).

78. Simultaneously, a chemist named Leo Sternbach serendipitously discovered the sedative effects of the benzodiazepines. Valium, Librium, Versed, and other drugs in that class were eventually tested on animals. It was found that they placated aggressive animals (some of the time), but in humans they proved useful as anti-anxiety medications. There is no clear correlation between aggression in animals and anxiety in humans. Indeed, the two emotions are just that, two separate emotions. Also in the 1950s, tricyclic antidepressants appeared on the scene. Like chlorpromazine – which they structurally resemble – they were originally designed to

be antihistamines, but when tested on human patients they produced sedation.

79. The study of depression and anxiety in animals is perhaps the most perplexing type of research. Cocaine, opiates and amphetamines would qualify as potential antidepressants as screened by many of our present animal models. For humans they are not satisfactory, although we now know that they act on several neuronal sites in common with modern antidepressants. The first successful treatments for depression materialized as they always do - by accident. Iproniazid (derived from surplus hydrazine) was originally given to TB patients after World War 11 in hopes that it would help them clear their secretions. It did not. But the staff noticed that the patients receiving it were much happier than those not receiving it. Hence it came to be used as an antidepressant. After iproniazid's properties had been demonstrated in humans, it was tested on animals. The results in animals were noncontributory to its use.

80. Pharmacologists learned that iproniazid exerted its effects by inhibiting mono-amine oxidase. Mono-amine oxidase is an enzyme that breaks down norepinephrine. Too little norephinephrine can lead to depression. The class of drugs called mono-amine oxidase inhibitors (MAOI) work because they increase the presence of norepinephrine. Reserpine, a derivative of snakeroot, helped to elucidate the pathophysiology of mental health. Physicians noted that high blood pressure patients who received reserpine became depressed or had mood swings. When they stopped taking reserpine their moods returned to normal. This helped elucidate depression's biochemical basis. But when researchers successfully interrupted reserpine's depressive effects in animals using MAOI and tricyclic antidepressants, it created two monsters: one, the conclusion that depression was a simple matter of depleted monoamines and two, the reserpine animal model. According to scientists who wrestled with these "monsters,"

> Most of the approximately one hundred compounds that reached some stage of clinical trials in the last 25 years did so because they could "qualify" on these tests. Gamfexine was the first drug that failed to show a correlation between animal tests and human trials. Its effect on cats was exceptional but it worsened the clinical status of human

> patients, two of whom had to be prevented from committing suicide. Gamfexine was first in a long line of failures.
> …Whether the "censorship" practised by these animal models prevented us from developing chemically novel antidepressants remains an unanswered question. We do know that in the last 25 years not a single compound has been discovered which is unequivocally better in clinical efficacy than the very first drug of this class. It was the very failure of these animal models in screening out ineffective compounds that ushered in the next stage of psychopharmacologic research.[23]

81. MAOIs discovered clinically, like iproniazid, or synthesized to mimic iproniazid's effect, have worked out well. But contrast these victories with Meritol, which was released in 1986 after extensive animal testing. Meritol was promptly withdrawn secondary to severe life-threatening side effects including kidney failure, liver failure, haemolytic anaemia and deaths. Mianserin was also introduced as an antidepressant after animal testing. Unfortunately, it caused severe problems with patients' blood. Ironically, the side effect could have been predicted by *in vitro* studies of human cells. We emphasize, animal models did not work, but actually studying human cells would have. Why is this such a difficult reality to embrace?

82. By the 1970s, it was clear that the effectiveness of MAO inhibitors and tricyclics pivoted around their effect on the neurotransmitter serotonin, as clinical evidence linked serotonin to depression. Autopsies on people who committed suicide showed lower levels of serotonin in the brain than in people who died of other causes. The concentration of a serotonin metabolite, 5-HIAA, was lower in the cerebral spinal fluid of depressed patients versus nondepressed. Subsequently, treatment with medications that raised levels of serotonin showed antidepressant effects. It was then left for *in vitro* methods to find and test a chemical that would make more serotonin available to the nerves that influence depression.

83. Such work resulted in Prozac. Though the selective serotonin reuptake inhibitor, zimeldine was actually first discovered in 1971, Prozac (fluoxetine) is the first efficacious SSRI (selective serotonin reuptake inhibitor). Zimeldine had tested

safely in animals but caused paralysis in humans and was withdrawn from the market. Ironically, Prozac, which is relatively harmless to humans, causes high blood pressure and increased heart rates in rats.

84. Not all antidepressants work on all depressed people. For instance distinct brain differences, revealed in brain scans, showed that although Prozac reached the right brain areas, the shift in brain metabolism never occurred in some people. This is important, not just to the afflicted, but also to our argument. If subtleties like this affect organisms within one species – humans – why would anything we can borrow from animal models be substantive? Many scientists have recognized and spoken out on the issue of animal testing of psychiatric medications:

> Two major points emerge from our reading; the surprisingly poor track record of most if not all animal models to date (a) in accurately predicting clinically effective antidepressants and (b) in generating new and conceptually liberating hypotheses of the pathophysiology of depression. These observations are highlighted by the fact that almost every significant advance in antidepressant drug treatment from the discovery of iproniazid and imipramine to the recently introduced "second generation" class of antidepressants has resulted either from astute clinical observations or serendipity; a far cry from a planned, predictive, screening test. In fact many second generation antidepressants such as iprindol, mianserin, trazodone and salbutamol should be classified as false negatives on the conventional drug screening models (i.e. ineffective during preclinical screening but clinically efficacious). Conversely, a series of compounds, predicted to be at least as effective as imipramine, were reported to be clinically ineffective (i.e. false positives).[24]

85. Anomalies in research for other psychiatric conditions reinforce the ineptitude of animal models. Scientists have attempted to learn more about panic attacks, for example, by making mice panicky. Consider the following definition from the *DSM-IV*, which is used by psychiatrists to describe mental-health disorders:

> A panic attack is…the sudden onset of intense apprehension, fearfulness, or terror, often associated with feelings of impending

doom. During these attacks, symptoms such as shortness of breath, palpitations, chest pain or discomfort, choking or smothering sensations, and fear of "going crazy" or losing control are present.

Now imagine looking for these symptoms in a caged mouse or monkey.

86. Patients with anxiety disorders underwent MRI and SPECT scans and the scans showed an unusual distribution of benzodiazepine receptors in the brain. Using PET scans, scientists found that people with bipolar (manic-depressive) disorder have thirty percent more of an important class of signal-sending brain cells. These are but two examples out of many human studies that have yielded useful, unequivocal results.

87. Should they look for signs of schizophrenia in mice to decipher schizophrenia? No. It was clinical experience and self-experimentation that disclosed schizophrenia as a disease of the brain and not aberrant personality or the work of witches. A Swiss chemist Albert Hofmann was working with the fungus ergot when, after a long day, he felt unusual and dizzy. He went home and experienced hallucinations similar to those experienced by schizophrenics. He went back to lab the next day and purposefully took the chemical derivative of ergot that he had been working with the day before – lysergic acid diethylamide, which we call LSD. Hofmann's second "trip" was the same. His serendipitous finding suggested that schizophrenics might have too much of a chemical similar to LSD that cause their disturbances. Further human-based observations helped establish the biochemical basis of this mental illness.

88. Genetic research has made diagnosing psychiatric illness easier, as it appears to run in families. Gene research has actually identified one cause of schizophrenia as a defect on chromosome 6. Comparisons of PET scans conducted while schizophrenics were hallucinating as well as while they were not, allowed researchers to see which parts of the brain are active during psychotic breaks.

89. Using brain scans, scientists found that introverts have more blood flow and activity in brain areas known as the frontal lobes and in the anterior thalamus, which are believed to be responsible for remembering, problem solving, and planning.

In contrast, extroverts exhibit more activity in the anterior cingulate gyrus, temporal lobes and posterior thalamus – areas considered more involved in sensory processing such as listening, watching or driving. Considering these fine distinctions in personality strictly within the human species, does it not seem probable that mental disorders are governed by equally subtle differences?

90. The animal model can otherwise botch medications too, with psychiatric ramifications. Many medications were tested on animals without apparent side effects, only to cause severe psychiatric disturbances in humans. Hallucinations occurred in patients given acyclovir, amphetamines, anticholinergics, antidepressants, antihistamines, barbiturates, benzodiazepines, isoniazid, ketamine, levodopa, methylphenidate, pergolide, and many other medications. Psychosis was seen to develop in patients taking steroids, anticonvulsants, bupropion, clozapine, cycloserine, quinidine, trimethoprim-sulfamethoxazole, and many others. Depression was found in patients taking HMG-CoA reductase inhibitors, isotretinoin, mefloquine, vinblastine and many others. Patients taking oestrogens, sumatriptan and other seemingly unrelated drugs experienced panic attacks. Procaine derivatives gave some people a feeling of impending death. Calcium channel-blockers resulted in some patients becoming depressed. The February 13, 1998, issue of *The Medical Letter* listed over one hundred medications and classes of medications that provoke psychiatric disturbances in human patients. Animal testing did not and cannot predict these things.

91. As seen, beneficial research, which has actually helped people with mental illness, historically issues from nonanimal based research. As a direct result of the ineffectiveness of animal modelling of mental illness, clinical psychologists largely ignore studies on animals. A study in 1979 revealed that only 7.5 percent of the articles referenced by scientists contained experiments on animals.[25] A similar study in 1986 revealed that only 33 out of 4425 (0.75 percent) references in the clinical psychology literature were animal studies. In reviewing the 1984 volume of the *Journal of Consulting and Clinical Psychology,* Kelly found only 0.3 percent of references were animal-based. In reviewing the 1984 volume of *Behaviour Therapy*, a journal that one would expect to use animal data, Kelly found only two percent of references cited referred to animal models.[26] A study published in the November

1996 issue of *American Psychologist* reported that only 5.7 percent of clinical psychologists felt that completely banning animal experimentation would be detrimental to their practice.[27] However, the funnelling of grant monies earmarked for mental illness study into animal labs continues. As one scientist sums up,

> Many of the psychotropic drugs were discovered by chance when they were administered for one indication and observed to be helpful for an entirely different condition. The history of the development of both the major antidepressants and the antipsychotic drugs points up the fact that major scientific discoveries can evolve as a consequence of clinical investigation, rather than deductions from basic animal [-modelled] research.

Conclusion

92. It is disturbing when one hears from medical colleagues that they frequently look back on their clinical learning and practice history with critical regret. For example, the problems of iatrogenesis and the poor results from former and ongoing protocols can prove demoralising for doctors and other health care professionals. We ask: How much does this potentially preventable situation result from the use of animals in biomedical research? Science is such a successful philosophy because new theories are formed and old ones abandoned, based on evidence. The evidence demonstrates that using animals as models for humans is not beneficial to humans today.

93. The animal model is a failed paradigm, which should be, and fortunately is being, replaced by gene-based medicine. In light of the knowledge we have obtained about interspecies differences, vis-à-vis the Human Genome Project and studies like the following, it should come as no surprise that trans-species extrapolation is unreliable. Among 10 medications withdrawn from the US market between 1998 and 2001, eight had more severe side effects in women than in men. The 10 drugs were Pondimin, which led to valvular heart disease; Redux, which also led to valvular heart disease; Rezulin, which led to liver failure; Lotronex, which led to ischemic colitis; Seldane, which led to a life-threatening heart condition known as Torsades de Pointes

(TdP); Posicor, which lowered heart rate and caused drug interactions; Hismanal, also caused TdP; Propulsid, also caused TdP; Raxar, also caused TdP; and Duract which led to liver failure. All but Raxar and Duract were more toxic to women. A study in *Science* revealed that one strain of mice could have a gene removed without obvious adverse effects while a similar strain of mice would die without the gene. If men cannot predict the effects of a drug for women and one strain of mice cannot predict what will happen to another if a gene is removed, is it not likely that medical research has reached the level of study that distinguishes one species from another and even individuals from each other? If men cannot predict drug response in women, how will monkeys do it?

94. We conclude that the abandonment of animal models is absolutely vital for medicine to advance. Modern-day molecular biology has revealed differences between species and the presence of these differences is explained by evolutionary biology. Paradigm shifts, such as occurred in physics in the early 20th century do occur. It is important to remember that when a paradigm shift occurs it does not mean that everything that went before it was wrong. Modern physics did not refute nor negate Newton's laws but only modified them. Newton's laws are still used daily, but Newton's physics cannot explain objects at speeds near that of light, nor can it explain the effect gravity has on light. Hence a paradigm shift occurred. Likewise, animal models were successfully used to explain areas of physiology or anatomy that were less sophisticated than those we are studying today. Modern-day biomedical research methodologies, such as those listed earlier, could have been used to discover everything that animal models were used for in the past, but they also give us data and discoveries that animal models never could and never will.

95. Using animals to model humans should be abolished because this practice so frequently leads to human death or suffering and so rarely leads to cures or treatments. Society need not fear that by abolishing animal models for the study of human disease, they would be asked to give up medical progress. The effect would be precisely the opposite – it would lead to greater scientific excellence in medical research, greater safety, a greater expectation of sound results, and far higher probability of cures for human illness.

96. **We would actively support the establishment of a new centre for neuroscience research in Cambridge that would genuinely advance the search for treatments for distressing human disorders. Such a centre would place Cambridge at the forefront of global science, would contribute to wealth creation through the knowledge-economy, and would certainly not involve research on monkeys or, indeed, any animals.**

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