National Anti-Vivisection Society (NAVS)
Lord Dowding Fund for Humane Research (LDF)

Proposed Centre for Behavioural Neuroscience at the University of Cambridge

NAVS response to the comments of Lord Sainsbury, minister at the Department of Trade and Industry (DTI) in support of the new primate lab

Ignoring the concerns and protests of local people, Lord Sainsbury, minister at the DTI, has thrown the Government's weight behind the University's appeal against refusal of planning permission.

Lord Sainsbury states that his department would regard the proposed primate laboratory as *"nationally important"*.

The minister asserts that with our *"world class neuroscience"* such a centre would *"consolidate the UK's position as a global leader"*, and that the centre brings together scientists to work in an inter-disciplinary environment using state-of-the-art facilities. Lord Sainsbury feels that such centres must be nurtured so that they can enjoy the modern facilities required for leading-edge research.

All very laudable objectives which everyone can support. After all, we all have a stake in good medical research. The mistake the minister makes is the assumption that such a leading-edge centre must use animals. Furthermore, the vast sums of money spent on such research must go to sophisticated, well thought out projects which are relevant to our own species.

The UK will continue to have world-class neuroscience without the setting up of a centre to conduct work on non-human primates, or any other non-human mammalian species. Ground-breaking, innovative neurological research is being conducted in the UK without the use of animals, such as at the Neurosciences Research Institute at Aston University (see below).

Experience has shown that both behavioural neuroscience and other neurological experiments on animals are fundamentally flawed due to species differences (see below).

Aston University: world class research, based on study of humans:

Outside of Cambridge University, scientists are committed to promoting the UK as a centre of excellence without the use of animals. The Neurosciences Research Institute at Aston University is a prime example of such foresight, with its plans for a new 'Academy of Life Sciences' to open in April 2004. The £8 million Academy will provide the opportunity for innovative cross-disciplinary work by the integration of clinically related research in neuroscience. It will include research groups working on behavioural and cognitive sciences, neuroimaging, vision, ophthalmic and physiology optics.

The claims of the animal researchers who want the centre:

In his support for attempts to overturn the refusal of planning permission, Lord Sainsbury quotes researchers from the field of animal neuroscience, who claim that the centre: *"promises internationally competitive science"* and is *"very likely advance our knowledge significantly in the field of central nervous control of behaviour"*. It is also claimed by those in the industry that *"Medical research, pharmaceutical research, and our knowledge of the brain/ mind, all will benefit enormously from this initiative"*.

But is this really the case? Let's look at the facts:

New techniques avoid problems of species differences:
Knowledge in the field of central nervous system control of human behaviour is constantly increasing, due to rapidly advancing, innovative technology in the field of neurology research for the study of human volunteers (see below).

Medical research:

The physiological (the functional reactions in the body) response of an animal to a painful or distressing stimulus varies not only between species but between individuals and is determined by the genetic makeup of an animal (1).

Non-human primates, despite their evolutionary closeness to us, are distinct from us in the way they express genes in the brain ("expression" of a gene is the activity or product that the gene causes to occur in the body). There are even big differences in gene expression between humans and chimps, although gene expression between chimps and other non-human primates is similar (2).

Another hurdle when using animals to model human nerve diseases (or any other disease for that matter) that has not been overcome is that the human form of the disease can never be completely replicated in an animal. Animal models of the neurodegenerative disease Alzheimer's, for example, do not develop the characteristic 'neurofibrillary tangles' or show significant nervous system degeneration (3).

Pharmaceutical research:

One of the major causes of death in the western world is from adverse reactions to drugs despite that all pharmaceuticals have been tested on animals for safety and efficacy before entering the market.

An anti-Parkinson's disease drug, tolcapone (Tasmar) was withdrawn from the market in 1998 for being linked to deaths from liver disease (4). Similarly, the antidepressant Seroxat was also linked to liver damage, in 1997 (5). The safety of donepazil for Alzheimer's came under review in 1999 resulting in updating of product information (6), and clinical trials of a potential Alzheimer's vaccine were suspended this year when participating patients began experiencing side-effects to the nervous system (7,8). The vaccine had been hailed as *"revolutionary ..following encouraging tests on animals"* (9).

Drugs which may appear to cure a disease which has been artificially induced in laboratory animals are not guaranteed to do the same for people. Only in humans can the relationship of subjective and discriminative drug effects be assessed at the same time (10). The therapeutic effects of the appetite suppressant fenfluramine for autism and its potential to reduce suicidal tendencies, for example, were discovered in people and could not have been predicted in animal experiments (11).

Knowledge of the brain/mind:

Little, if anything, can be gained by studying the brains/minds of non-human animals. The behavioural response of an animal to a painful or distressing stimulus varies not only between species but between individuals (1).

The processes involved in behavioural responses in humans is known to be more complex than in other species (12), and no animal species reacts to behaviour altering drugs in the

same way as a human being would (13). For example caffeine, which can induce panic attacks in people, has conflicting results in animal models of anxiety (14).

As for the human 'feeling state', there is no parallel that can be drawn from animals, as they cannot tell us how they feel. Depression, for example, is a complex human reaction (15) and there is no animal that can model the symptoms of schizophrenia (16).

Primate neuro-research:

Currently Cambridge neuroscientists are working on common marmosets. However, at the new £24 million centre for neuroscience proposed by the University of Cambridge they would conduct research on macaques as they believe marmosets do not make good models due to their small brains (17).

Macaques as experimental models for human diseases:

For two years an investigator from the NAVS Special Investigations Department worked undercover as a laboratory technician inside two British research institutions, one of which was the Institute of Neurology. Here, in the Sobell Department of Neurophysiology, a researcher was using macaques for a study of the nerve connections between the brain and muscles of the hand. For the purpose of the experiments, the macaque skull was fitted with a headpiece and recording/stimulating electrodes in various parts of the brain. The intention was to study the effects of brain stimulation on learned tasks and to this effect wires were connected from the headpiece directly to selected muscles of the forelimbs. A dye was injected into the parts of the brain studied so that the nerve connections can be traced after the monkeys have been killed (18).

However, it is unlikely that progress will be made in the study of the human brain by using laboratory animals. As researchers at two prestigious institutions, the Salk Institute and the University of California wrote: "What is known about the neuroanatomy of the human brain? Do we have a human cortical map corresponding to that for the macaque? And what does the human equivalent of the connectional map look like? The shameful answer is that we do not have such detailed maps because, for obvious reasons, most of the experimental methods used on the macaque brain cannot be used on humans ...For other cortical regions, such as the language areas, we cannot use the macaque brain even as a rough guide as it probably lacks comparable regions" (18).

Instead of studying brain function in macaques, it would be better for researchers to apply scanning techniques to human patients and volunteers, and to study human post-mortem specimens. Researchers would then be learning about humans and not monkeys.

Parkinson's disease research:

Parkinson's disease is unique to humans (19), slowly progressing, whereas in the artificial lab disease 'model', using the drug MPTP, the disease is rapid in its course. There are differences in nerve degeneration and the transmission of nerve impulses in naturally-occurring human Parkinson's disease and MPTP-induced Parkinson's disease in animals (20). Also, there are major differences at both the behavioural and neurochemical (nerve chemistry) levels between marmosets and cynomolgus monkeys when administered MPTP, making it impossible to predict with any certainty how results of macaque and marmoset experiments can be applicable to humans (21).

Macaques:

One British researcher had been working on macaques to investigate treatment for Parkinson's disease since 1997. He had been inducing neurodegenerative symptoms of the disease in the macaques by giving them the MPTP and then performing surgery on the animals as an approach to 'treatment'.

However, 6 months ago the Home Office put a freeze on his work, demanding further justification for the research and imposing modifications to his experimental procedures (17). In 1999 the government advisory body, the Animal Procedures Committee (APC), voiced concerns about the use of macaques in MPTP-induced Parkinson's disease. One reason was due to the differences in brain architecture between human beings and macaques, raising doubts about the transferability of results. Nevertheless, the APC decided to grant a project licence anyway (22).

Marmosets:

There are differences between MPTP-induced Parkinson's in marmosets and human Parkinson's patients - the absence of Lewy bodies (as seen in Parkinson's patients) in marmosets (22).

Previously, the rather poor reason given by researchers for the use of marmosets was their small size. Now, they are citing the difficulty being that the animals' brains are too small (17). Despite these drawbacks, an application relating to Parkinson's disease involving several hundred marmosets was seen and approved by the Animal Procedures Committee during 1999. The planned procedures were rated in the 'substantial' severity category (22).

Parkinson's disease experiments on animals - non-animal replacement techniques:

- In primate experiments where electrical activity of brain is recorded after injection of drugs that affect brain function (MPTP), human patients could be studied instead with scanning techniques. Patients in whom Parkinson's disease has been induced with MPTP underwent brain scans using high resolution PET and the drug fluorodopa (23).
- Surgical lesions in the brain, located by electrodes while the patient is still conscious, are a normal, common procedure in the treatment of Parkinson's and are known to be effective (24). A potentially successful new treatment method involves deep brain electrical stimulation (25,26).
- Behavioural changes in patients in whom corrective lesions for Parkinson's disease have been made have been studied post-surgery by MRI scans of their brains (27).
- Microelectrodes have been used in human patients for detection of the areas where lesions need to be made in the brain, for recording and stimulating. In this way, tremor and movement cells can be located (28).
- The effect of patient's movement on the lesioned brain has been assessed in human Parkinsonian patients (29).

Other primate neurology research:

The following experiments carried out at three different institutions provide further evidence of the futility of neurological research using primates.

University of Cambridge:

The level of dopamine, a chemical found in the brain, was studied in the marmoset after destruction of an area of the brain with toxic chemicals, in order to assess the relationship of dopamine to disorders such as schizophrenia. Behaviour was studied as well as brain chemistry. When the monkeys had learned to retrieve objects, they were injected with amphetamines to see how this affected their performance. The study merely confirmed previous findings and furthermore, the researchers already knew that this type of brain damage affected behaviour (30).

Oxford University:

An area of the brain was removed from Macaque monkeys so that their performance of visual memory tasks could be compared with monkeys that had previously had a different part of the brain removed, and with normal monkeys (31). It would have been more logical to study amnesic, brain-damaged patients rather than deliberately brain-damage monkeys.

In another experiment 32 lesions were made in the brains of 6 macaques so that the researchers could compare how monkeys with multiple lesions in their brains performed tasks, compared to those without lesions. In a pilot study, one monkey's brain was so badly damaged he could hardly move his arm but was still made to perform in 2000 trials of task training. The results contradicted those obtained from human studies (32).

London:

At the Institute of Neurology electric shocks were given to the spinal nerves of 4 squirrel monkeys in order to compare nerve control of their arm movements with that of cats and macaque monkeys. The skull was opened and part of the spinal cord was deliberately damaged (33). The animals were fully anaesthetised during surgery, but the drug used for the remainder induces only light anaesthesia, has poor pain-relieving properties and is not recommended for non-human primates (34,35). The team had carried out this experiment on squirrel monkeys before, and the transmission of nerve impulses from this area of the brain and spinal cord has been studied by others, in people. The researchers stated: "We recognise the dangers of making these comparisons both between laboratories and between species".

Non-animal research in neurology:

An editorial comment from a scientific journal in the early 1990s provides an appropriate introduction to this section:

"Until the early 1970s, knowledge about the living human brain had been derived mainly from surgical case studies. These were supplemented with behavioural observations of lab animals, many of whose brains had been physically altered through surgery. Today, sophisticated imaging techniques have opened more efficient, revealing - and certainly less bloody - avenues for neuroscience researchers. These techniques, formerly recognised primarily for their utility in diagnostic procedures, allow brain scientists to peek inside the skull non-invasively and with minimal trauma to the subject" (36).

Humane Alternatives: Non-animal techniques better for humans and animals

Substantial evidence in the scientific and medical literature demonstrates that neurology research can progress without the use of animals.

Human brain imaging:

In recent decades a wealth of brain imaging techniques have been developed to assist neurologists with the non-invasive study of human brains. These include:

- Functional magnetic resonance imaging (fMRI) tracks brain activity by monitoring blood flow. This has allowed neuroscientists to understand which areas of the brain are active during specific tasks (37).
- Positron Emission Tomography (PET) allows areas of the brain which are active during a specific task, such as thinking or experiencing pain, to be identified (38,39).
- Cortical Evoked Potentials (CEP) measures the electrical component of electromagnetic brain pulses and Magnetoencephalography (MEG) measures the magnetic component. In combination, CEP and MEG accurately identify areas of the brain involved in processing information for a specific activity (38).
- Transcranial magnetic stimulation (TMS) applies magnetic pulses to the brain which then stimulate or suppress activity. This has been used to study visual attention, memory and recognition (37).
- Repetitive TMS (rTMS) creates a virtual lesion for neuroscientists to experiment on just as they would by cutting the nerves in an animalís brain to see the functional response. Thought processes have been investigated using rTMS (37).
- A combination of TMS and fMRI is being used to probe changes occurring in the brain associated with diseases such as schizophrenia (37).
- A US study has used brain imaging techniques to investigate the brains of identical twins and fraternal pairs to understand how genetic factors influence the volume of grey brain matter. By knowing which parts of the brain are under genetic control researchers know where to look for brain degeneration in diseases such as schizophrenia (40).
- Scientists supported by the Lord Dowding Fund have developed a new imaging technique known as Synthetic Aperture Magnetometry (SAM). By using measuring electrical and magnetic pulses SAM can identify the region of the brain responsible for signals and their depth when triggered by particular stimuli. SAM is currently being used to study the experience of pain associated with irritable bowel syndrome and non-cardiac chest pain (41).

Molecular models:

- Certain strains of Escherichia coli produce amyloid fibres similar to those that accumulate in the brains of Alzheimer's and other degenerative brain disorder patients. E coli is therefore used as a molecular model to study amyloid formation during the design of drugs to treat or prevent human amyloid diseases (42).
- Brain cells which need dopamine to function and those that do not can be isolated

from human foetal brain tissue. Using this molecular model a study was performed to understand why the degeneration of dopamine dependent brain cells occurs in neurodegenerative disorders such as Parkinson's disease. A particular protein was identified as a causal factor in dopamine dependent brain cell death (43).

Patient studies:

- Lord Dowding Fund has supported research using Parkinson and schizophrenia patient volunteers to investigate visual abnormalities caused by the failure of dopamine systems in the brain. The effectiveness of potential therapies are assessed by observing the effect on the patient's vision (44).

Epidemiological studies:

- In the United States, nuns are donating their brains after death for research. This allows a unique insight into potential causes of Alzheimer's by studying the brains of people who have led similar lives so that many epidemiological variables are absent. It has already been discovered that the likelihood of someone contracting Alzheimer's can be predicted from linguistic abilities in their early twenties (45).

Alternative techniques, relevant to humans, are the future:

Outside of Cambridge University, scientists are committed to promoting the UK as a centre of excellence without the use of animals.

The Neurosciences Research Institute at Aston University is a prime example of such foresight, with its plans for a new 'Academy of Life Sciences' to open in April 2004. The £8 million Academy will provide the opportunity for innovative cross-disciplinary work by the integration of clinically related research in neuroscience. It will include research groups working on behavioural and cognitive sciences, neuroimaging, vision, ophthalmic and physiology optics.

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