Europeans for Medical Advancement

Where animals are used as surrogate humans, for example to develop medicines, as 'models' of human disease, to test surgical techniques or in toxicity testing (as listed in your background notes p10-11) the practice results in substantial harm to human health and safety. There is abundant evidence for this in the published scientific literature and we have collected many examples together in our book "*Sacred Cows and Golden Geese*" - please find a copy enclosed. As a brief summary, a short list of some of the more obvious examples follows:

Developing medicines:
Scores of treatments for stroke have been developed in animals but not a single one of them has been successful in humans - rather, they have harmed patients in clinical trials. The arguable success—the clot dissolving drugs—came from cardiac medicine where they were used in heart attack patients and were subsequently applied to stroke.

Hormone Replacement Therapy, designed to reduce women's risk of cancer and heart disease based on research in animals, actually doubles women's risk of cancer and heart disease.

Models of human disease:
Despite decades of effort and investment of huge sums of money, experiments on animals have misled researchers. In fact, according to the US National Cancer Institute, we have lost cures for cancer because of experiments on animals.

AIDS research in animals has likewise consumed vast amounts of resources but produced nothing of value to clinical medicine. The first experimental vaccine; Aidsvax, has been pronounced a failure this year. It protected chimpanzees from infection, but failed to protect 8,000 high-risk volunteers in the trials.

Testing surgical techniques:
Extracranial-intracranial (EC-IC) bypass surgery for carotid artery disease was tested in dogs and rabbits and consequently approved for humans. Only after thousands of operations did surgeons discover that the procedure was killing more patients than it saved.

Performing radial keratotomy (corrective eye surgery) on humans as it had been performed on rabbits resulted in many patients being blinded.

Toxicity testing:
Countless drugs, which have been safety-tested in animals, go on to cause serious side-effects, including death, in humans. Adverse drug reactions are the fourth leading cause of death in the Western world, killing over 100,000 people every year in the US alone. Clearly, the animal tests are not an effective safety net. The fact that 80% of drugs fail in Phase I clinical trials after passing animals tests is enough in and of itself to indict the animal testing system.

Many environmental poisons have been permitted continued sale and damaging exposure to humans because the manufacturers were able to cite safety data from animals. The most obvious examples include cigarettes and asbestos, both of which were claimed to be safe long after human epidemiological data had shown otherwise. The price of such unwarranted faith in animal experiments has been many millions of human lives.

Not only are there myriad empirical examples of the failure of the animal model in biomedical research, but there is a sound scientific explanation of why the paradigm fails and, indeed, why we should expect it to fail. The explanation given here is the briefest summary possible - we strongly recommend Chapters 1 and 2 of "*Specious Science*" (enclosed) and "*Brute Science*" (LaFollette and Shanks) for a fuller explanation than space allows here.

Predictability

A model 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*. 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 of people in France were infected with HIV through blood transfusions because the contaminated blood had been tested on primates and no adverse effects observed.

Only by comparing the results from testing each given substance or procedure in an animal species with data from humans 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.

Animal experimenters will insist that animals are still necessary because without them, 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 do better than the non-animal methods 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 as we will very briefly explain below.

Is inter-species extrapolation feasible?

Comparative biology reveals that many gross anatomical features are conserved across the animal kingdom, for example all mammals have hearts, lungs and immune systems and share many of the same cell types and tissues. This is not surprising since all mammals evolved from a common ancestor and all have their genetic material encoded in the same language; that of DNA.

More recent studies in molecular biology and genetics have revealed that very small genetic differences between species can be of enormous biological significance. The difference may

not even be in the *sequence* of a gene but rather in the way it is *regulated*, which may have dramatic morphological and physiological consequences.

As an example, humans and chimpanzees are 99% identical at the DNA level, yet no-one could mistake the two species as one. Clearly, very small changes in gene sequence or regulation can lead to very large differences between species - indeed, this is what evolution is all about. In fact, all mammals contain to a large extent the same genes; it is the differences in how these genes are expressed that accounts for the enormous diversity of living systems.

To illustrate this metaphorically, it is as though all mammals share a common genetic keyboard on which different phenotypic tunes are being played. Very different tunes are created from the same notes by pressing the keys in a different order and for different lengths of time.

Within any given species, genes interact with each other in *networks*, which give rise to *complex* relationships where the behaviour of the whole system depends on interactions between its parts in a non-linear way. Living organisms such as mice, monkeys and men are examples of complex systems, which differ from each other in *unpredictable* ways (an inherent trait of complex systems); thus negating linear extrapolation between them.

In summary: small variations at the genetic level not only define a species but confound the ability of one species to 'model' another in aspects such as disease mechanisms and drug effects.

The success and credibility of science are anchored in the willingness of scientists to obey two rules: 1) expose new ideas and results to independent testing and replication by other scientists; 2) abandon or modify accepted facts or theories in the light of more complete or reliable experimental evidence.[1]

In this age of technological advancement, we have reached the point in our knowledge of biology where animal models are no longer of value and will in all likelihood mislead us. Therefore, this archaic paradigm must be replaced if we expect to pursue scientific knowledge in accordance with the rigorous standards that ensure scientific integrity, advance scientific knowledge and improve the quality of human life. Using animal models in predicting human outcomes of disease delays medical progress by providing false and misleading data - and actually costs human lives.

[1] Robert Park, *Voodoo Science: the road from foolishness to fraud,* Oxford University Press 2000, p3

Question 2: What are your views about the use of genetically modified animals in research?

Many scientists claim that genetically modified animals make better models of human diseases but this is fallacious. Such claims fail to acknowledge the enormous influence of the genetic environment of individual genes, i.e. the networks of interactions between genes, as mentioned in the answer to question one.

A gene is not an independent unit but part of an integrated system. A human gene placed in a mouse will be expressed in a completely different way than in its human environment. Additionally, 'disease genes' (apart from those of single-gene disorders like sickle cell anaemia) do not automatically cause disease, even in their natural host, unless triggered by particular environmental conditions. Even if the precise conditions that precipitate the disease in people were known, they would almost certainly be impossible to replicate in animals.

According to FRAME: "Hoping to understand the functions of human genes and cure human genetic diseases by introducing one or even a few human genes into animals is a simplistic, and possibly misleading, approach to medical genetics. It ignores: (a) the important contribution of the cytoplasm and extrachromosomal DNA in modulating gene expression and determining the phenotype; and (b) the complex interactions and control processes occurring between different genes."

Writing in the journal *ATLA*, T. Ben Mepham et al. explain why transgenic animals are nothing more than an empty promise:

It is apparent from an analysis of some transgenic disease models that the *actual* benefits of using the models are rarely completely equivalent to the *potential* benefits...The currently available transgenic models for cystic fibrosis (CF) illustrate this point. None of the strains is ideal, with either the genotype and/or the phenotype of the mouse failing to accurately model the human condition...There are several limitations in relation to the usefulness of the current approaches to developing transgenic disease models, particularly since many diseases are multifactorial. Problems persist when extrapolating data obtained by using such transgenic animals to the disease condition in humans.[2]

For example, mice with added human cystic fibrosis genes fail to model the human condition correctly; suffering principally from bowel disorders rather than lung disorders, which is the major problem for human sufferers of the disease.

Many human cancers have been 'replicated' in animals by inserting some of the genes involved. "One might expect that these animals would mimic humans symptoms, not just the genetic mutations. In fact, that is usually the exception, not the rule."[3] Clearly, adding a human gene or two does not make a human out of a mouse.

Question 3: What is your view about the use of alternatives?

Firstly, the word 'alternatives' is a misnomer. If a technology or model does not work, or is counterproductive, it should be abandoned. A scientifically invalid practice cannot be replaced with an *alternative*. We need *viable* methods, not *alternatives* to nonviable ones. This point is more important than a mere argument over semantics:

The 3Rs and looking for Alternatives are practices accepted by those involved in research using animals. Based on the assumption that experiments on animals, though unpalatable, are scientifically valid, leading to cures and treatments for human disease, proponents of the 3Rs advocate reducing, refining and replacing animal experiments with 'alternatives'. The principle clearly has merit from an animal welfare perspective. However, it makes no scientific sense because if a practice does not work, there is little point in reducing or refining it! The 3Rs have unfortunately become a smokescreen, which allows the continuation of animal experiments to seem acceptable - as long as the 3Rs are applied. The industry could not have dreamed up a better PR campaign!

Those who endorse the 3Rs and Alternatives promulgate the *'necessary evil'* view of animal experiments and say that they cannot be abolished until all such experiments, of which there are millions, are replaced by Alternatives. This would be a never-ending process. Animal experimenters claim that that each and every experiment must be assessed on a case-by-case basis for scientific validity and justification. However, science tells us otherwise: intractable differences between species mean animals *cannot* 'predict' how the human body will respond to a disease or a drug. Their use violates the most fundamental principle of biology: evolution. The whole 'animal model' paradigm should be rejected as unscientific.

The 3Rs serve to deflect attention and debate away from the very real issue of the scientific validity of animal experimentation. While appearing to focus attention on concern for the welfare of laboratory animals, those promoting the 3Rs avoid entering into dialogue on the justification of using animals as models of human disease. The scientific literature of the last 100 years or so reveals sufficient evidence to demonstrate that using animal data in medical research is misleading, dangerous and wasteful of resources.

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.

Animal experimentation continually falls short of satisfying the rigorous criteria that define real science - accuracy, predictability and applicability. Applying animal data to humans meets none of these requirements consistently. Why submit another species to pseudo-scientific exploration of human disease when human-based methods are available? By contrast, there exist many rewarding human-based practices, some time-honoured and some new, that provide accurate, usable information about our diseases and their cures. These methods do not require the guesswork that accompanies extrapolations from animal-data to humans. Further research and funding of the areas listed below would remove animal experimentation's enormous inadequacy and dangers:

1. Epidemiology
2. *in vitro* studies
3. Autopsies
4. Post-Marketing Drug Surveillance
5. Pathology
6. Genetics/Genomics
7. Combinatorial Chemistry
8. High-Throughput Drug Screening
9. Technology
10. Research with human tissue
11. Clinical research/ observation
12. Mathematical & computer modelling
13. Artificial Neural Networks
14. Microdosing with PET imaging
15. Stem cells
16. DNA chips
17. Prevention
18. Basic sciences such as chemistry and physics

And this is just a partial list. Many examples of each type of research are given in the two books enclosed. Non-animal methods, i.e. human based methods are the **only** way to find cures and treatments for human diseases, or to assess toxicity to humans of new drugs or chemicals.

Research involving *in silico, in vitro,* microdosing or neuroimaging have virtually unlimited potential - which will only increase with improvements in technology. They have the potential to harness all of our burgeoning knowledge of the human body and its diseases to the task of treating, curing and preventing those diseases.

In vitro techniques have a long and illustrious history, even changing the course of drug discovery with Sir Alexander Fleming's discovery of penicillin in 1928. Fleming's discovery of penicillin opened the door to the discovery, through classic *in vitro* research of almost all the classes of antibiotics we have today—the tetracyclines, the polyethers, mycins, macrolides, and aminoglycosides. The same kind of agar plate Fleming saw growing penicillin was used to develop the agar diffusion assays that found these new classes of antibiotics.

Advances in this technique paved the way for the discovery of other chemicals that led to drugs such as cyclosporin (used to prevent organ rejection), the avermectins (used against parasites), and the statins (cholesterol lowering drugs). In the 1960s, Taxol was discovered at the National Cancer Institute (NCI) in the United States through *in vitro* assays on human cells. Subsequent *in vitro* studies demonstrated the mechanism of action and revealed that it was effective against some cancers. Testing the drugs on isolated systems using *in vitro* techniques allows scientists to manipulate the chemicals in ways that are not possible in intact organisms. Both animal-derived tissue and human-derived tissue are used in this process; however, human-derived tissue is superior because it allows scientists to achieve a much better approximation of what the chemical will do in the human body.

In vitro technology continues to advance in other new and remarkable ways, taking maximum advantage of automation and computerized systems to accelerate and refine the collection and analysis of data. For example, Rice University scientists have designed the first fully automatic, computerized system that can track the movement of individual cancer cells growing in a three-dimensional culture of living tissue. The system can be used to categorize the metastatic patterns of different cancers. It can also help test the effectiveness of therapeutics that prevent cancer or slow cancer growth. Two types of cancer cells were used in the experiments that led to this breakthrough—a strain of breast cancer and a variant of skin cancer. "Studying tumor cell invasion in live cultures in real time is a significant advance," said study co-author Larry McIntire, chair of Rice's Institute of Biosciences and Bioengineering. The system not only enhances knowledge about how cancer invades tissues, it dramatically alters the methodology by which

scientists study the movement of cancer cells in living tissue. It is only through these *in vitro* studies of 3-D cell migration that scientists are able to gather data on critical factors that influence metastasis.

These and other important discoveries discussed earlier prove that *in vitro* technology is the cornerstone of medical research. Even the US government acknowledges this: "There is virtually no field of biomedical research that has not been affected by *in vitro* technology." As human tissue becomes more accessible to researchers, *in vitro* technology utilizing human tissue will no doubt lead to even more stunning breakthroughs. As Martin Ferguson of Ardais (a company using human tissue) stated, if scientists begin using human tissue, they "are going to find some very low-hanging fruit for druggable targets."

Testing directly in human tissue rather than in animal models allows drug development teams to obtain vital information about what their gene of interest is doing in a human system. Because animal models are not predictive of how drugs will behave in humans, obtaining information directly from human tissues is a critical step in choosing one target from many candidates. Even after the drug development process has begun, determining where a particular gene is expressed in other, perhaps unexpected sites within the body may assist researchers in the design and interpretation of pre-clinical or clinical studies.

According to Julia Wulfkuhle, a research fellow at the Food and Drug Administration / National Cancer Institute's clinical proteomics program, the best way to get accurate information for new drug development is to use human tissue. As she has noted, proteomics in cancer research has broadened the ability to identify specific changes in a tumor and target those changes; therefore, using human tissue for protein profiles offers "a truly *in vivo* approach" and allows analysis of variation across populations.

The work of J.A. Angus, of the Department of Pharmacology at the University of Melbourne, provides an example of how human-derived tissue is used in the drug discovery process. Angus and colleagues obtained heart tissue from human patients who had undergone heart transplant surgery. They studied the left and right main epicardial arteries in the tissue, and found them to have an abundance of plaque. They also obtained and studied healthy hearts that were not suitable for organ donation, as well as heart tissue from patients undergoing heart operations with cardiopulmonary bypass. (A small amount of heart tissue is removed during these operations to allow the placement of the cannulas necessary for bypassing the heart and lungs.) In doing so, Angus' group was able to compare the effects of various chemicals, such as nifedipine, sumatriptan, and potassium, on these arteries, thus shedding light on a heart condition known as variant angina. They also found that tissue from humans, rabbits, and dogs all responded differently to the chemical acetylcholine. Angus stated, "This is a clear example of how coronary microvessel pharmacology varies among three species and makes extrapolation from animals to man quite hazardous."

Angus continues, "The use of human tissue in pharmacodynamic studies is becoming appreciated as we learn that experimental animal-tissue assays do not always reflect human receptor homology and tissue structure."

The study of human male infertility at Birmingham Hospital (UK) is another good example of the value of human tissue in research. Scientists there were able to establish a method by which human testicular tissue obtained from biopsies could be transported and stored in such a way to maintain its cellular function. Now, they have established a tissue bank of samples, enabling vital research to take place using human tissue rather than rodent and primate tissue, which had been used before. Their research has shown for the first time in immature human sperm cells that human cells have active potassium channels but inactive calcium channels—data that was in marked contrast to that obtained by researchers working with rodents. Dr. Ian Brewis, one of the researchers on the team, stated, "We look forward to further

demonstrating that human research is the way forward. Already co-workers are taking notice of our work and discussing the limitations of animal work and potential of their work becoming more human orientated."

Until recently it was impossible to analyze individual subpopulations of cells in a tissue sample. However, high-throughput microdissection technology, such as that developed by Laser Capture Microdissection: Arcturus Engineering Inc. (Mountain View, CA) changed that. It is now possible to study individual cells in a tissue sample. This means that within a single tissue sample scientists can study normal epithelium, premalignant cells, and cancer cells. Different genes and proteins are found in each of the different cell lines. This is a boon for studying which proteins and genes are involved in a disease.

A technology called Raman Spectroscopy can analyse living cells. Scientists can put human cells in the Raman Spectroscope, stimulate a specific part with a laser and analyze the data it receives back to determine the chemical composition. Every cell has a different "fingerprint" depending on what chemicals it contains. By injecting the tissue with a drug the scientists can analyze the changes in the data and predict what will happen when the cell, in a human, is exposed to the same drug. The speed of the Raman Spectroscope enable scientists to watch the movement of a particular amino acid in enzymes at work, or a particular base of DNA while it is being transcribed, replicated or complexed to a transcription factor.

The discovery of the plant compound cyclopamine's ability to kill brain tumor cells, illustrates the fact that the use of animal models during the drug discovery and development process creates unnecessary redundancy, often resulting in confusion and delays. Cyclopamine is a chemical isolated from a weed that grows in mountain meadows in the western United States. Researchers at the Howard Hughes Medical Institute discovered that cyclopamine effectively killed cultured mouse medulloblastoma cells and tumors implanted in animals, as well as medulloblastoma cells extracted from human tumors. (Medulloblastoma is an aggressive brain cancer that affects some children, and currently there is no effective treatment.) The researchers found that the compound blocks a signaling pathway that appears to be important for the survival of this particular cancer. Since cyclopamine proved to be effective in human cells using *in vitro* technology, there was no need to use cultured mouse cells. Moreover, had the cyclopamine proved ineffective in mouse cells, the researchers either would have abandoned the hypothesis, or tested it on human cells, regardless of the outcome with the mouse model. Either way, the mice were a waste of time and resources. Had the researchers stopped if the cyclopamine had failed in the mouse model, they may not ever have uncovered a possible treatment for the disease in humans. Had they continued on anyway with *in vitro* investigations using human cells, then why would they bother with a mouse model to begin with? One wonders how many prospective drugs have been abandoned for not working in animal models, when they would have proved lifesaving for humans. By the same token, using animal models to duplicate results demonstrated in human tissue wastes valuable time and resources, which underscores the urgent need to abandon the animal model in favor of the non-animal technologies that hold much greater promise for delivering safe and effective medications to patients in need.

A recent editorial in *Nature Reviews Drug Discovery* stated:

In Tamoxifen's case, a drug first developed as a potential contraceptive languished for many years before its present application was found. Furthermore, its propensity to cause liver tumours in rats, a toxicity problem that thankfully does not carry over into humans, was not detected until after the drug had been on the market for many years. If it had been found in preclinical testing, the drug would almost certainly have been withdrawn from the pipeline. With the COX2 inhibitors, Rod Flower notes that the transgenic animal models used to test the hypothesis that COX2 would make an anti-inflammatory target gave results that, if relied upon, might have killed the project.

As Dr. Miles Weatherall, former director of Establishment, Wellcome Research Laboratories wrote in *Nature*:

Every species has its own metabolic pattern, and no two species are likely to metabolize a drug identically. Small differences in the rate of conversion of drug to inactive, or toxic, metabolite can have large effects on the concentration of active substances at the point of action. Most experiments to seek toxic effects in whole animals involve oral administration; differences in diet, gut physiology, rate of passage and liver enzymes raise serious questions about the relevance of findings in rats or mice to man. Compounds that are not absorbed in laboratory animals are not, with minor exceptions, ever tested in man. Nobody knows how many drugs, which would be useful in man, may have been lost in this way. Similarly compounds toxic in laboratory animals at doses near the predicted therapeutic level do not receive trial in man, so it is never revealed whether they would actually have been harmful in man. Thus we lack the evidence of the false positive element in animal toxicology studies, so it is easy to give more weight to such studies than is justifiable.

Graham Lappin, the Head of Research and Development at Xceleron Ltd, York Biocentre, and R. Colin Garner, the Chief Executive Officer at Xceleron Ltd. stated in *Nature Reviews Drug Discovery*:

The move from animal data to humans is done using a mathematical modelling process known as allometric scaling. Allometric scaling can be very misleading, as it is only about 60% predictive. Allometric scaling models are further complicated because substantial differences in clearance rates are found between animal species, a fact that calls into question which model is predictive of humans. Alternatively, a number of lead candidates might come out of a drug screening programme with similar pharmacological activities and identical animal ADME parameters. Which of these leads would make the best drug?

They then go on to describe human microdosing with accelerator mass spectrometry (AMS) and positron emission tomography (PET) technology and then continue:

The use of the ultrasensitivity of AMS and PET permits new approaches to obtaining crucial ADME data for selecting drug candidates. Microdosing studies are dependent on these ultrasensitive analytical techniques because only they have the necessary sensitivity to follow the fate of a trace drug dose in the human body. PET provides real-time data on drug disposition, whereas AMS is used to analyse drug and metabolite concentrations in body fluids withdrawn at time intervals after dosing.

The proposals of the EMEA [European Agency for the Evaluation of Medicinal Products] are to be welcomed, as they move the focus of early drug development away from laboratory animals to conducting safe and ethical studies in humans. The move to reduce animal usage... permits some of the resources previously spent on animal studies to be spent on human investigations.

As Jurgen Drews, former president of Global Research at Hoffman La Roche, has said:

For a long time it was considered necessary to carry out ADME studies on rats and dogs, or even on small primates such as marmosets. Yet these experiments were often disappointing in view of their lack of carryover to human beings. Only in recent years have models been developed from comparative analysis of a variety of animal species that allows more precise prediction about effects in man. *Despite any existing uncertainties, ADME studies on human subjects remains the basis for establishing correct dosages for patients and for the development of appropriate dosage schemes.* [Emphasis added.]

Dr M. G. Palfreyman, Dr V. Charles and J. Blander stated:

Mice and humans have more than 95% of their genes in common, yet mice are not men, or women.... Although cell-based and animal models of disease have been the cornerstone of drug discovery, it is increasingly apparent that they are of limited predictive value for complex disorders...One of the major challenges facing the drug discovery community is the limitation and poor predictability of animal-based strategies. Over the last decade, drug discovery has largely been based on finding targets in animal models and then identifying the human homologue...many drugs have failed in later stages of development because the animal data were poor predictors of efficacy in the human subject... One of the overriding interests of the pharmaceutical and biotechnologies industry is to...create alternative development strategies that are less reliant on poor animal predictor models of human disease...Although the species [chimpanzees] share more than 98.9% gene identity [with humans], the expression of genes in the brain was more than five-fold greater in humans than in the chimpanzees....Differences from mice were even greater. These differences reinforce the importance of using human disease models in drug discovery as a real predictor of human efficacy... Discovery of drugs that act on the human central nervous system, are best studied in human-cell based systems.

Referring to the use of human cells, the scientists state: "They are clearly superior to those obtained from animals."

Finally, just a few words on *in silico* approaches:

Not only can molecular modelling programs create new molecules from various combinations of existing molecules, they can also use evolutionary techniques to test the data and eliminate the poor performers, just as in nature we see the application of the "survival of the fittest" principle. In this way, virtual evolutionary techniques can help scientists design more potent and precise drugs.

The importance of determining the three-dimensional structure of a molecule is illustrated by the success in 2001 of a team of researchers, including scientists at the pharmaceutical firm Glaxo SmithKline, in determining the three-dimensional structure of pregnane X receptor (PXR), a liver enzyme that plays a key role in breaking down more than half of all drugs. "Unraveling the structural basis of how PXR recognizes an array of different...compounds is critical to our understanding of how harmful compounds are cleared from the body and may also improve our ability to predict and avoid dangerous drug-drug interactions," writes Dr. Matthew R. Redinbo, of the University of North Carolina in Chapel Hill, and his colleagues.

Screening that has taken weeks using cell-based assays can be accomplished in a computer model in less than a minute. Today, a wide range of predictive software is available, from GastroPlus, a simulation that looks at the absorption of a drug in the human GI tract by Simulations Plus (Lancaster, CA) to ComGenex's Pallas suite for predictions of pKa, logP, logD, metabolism and toxicity and Pharsight's (Mountain View, CA) clinical trial simulations.

ComGenex now markets a number of large databases of characterized compounds, including a collection of toxicological data from *in vitro* tests on human fibroblasts of 50,000 compounds. Clearly there is so much good human-based data that relying on animal-based data is a waste of precious time.

Question 4: What is your view about ethical issues relating to the use of animals in research?

Europeans For Medical Advancement has no ethical position on using animals in research, other than the human ethical issue that people suffer the consequences of biomedical use of animal models. Patients and volunteers are at risk in clinical trials because those trials follow directly after the animal testing phase, which, as we have explained, gives no guarantee of safety whatsoever. Consumers are exposed to hazardous chemicals because risk assessments in animals preclude scientific risk assessments using human based assays. All of us are denied medical progress because research is confounded and delayed by a deluge of irrelevant animal data.

If animal experiments do, in fact, advance human medicine, **then** there is an ethical issue as to how much suffering should be allowed in return for benefits to humans. But if, as we maintain, animal experiments do not advance human medicine, there is no issue other than the fact that conducting animal experiments is absurd, is unethical for both animals and people and should cease immediately.

In your background notes (p20) you ask if medical research would be slowed down by ending the use of animals. In actual fact, medical research would be accelerated because the major contribution of animal experimentation is to slow down medical research. Scientists follow endless false leads from animal experiments: cures for cancer, for example, are announced in mice virtually every week but none of them ever translates to clinical success. It is apposite to quote here Dr Richard Klausner's comment, when he was Director of the National Cancer Institute, that:

"The history of cancer research has been a history of curing cancer in the mouse... We have cured mice of cancer for decades - and it simply didn't work in humans".

Question 5: What is your view about the UK regulations on research involving animals in the UK?

The cost-benefit analysis (COBA) is central to ASPA in theory but is utterly ignored in practice. If the COBA was properly conducted, no experiment involving animals as models of human disease or as toxicity screens would be licensed. Irrespective of whether the cost is measured in terms of costs to animals or to people, the benefit to people **must** be demonstrated. We contend that such experiments not only provide no benefit for people, they are demonstrably harmful. Therefore, if the COBA was conducted scientifically, the outcome would always (in such cases) be negative.

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The concept of evidence-based medicine has been established by the research community as the best method of determining the value of research. There is currently no evidence that animal experimentation is beneficial to clinical research and yet it is clearly funded in preference to clinical research - which, as acknowledged by the MRC, BMJ and others, is in crisis. This situation is evidently not in the best interests of patients.

Professor Colin Blakemore, chief executive of the MRC, said: "Clinical research is at the heart of the MRC's mission to improve and maintain health. But more money will be essential if this vitally important area of work is to be carried forward." [4]

Currently, there are only 50 clinician scientists across the UK, and the MRC funded just eight clinical trials in 2001-2, of which only four were new. "A failure to underpin clinical research now will result in a cost to human life, maybe not today or tomorrow, but certainly over the next 10-20 years." [5]

It is imperative that evidence is produced to support the value of animal experimentation before further valuable and scarce resources are allocated to it, when they are clearly needed for clinical research.

"The vast majority of drugs - more than 90 per cent - only work in 30 or 50 per cent of the people," according to Allen Roses, worldwide vice-president of genetics at GlaxoSmithKline. This means that most drugs are at best useless, and even possibly dangerous, for many patients. "Neither those who pay for medical care nor patients want drugs to be prescribed that do not benefit the recipient. Pharmacogenetics has the promise of removing much of the uncertainty" [6] adds Roses. This is precisely our point: instead of wasting money on animal studies, we should be investing in pharmacogenomics and other relevant human-based approaches. Professor Sir Michael Rawlins, chairman of the National Institute for Clinical Excellence, bemoaned the fact that the animal study regime, which could take up to six years, was "utterly futile".[7]

The COBA should certainly be published because it represents the justification to the public of research that is done in their name, with their money, for their supposed benefit. Scientists should be accountable to society, particularly with respect to issues that are of such concern to society.

According to Lord Winston, "Science is done on behalf of, and funded by, people as taxpayers or consumers. It belongs to them."[8]

Question 6: What do you think about the information that is available to the public about research involving animals?

The information available to the public is completely inadequate for the purposes of anyone wishing to make an assessment of the justification that has been made for experiments which are of concern to them (whether as a patient with an interest in particular research or as someone interested in animal welfare or as a taxpayer or for any other reason). The public has a right to know what types of experiments are being conducted on its behalf and with its funding.

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Clearly, information regarding the nature of experiments and their COBA should be published **before** the experiments are conducted if there is to be any meaningful engagement with the public or any opportunity for independent scrutiny of applications before they are granted.

The secrecy enshrined in the regulations is plainly to the detriment of science, of animal welfare, of public understanding as to how its money is being spent, and of open debate.

In a recent debate in the House of Lords (17th Oct 03), Lord Lucas called for better access to information regarding animal research. He made the point that one of the "principle causes of animal terrorism" was the way information was withheld from the public. He said, "We are not allowing any legitimate democratic discussion of these matters and we should not be surprised when that causes ulcers to erupt on the body politic".

Professor Colin Blakemore said, "Medical science is advancing so fast and has to grapple with ethical issues in fields such as genetics, stem cells and animal experimentation. It's vital that people know about the legal and ethical safeguards and trust scientists to do the work. But that trust will only come if we're willing to talk openly about what we're doing and why it's important. If scientists don't do more to engage with the public about their work, people will remain confused and sceptical of the benefits that medical research can bring."[9]

It is clear that people or institutions with a vested interest in research involving animals cannot be trusted to provide balanced information about that research. A study in *Science* in 2001 found that institutional animal care and use committees (IACUCs) will approve animal experiments at their own institution, which they would reject at a second institution.[10] People working for institutions that use the animal model are and will continue to be pressured to state implicitly or explicitly that the animal model is viable.

Europeans For Medical Advancement believes that medicines that were developed using animals should be labelled as such. There should be a health warning to the effect that new medicines have been tested on animals but that animal tests frequently give different results from tests on humans. Until the new medicine has been shown through long-term human administration to be safe and effective, consumers should consider using older, established medicines instead.

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[9] *Times*, 1st Oct 03

[10] Scott Plous and Harold Herzog, *Science* 2001; **293**: 608-9

[Europeans for Medical Advancement also submitted the foreword (written by Jane Goodall PhD) to Jean and Ray Greek's book "Sacred Cows and Golden Geese, The Human Cost of Experiments on Animals"]