

ANIMAL MODELS

One of the major ways in which animals are used in medical research are as 'models' of human diseases such as Parkinson's, Alzheimer's or diabetes. However most of these diseases do not naturally occur in animals, and where they do the disease behaves in quite a different way so the gross symptoms of any given disease (but never the human disease itself) have to be artificially induced in the animal model, or 'disease genes' are inserted into their own genomes. Yet artificially creating symptoms in this way not only inflicts a great deal of suffering on the animals used but it also fails to address the underlying causes and natural progression of the human disease.

The induction of disease or illness in laboratory animals can include deliberate infection, surgical damage of regions of the body, manipulation of the animal's environment (using Ultra Violet radiation, heat or similar techniques) or the injection of damaging drugs and chemicals.

The basic and flawed assumption is that these animal models behave as simple 'stand-ins' for humans and where species differences are known, these can be 'accounted for' in the assessment of results. In fact the animal species most commonly used in these experiments – rats, mice, cats, dogs and primates – have quite different body structures, biochemistry, behaviour, needs and responses. The supporting biology and chemistry of each species is very different and consequently the disease-like conditions that result from this type of experimentation can only ever hope to be, at best, a superficial likeness to the human condition. They can never replicate the human disease or the multifarious and complex physical and psychological manifestations of the human condition.

Examples of using animal models to investigate brain diseases such as Parkinson's Disease, stroke and epilepsy are discussed in the BUAV factsheet U3 Neurological Diseases. This factsheet looks at some recent examples where the use of animals as models for humans has resulted in misleading results, perhaps even delaying progress into understanding devastating human diseases.

Rheumatoid Arthritis vs. Collagen Induced Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease. This means the immune system of an RA sufferer produces antibodies against the body's own tissues, autoantibodies. This effectively leads the immune system to attack and destroy body tissues as if they were foreign 'invaders' such as viruses, bacteria or transplanted tissues or organs.

There are currently over 600,000 sufferers of RA in the UK, experiencing symptoms such as chronic pain, inflammation and joint deformity. Current treatments include non-steroidal anti-inflammatory drugs, steroids (in tablets or by injection) or non-specific immunosuppressants.

Two important types of white blood cell involved in immune responses are B cells and T cells. B cells are effectively responsible for producing antibodies, though they cannot do this without the help of T cells. T cells recognise the difference between 'self' and 'non-self' molecules. Therefore it has long been thought that autoimmunity is initially induced when T cells mistake 'self' for 'non-self'.

RA does not naturally occur in rats and mice so to create an animal model of the disease autoimmunity must be induced. Researchers have classically done this by immunising animals with self molecules (usually collagen). However, the kind of

autoimmune response is quite different to that seen in human RA sufferers.

A report from the Association of the British Pharmaceutical Industry (ABPI) entitled 'Agenda for Health - Supporting the Science Base' published as long ago as 1992 stated:

'The need for a new generation of DMARDs (disease modifying anti-rheumatic drugs) is clear. To this end the pharmaceutical industry has implemented many research projects over the past 20-30 years to exploit advances emerging from fundamental laboratory studies in the belief that they may be the key to the control of joint erosion. Despite an expenditure of hundreds of millions of pounds and the synthesis and evaluation of thousands of compounds, no cure has been found'.

In 1998 a team from University College London lead by Professor Jonathan Edwards published a new theory on disease progression in RA patients based on clinical observations¹. Professor Edwards suggested that human autoimmunity worked in a very different way to the animal model. The T cells do indeed mistake 'self' for 'non-self' molecules, but this is because autoantibodies produced by the B cells fool them into making that mistake. Therefore, it is the B cells that are ultimately responsible for RA in human sufferers, not the T cells as in the widely used animal model.

Professor Edwards has told the BUAV,

'[The standard animal models of RA] are self-evidently wrong for any analysis of causality and disease system dynamics or assessment of drugs aimed at underlying causal pathways. They might have been useful for studying non-specific inflammatory mechanisms but I am not convinced they have contributed significantly to treatment of any sort. I believe this is an important reason for the lack of progress in treatment of RA'.

In other words, not only have tens of thousands of animal experiments failed to lead to any meaningful treatment, they have in fact been positively harmful by leading research up a blind alley. But still some researchers persist in using the animal model

(licensed, of course, by the Home Office). In August 2000 a paper was published by researchers at the Kennedy Institute of Rheumatology in London describing the effect of cannabidiol (a non-psychoactive ingredient of cannabis) in mice with collagen induced arthritis (CIA)².

In this experiment, funded by the Arthritis Research Campaign, mice were subjected to a series of injections of collagen, a constituent of the pads of cartilage which protect the ends of bones and are broken down in the course of arthritic disease. This causes the animals' immune system to attack the animals' own collagen, causing an arthritis-like response. Researchers used collagen from cows to induce an acute form of CIA and from mice to induce a chronic relapsing form of CIA.

Once mice started to show clinical signs of arthritis they were given cannabidiol via a tube pushed down their throats or via injection into the abdomen, for 10 days (in those mice given acute disease) or 5 weeks (in those mice given chronic disease). More than 110 mice were used in this experiment.

Symptoms of CIA the mice suffered include:

- swollen, red and inflamed joints
- stiff and immobile joints
- painful joints

However 42 of the mice were used as controls and thus received no treatment for the symptoms of the CIA.

At the end of the experiment all of the mice were killed and had their hind paws cut off. These were then cut into slices and examined for joint damage revealing the full extent of the injury inflicted by the researchers. The researchers classified the damage to the animals joints as mild (inflamed membranes around the cartilage), moderate, or severe (where cartilage and bone has been destroyed altering the structure of the joint).

All of these conditions cause pain and discomfort and prevent animals carrying out normal behaviours such as exploring, grooming etc, which in itself can cause considerable distress.

Multiple Sclerosis vs. Experimental Allergic Encephalitis

Multiple Sclerosis (MS) is a devastating disease of the Central Nervous System (i.e. the brain and the spinal cord), affecting 0.1% of the population. Symptoms are many and varied and can include; tiredness, vision problems, loss of balance, bladder problems, slurred speech, difficulty swallowing, stiffness and spasticity.

The cause of the disease is unknown but for many years MS has been thought, like rheumatoid arthritis, to be an autoimmune disease, where a patient's immune system mistakenly attacks parts of its nervous system. This assumption was based largely on superficial similarities between MS and an artificially induced condition in laboratory animals called Experimental Allergic Encephalitis (EAE). All subsequent treatments have been based on this theory, when in fact there are astonishing differences in the induction, symptoms and progression of EAE and human MS.

EAE is induced in animals (usually mice but also rats, rabbits and monkeys) by injecting them with cells and tissues of the nervous system to trigger an immune response. Although EAE causes some MS-like symptoms (such as weakness, paralysis, incontinence etc), there are significant differences between the two conditions:

- EAE either kills animals or leaves them with permanent disabilities. In humans, MS attacks generally subside and reoccur.
- Animals with EAE also suffer severe nerve inflammation, whereas in MS inflammation is usually mild, if present at all.
- The time course of EAE is also entirely different to MS.
- The EAE model is not induced in a way which mirrors the rise of MS nor does it show the range of clinical symptoms and progression of the human disease.

Despite extensive research and a vast research literature (where more animals have been given EAE than there have been cases of human MS) the

cause of the clinical condition remains unknown. There is, to date, no effective treatment.

Neurology experts from Glasgow University and the Leiden University Medical Centre caused controversy in 2002, when they published an article suggesting the commonly used animal model of MS was so inappropriate that its use had actually delayed progress in MS research³. They state "*Treatment protocols in EAE are many but those used in humans, based on the findings in animal EAE, have singularly failed in alleviating the symptoms and signs of MS*". They go on to say "*The acceptance of EAE as a model for MS is an unfortunate error that has its basis on faith rather than science*".

The Glasgow and Leiden neurologists argue instead that MS is caused when support cells called astrocytes malfunction - perhaps as a result of genetic and environmental triggers. They claim that there is increasing evidence that astrocytes go awry in MS patients. What these neurologist are now saying, mirrors what animal protection groups like the BUAV have been saying for years, that EAE is significantly different from MS. Furthermore, because research into MS has, for many years, been based on these misleading animal experiments, vital research into the human condition has actually been delayed.

¹ Immunology 1999 Jun;97(2):188-96

² Proc Natl Acad Sci 2000; **97**:17; 9561-6

³ J R Coll Physicians Edinb 2002; **32**: 244-265

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