



Lord Dowding Fund for Humane Research 2005

Summary of

RESEARCH PROJECTS

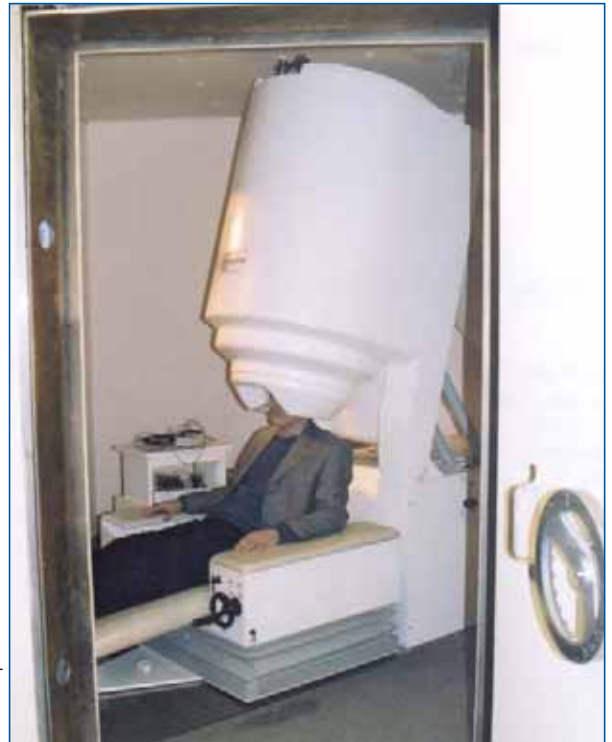
Summary of Research

Modern neuroscience at Aston University supported by the Lord Dowding Fund for Humane Research.

Tim Phillips / LDF



Tim Phillips / LDF



Lord Dowding Fund for Humane Research Summary of Research Projects 2004 - 2005

The Lord Dowding Fund for Humane Research (LDF) supports, sponsors, and funds better methods of scientific and medical research for testing products and curing disease, which replace the use of animals. It also funds areas of fundamental research which lead to the adoption of non-animal research methodology.

We believe that non-animal methods are not only humane, but are more advanced and reliable than animal research. The future of science lies with the types of methods being advocated here, and not by stubbornly sticking to cruel, outdated and unnecessary animal experiments.

The projects featured here were supported by the Lord Dowding Fund in 2004, with many continuing to receive support in 2005. Our projects included the fields of cancer, infection, back pain, replacing animals in education, and a major commitment in brain research. In 2004 alone, this represented research expenditure of £340,000.

Brain Research

In the face of Government support for more neuroscience experiments on primates, the LDF has in recent years made a huge commitment in this field to show that there is a better way. A series of exciting neuroscience projects at Aston University and the University of Newcastle upon Tyne will culminate next year with the funding of a new functional imaging facility for humane research at Aston University.

LDF neuroscience facility

Functional Magnetic Resonance Imaging (fMRI) is important in the development of research into mental health disorders. The technique enables visualisation of brain cortex function, in response to physical tasks, by detecting an increased flow of oxygenated blood in areas of nerve activity. The LDF grant will cover the full running costs for the new Siemens Trio 3-tesla MRI system. This system is rapid and has a high sensitivity to the changes in blood oxygen that form the basis of fMRI.

The World Health Organisation has predicted a surge in mental and neurological illnesses over the next 20

years. Animal researchers have seen this as a reason to increase experiments on non-human primates – as evidenced by the attempt by Cambridge University to build a huge monkey laboratory. The UK already experiments on more monkeys than any other country in Europe, yet by contrast, the commitment to modern, innovative non-animal research is poor. It took 15 years to secure the funding for the MEG brain imaging facility at Aston University, which is the only one of its kind in the country. In comparison, Japan has around 20 MEG laboratories.

The LDF will be supporting the new Aston facility from 2005 until at least the end of the decade.

The design of novel neurotoxicity assays using human tissues

The study of substances which are poisonous to human nerves presents a challenge because of the complexity of the central nervous system (CNS), consisting of the brain and spinal cord. The distinct areas of the brain communicate with each other through a

network of nerve tissues. These tissues have a limited ability to regenerate and are more vulnerable to irreversible damage when exposed to a toxin than other tissues. Therefore it is essential to evaluate the potential toxicity of therapeutic drugs and their breakdown products in relevant models of the human brain.

Current evaluation of the toxicity of a substance to the nervous system involves administration to an animal and observing behavioural changes – meaning animal suffering and results that poorly predict the human situation.

With LDF support, Dr Mike Coleman at the School of Pharmacy, Aston University, is developing a system for testing potential neurotoxins using co-cultures of human nerve cells.

It is estimated that over 2 million mice are used annually in nerve toxicity studies worldwide.

Mercury, for example, continues to be tested on animals despite its devastating effects on the nerves having been well documented in humans since the 1960s. To test the neurotoxicity of mercury, monkeys are exposed to it whilst still in the womb. The long-term effects of mercury on the eyesight and hearing are also measured in primates.

Many primates are still used to test neurotoxic agents, such as the street drug ecstasy. In the UK in 2003 there were a total of 3,500 experimental procedures involving toxicity evaluation in primates. Worldwide, approximately 10,000 primates are used specifically in neurotoxicity studies, up to half of these in the USA.

Animal brain tissues are used widely *in vitro* (in culture) to study neurotoxicity. However, the effects of a specific toxin can differ widely between animal and human tissues. For example, although much research has been directed at the development of primate models of human Parkinsonism using MPTP, the drug-induced condition still does not adequately mimic the human disease. Recent studies of human brain biochemistry indicate that many brain



Tim Phillips / LDF

disorders and the effectiveness of drugs to treat them depend upon biochemical systems unique to humans. There is a need for a dependable human-based model for human neurotoxicity.

The design of culture tests which reflect the unique sophistication of human brain tissue is in its infancy, due to the difficulty in obtaining human nerve tissue, its deterioration after death, inconsistency, high costs and risk of infection. Isolation of nerve cells from human embryonic tissues raises ethical concerns and data produced from waste tissues is not reproducible.

As a first step in the replacement of animals, Dr Coleman's test system has been designed using human cell lines to reliably detect potential neurotoxicity. The project uses cells from a human teratocarcinoma (tumour type) cell line, chemically treated to form nerve cells, and human astrocytic cells – brain cells responsible for regulation of immunity

and inflammation. Nerve cells are more resistant to toxicity when in contact with astrocytic cells (large neuroglia cells of nervous tissue). The astrocytic cells will be grown on cellulose inserts placed on top of the other cell lines.

It is essential to determine whether toxic breakdown products can be produced from an apparently harmless substance. Therefore, to break down substances, enzymes normally present in the human brain are placed in a compartment above that containing the cells, separated by a cellulose membrane barrier. The system will reflect the complexity of the human brain and be maintained at body temperature in a water bath.

The toxicity of a substance to the nerve cells will be detected by studying damage to mitochondria within the cells with the use of a fluorescent dye. Mitochondria are the principle energy store or 'powerhouse' of the cell and

From 2005, the LDF will be funding a new functional imaging facility for humane research at Aston University.

Summary of Research

**Dr Paul Furlong
of Aston
University.**

regulate nerve cell viability. Also, as a number of compounds are capable of inducing apoptosis (selective cell death) flow cytometry (a method of counting cells and measuring their viability while they are in suspension) will be used to quantify the final stages of apoptosis in cell populations as well as cell viability.

Dr Coleman says this work intends to *“help reinforce the UK’s position at the forefront of worldwide endeavour to design and implement novel in vitro neurotoxicity tests, sufficiently predictive of the human situation to meet society’s needs for safe and effective toxicity testing without animal suffering”.*

“If a novel human tissue neurotoxicity test were able to model successfully even a narrow aspect of human neural damage sufficiently well to gain worldwide regulatory acceptance, several thousand animal neurotoxicity experiments would become obsolete.”

Central Nervous System Processing of Human Gut Sensation

Lord Dowding Fund scientists have developed a brain imaging technique to non-invasively record nerve cell activity in the human brain without the limitations encountered with previous techniques.

The technique is known as Synthetic Aperture Magnetometry (SAM) and has been developed by a collaboration between Dr Qasim Aziz of Hope Hospital, Salford and Dr Paul Furlong of Aston University.

It is known that when nerves in the brain are activated in response to an external stimulus, they generate electromagnetic signals. Cortical evoked potentials (CEP) are the electrical component of these signals and their size can be recorded by simple electrodes placed on the scalp. The magnetic component of the signals can be recorded using Magnetoencephalography (MEG) which identifies the location of the signals within the brain. The introduction of SAM means that not only can the region

**Dr Qasim Aziz of
Hope Hospital,
Salford,
overseeing
research.**

Tim Phillips / LDF



of brain responsible for the signals be identified, but the depth of the signals within the brain can also be measured. Previously, it was only possible to perform this depth measurement via invasive brain surgery.

Dr Aziz and colleagues are using these techniques to investigate functional gut disorders (FGD) such as irritable bowel syndrome and non-cardiac chest pain. FGDs affect between 10 and 20% of the UK population, with pain being the most commonly occurring symptom. A stimulus in the gut which would usually be non-painful is often perceived as painful by a FGD patient. This condition is known as visceral hypersensitivity and may be due to either hypersensitive nerves within the gut or abnormal processing of gut sensory information by the brain. For example, it has long been recognised that stress, depression and anxiety affect gut function.

Due to the inaccessibility of human gut organs and the lack of substitute models to study human gut pain, virtually all previous research on gut pain and hypersensitivity has been carried out on animals, mainly opossums, rats and primates. However, Dr Aziz’s group has developed the first human model for gut pain hypersensitivity. With LDF support this model has been further validated by

providing the first electrophysiological evidence that sensitisation of nerves in the intestines can be studied in humans.

Dr Aziz and colleagues have identified the brain regions that process oesophageal pain, i.e. pain experienced in the canal which transports ingested food from the throat to the stomach. Additionally, it has been demonstrated that with SAM it is possible to identify the region of the brain involved in swallowing, an area of research that has previously involved experiments using cats, sheep and primates.

MEG and auditory processing

Drs Caroline Witton and Paul Furlong at the Neurosciences Research Institute, Aston University, have been funded by the LDF to conduct experiments expected to highlight the redundancy of animal models in hearing research and assist the shift towards non-invasive experimentation in humans. They are using magnetoencephalography (MEG) to investigate nerve responses to sound in the human brain.

Auditory processing may fail in certain diseases and hearing research is vital to the understanding of the ability to perceive speech. Neuroimaging

Tim Phillips / LDF



Summary of Research

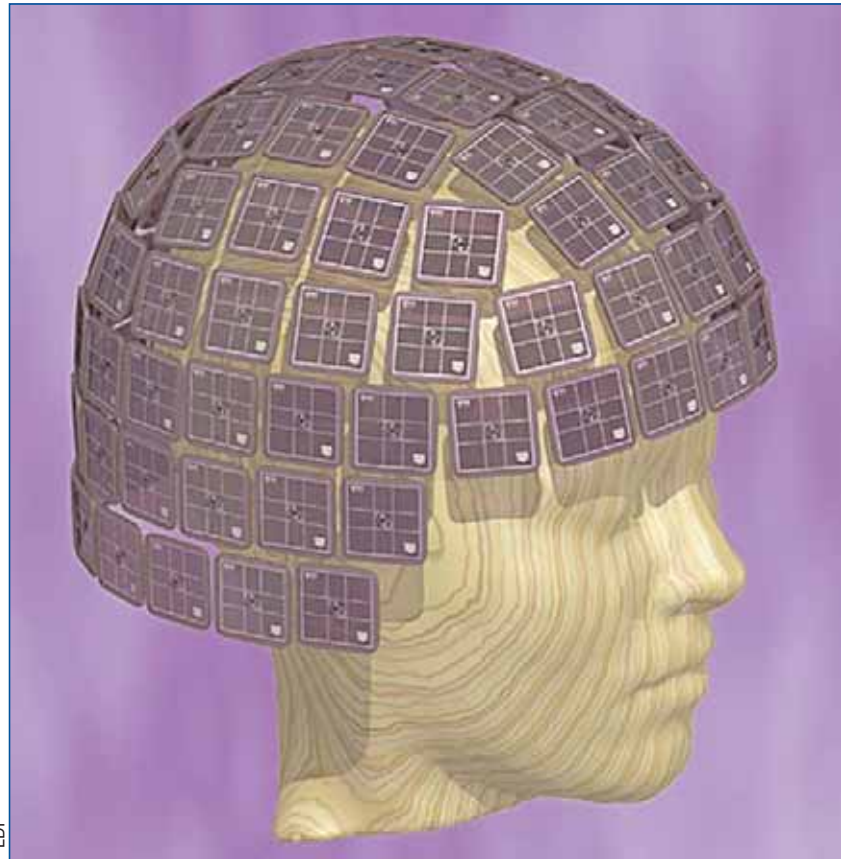
Brain research at the University of Newcastle upon Tyne.

techniques such as fMRI, and MEG are becoming a popular approach to such research and have identified specific areas of the human brain that respond to sounds. MEG can functionally characterise the auditory cortex, the area of the brain that processes sound, by measuring responses to sound over time (temporal) and the location of the sound (spatial).

The project uses MEG to differentiate between brain responses to sound patterns (frequency and amplitude) and sound movement. Also, to test the hypothesis that auditory motion is dependent on inhibitory nerve activity, MEG responses in patients with clinical conditions such as epilepsy, in which there is a reduced level of inhibition, will be assessed and compared with healthy control subjects. The effects of certain anti-epileptic drugs on auditory processing will also be examined.

A series of experiments is being conducted to measure brain responses to basic sounds. The researchers are attempting to find human analogues to areas in the brains of animals that have been studied previously by others. They are concentrating on the areas specialised for spatial and temporal information. Areas that respond to the stimuli are measured by a data analysis technique called Synthetic Aperture Magnetometry (SAM). The introduction of SAM means that not only can the region of brain responsible for the signals be identified, but the depth of the signals within the brain can also be measured. Previously, it was only possible to measure this depth via invasive brain surgery.

This is a significant field of research because elsewhere large numbers of animals are being experimented on for this purpose. Some involve brain recordings from conscious cats and monkeys, others the destruction or removal of brain tissue from ferrets or dogs followed by behavioural tests. There were 437 published papers involving animal research into hearing in 2002 worldwide. In November 2002 there were 16 such papers in one



LDF

monthly journal (*Hearing Research*) alone, using 73 chinchillas, 124 guinea pigs, 34 frogs, 8 gerbils, 114 rats, 10 toads, and 12 cats. Animal experiments concerned with recordings from the area of the brain to be studied (the auditory cortex) include studies on cats and monkeys. Large numbers of marmosets, bats and gerbils have died after being used for auditory cortex experiments.

According to Drs Witton and Furlong: *"Neuroimaging has the potential to save the lives of many animals, if researchers are provided with experimental evidence of the benefits of this technique."*

MEG brain imaging to study visual attention

We provided a research grant to Dr Kristin Pammer and Dr Piers Cornelissen at the University of Newcastle upon Tyne using magnetoencephalography (MEG) brain imaging in human volunteers as an alternative to primate research to study visual attention.

The research is important for our understanding of how the brain locates, selects and synthesises visual information. It will help to evaluate deficiencies in directed visual attention and lead the way to discovering possible causes for dyslexia.

Our attentional apparatus allows us to rapidly scan a scene, identify and collate the key features into an intelligible whole. How the different areas of the brain cortex communicate with each other is unknown. Particular areas of the cortex have been implicated in visuo-attentional mechanisms.

MEG measures the magnetic signals emitted by active areas of the brain cortex. MEG can measure brain activity as it occurs, identifying where in the brain information is processed and when different parts of the brain communicate. In addition, a new analysis technique called Dynamic Imaging of Coherent Sources (DICS) was used to evaluate connections in the cortex.

The combination of MEG and DICS provides an excellent method for the

Summary of Research

Studying of human male infertility at Birmingham Women's Hospital.

non-invasive investigation of human brain activity during natural cognitive tasks. The techniques can assess synchronous nerve networks and their dynamics over time across the whole human brain cortex, whereas in monkey experiments the brain nerve recording techniques can only measure a small number of cortical sites at a time.

A series of experiments are using human volunteers. The involvement of different areas of the brain will be investigated before, during and after fixing on a single scene or location without moving the eyes.

According to Dr Pammer: *"This research will provide a valuable contribution to almost any brain research that involves measuring the temporal dynamics of neural populations. Such areas include motion, vision, hearing, pain, touch, sensory integration – virtually any research that otherwise uses monkey models to predict behaviour in the human brain."*

Tim Phillips / LDF



Tim Phillips / LDF



Infertility

In vitro study of human male sperm cells

Funding of Professor Chris Barratt and Dr Ian Brewis continued for their research into the study of human male infertility at Birmingham Women's Hospital.

During previous research funded by the LDF, the Birmingham scientists established a method by which human testicular tissue, obtained from biopsies, can be transported and stored in such a way as to maintain its cellular function. This is an important step towards encouraging researchers to study sperm cell development in humans rather than rodents and primates. One in six couples in the UK is infertile and so there is a significant research effort.

Now that Dr Brewis and colleagues have established the tissue bank of samples, vital research will be undertaken. Much infertility research has focused on investigating ion (potassium and calcium) channels in

sperm and also immature germ cells before they develop into sperm. It is believed that these channels are crucial to enable sperm to fertilise the eggs. Preliminary research carried out by Dr Brewis has indicated that human cells have active potassium channels but inactive calcium channels. This is the first time that either of these has been demonstrated in immature human sperm cells and is in marked contrast to the data obtained by other workers in laboratory rodents.

In collaboration with Cambridge scientists, research has been carried out to ascertain the possibility of developing DNA microarray chips of the testicular material. These chips enable all the genes expressing proteins in a tissue to be identified. Early data from the chips is encouraging. This advance would allow all the essential genes expressed in the human testis (approximately 3000) to be examined on just one glass slide (1cm²). These will be the first in depth genetic studies performed on human testicular tissue.

Another process associated with infertility is apoptosis, or programmed cell death. In fertile men this is a protective mechanism to remove excessive or genetically damaged cells. However, an imbalance in this process may lead to sperm cells maturing in insufficient numbers or with defects. The development of a reliable human culture system would be a major breakthrough in this field. To date all research on apoptosis in sperm cells has been carried out on rodents, with attendant problems of species differences. There are several key differences in the way that humans and rodents produce sperm cells that makes the data acquired by this animal research unreliable. Dr Brewis and colleagues aim to develop a method to culture human seminiferous tubules (which carry semen through the testis). This will enable detailed study of the biochemical mechanisms of apoptosis in human male germ cells.

Dr Brewis states: *"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.”

Dr Brewis and Professor Barratt comment: “In the very large field of reproductive medicine there is still an overwhelming obsession with performing research in animals, particularly rodents but also livestock. We believe very strongly that this is totally unjustifiable and unwarranted as there is now good evidence that there are marked differences at the cellular, molecular, tissue and whole organism level between humans and animals. Co-workers, previously stuck in the mud with their animal work, are now taking notice of human research as a result of data we are currently producing. We are pleased to report that these researchers of international recognition are now discussing the limitations of animal work and the benefits of human research and are beginning to initiate human-based projects.”

Cancer Research

Improved cell culture methods for anti-cancer drug development

The LDF has been funding Professor Ian Cree of the Translational Oncology Research Centre, Queen Alexandra Hospital in Portsmouth, to develop improved cell culture techniques for testing the efficacy of anti-cancer drugs, using human cancer cell lines cultured in human serum.

Animal researchers grow cell lines in culture then graft these onto animals, usually mice, which are then dosed to determine the efficacy of new anti-cancer drugs. Alternative, and more advanced, approaches use tumour cells derived from patients, or cell lines which mimic the situation in the living body.

Although cultured cell lines are relatively inexpensive and give reproducible results rapidly, the relevance of these results to the efficacy of anti-cancer drugs on cancer cells in



Developing cell culture techniques for testing anti-cancer drugs at the Translational Oncology Research Centre, Queen Alexandra Hospital in Portsmouth.

LDF

human patients is not well established. There are differences between cell lines and cells taken directly from the patient. The growth rates of cell lines and tumour-derived cells differ. Cell lines consist of rapidly dividing identical cells, whereas cells taken from tumours are generally a mixed population consisting of cancer cells, the characteristics of which are determined by their environment, and non-cancer cells. Additionally, cell lines may lose some of the characteristics which they possess in the living body, due to prolonged culture. Because of these differences between cell lines and tumour-derived cells, there are differences in their sensitivity to drugs which kill cancer cells. For example, anti-cancer agents tend to target growing cells, so cell lines are more sensitive than tumour-derived cells.

The aim of this study is to generate defined media (the cell growth medium) and cell lines suitable for widespread use in testing new agents, in place of using animals. Professor Cree and colleagues have demonstrated previously that growth rate and drug sensitivity of the cell lines can be altered by reduced serum concentrations in culture. Cell lines are generally poor representatives of the tumours from which they are derived because they are adapted to cell

culture conditions. By altering the environment in which the cells are cultured, it may be possible to make cell lines behave more like tumour-derived cells. The response of the cell lines, cultured in altered conditions, to standard anti-cancer drugs, is being compared to a data set of known effects on tumour-derived cells.

Just over ten years ago, Professor Cree's team developed an assay called the Adenosine Triphosphate Tumour Chemosensitivity Assay (ATP-TCA), which measures ATP, the most basic fuel of living cells. The amount of ATP present in a cell population reflects the number of viable cells. This technique is being used to assess the toxic effects of the drugs on cultured cells. Professor Cree and colleagues have used ATP-TCA to look at both tumour-derived cells and cell lines. Over 9 years all data collected from ATP-TCA experiments, using different drugs tested on different tumour types, has been added to a database. This currently holds data for 1,400 human tumours.

Cell lines are being derived from cells obtained from small pieces of human tumour tissue representing common tumours, such as those in the breast, lung, bowel, stomach, ovaries, prostate and skin. The majority of the cell lines to

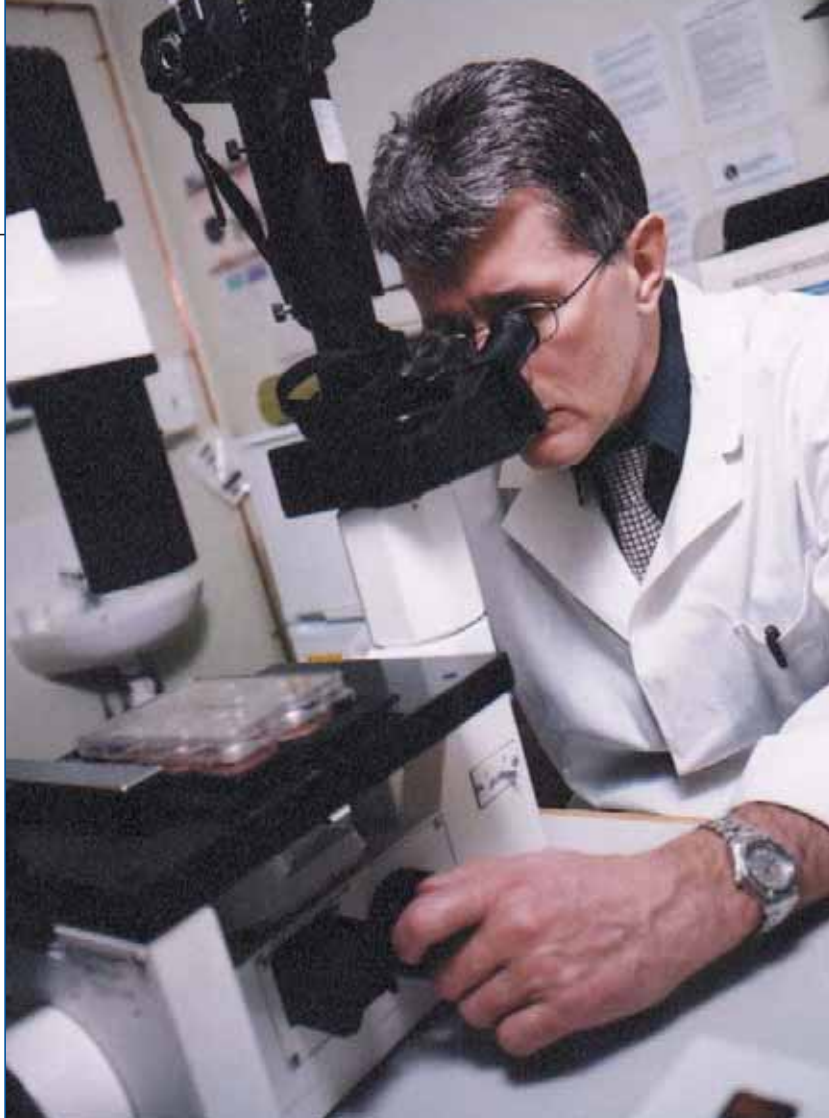
Dr Bird of Sheffield University is the first researcher in the UK to use human tissue models for the study of liver metastasis.

be tested are normally grown in media containing foetal bovine serum. Human serum at various concentrations is being substituted in this study. Serum-free media are also being tested.

Molecular fingerprinting of cells under culture conditions will be carried out by Affymetrix chip assays to enable comparison with representative tumour-derived cells for each of the tumour types tested. The intention is to set up a panel of cell lines whose sensitivity to anti-cancer drugs is representative of common tumour types. The results will be published and the methods will be free to scientists to use as needed. Pharmaceutical companies are likely to be able to use this data to identify new chemotherapeutic agents more accurately and effectively.

Professor Cree says: *“At present cell lines are such a poor model for likely human response that xenografts are used. Xenograft experiments use tumour cells (usually cell lines injected into animals so that tumours grow either within the peritoneum [the internal abdominal membrane or lining] or skin, followed in some cases by spread to other tissues. At any one time there are approximately 1,000 investigational new anti-cancer drugs being tested in human subjects for possible clinical use: the turnover is probably around 500 per annum. Each one of these is probably the lead compound from around 20 drugs tested in xenograft experiments, most of which include around 30 mice. I would therefore estimate the number of mice used in such experiments as at least 300,000 per annum. This figure is likely to be an under-estimate, as such models are used routinely in many cancer laboratories. While the majority of animals used are likely to be mice, there will be some use of rats, guinea pigs and rabbits for these experiments.*

“The proposed cell line testing methods could replace much, if not all, of the testing of the efficacy of anti-cancer drugs in animals prior to human studies...”



LDF

In vitro model for the study of liver metastasis from cancer of the colon

Dr Bird of Sheffield University is the first researcher in the UK to use human tissue models for the study of liver metastasis, where cells from an original cancer tumour spread to the liver and new tumours start to grow. Colorectal cancer (cancer of the lower part of the alimentary canal, or digestive tract) is the second most common malignant cancer in the UK with approximately 29,000 new cases each year. About 15,000 people die each year from cancer of the colon, mostly as a result of tumours developing in the liver.

With the support of the Lord Dowding Fund, Dr Bird is investigating the interaction between liver endothelial cells and tumour cells. This will allow better understanding of how tumours spread from the colon to the liver so that a suitable therapy may be developed. Animal cells and unsuitable human umbilical cord cells have previously been used for these investigations by other

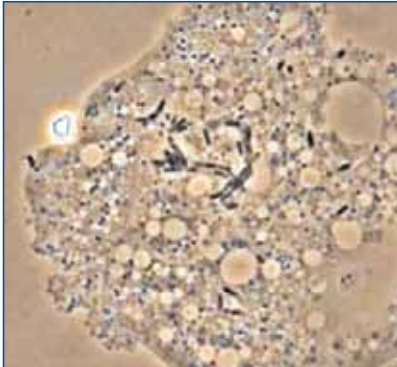
researchers. However, at the Royal Hallamshire Hospital where Dr Bird is based, partial hepatectomy operations are regularly carried out as treatment for metastatic liver disease, where sections of the liver containing tumours are removed from the patient. Due to the structure of the liver whole sections must be cut away rather than just the tumour, thereby giving Dr Bird access to the excess healthy liver tissue literally seconds after it is removed from the patient.

Using the liver tissue, Dr Bird has already established a bank of cultured liver cells, which may now be used to research the mechanisms of tumour formation. Previously, Dr Bird established an *in vitro* model of the gall bladder for cancer research investigations. **The Home Office has identified animal research for metastasis in cancer as involving substantial pain.** It is therefore hoped that by setting the precedent, of using human tissue, Dr Bird will encourage other researchers to follow suit.

Infection

The use of protozoa to model human infection

Professor Brown of Bath University is establishing a humane method of incubating bacteria instead of growing the bacteria inside animals, for the study of infection.



LDF

In the field of infection, experiments are carried out on bacteria: to screen for new antibiotics; to study the properties of pathogens (disease causing bacteria) to understand the mechanisms of antibiotic resistance and virulence; to investigate the survival of pathogenic bacteria in the environment. It is possible to grow the bacteria being studied in culture in the laboratory for use in research. However, experimental results from cultured bacteria are known to differ from clinical results observed in patients.

One predicted reason behind this dissimilarity is that bacteria found inside humans usually grow within macrophages (large cells found in various areas of the body that engulf foreign particles and micro-organisms) rather than as free-floating bacteria. It is believed that the macrophages aid the resistance of the bacteria by allowing them to lie dormant and undetected by the body's immune system. The bacteria can then burst out of the macrophages and unexpectedly expose the body to bacterial pathogens. If the body's immune system is too slow to respond this can result in death or serious illness. Bacteria cultured in the laboratory exist as free growing micro-organisms. Consequently, animals are used to grow

bacteria and provide a source of bacteria contained within macrophages.

Professor Brown is cultivating bacteria in the laboratory inside amoebic protozoa – single celled organisms. The protozoa act like macrophages by providing a capsule for the bacteria to grow inside. A study has already confirmed that the bacterium responsible for Legionnaire's Disease has very similar properties when grown inside protozoa to that obtained from human lung tissue samples. The LDF has been supporting Professor Brown to investigate the culture of various other bacteria inside protozoa and establish optimum growth variables such as time, temperature, oxygen supply, acidity level, etc. This will then provide a supply of bacteria for research without using animals as culture machines.

Back pain

Tissue culture system

Intervertebral discs are the cartilage between individual spinal bones which act as shock absorbers. Degeneration of the intervertebral disc (DIVD) is often implicated in chronic low back pain.

With an LDF grant, Professor Anthony Freemont and Dr Judith Hoyland hope to identify the causes of cellular changes underlying DIVD and use these to help

design new therapies. The University of Manchester team have shown *in vitro* that the cytokine (chemical involved in the immune system) interleukin-1 (IL-1) induces the cellular changes in DIVD and can be reversed with IL-RA (interleukin-1 receptor antagonist).

Traditionally, cell culture studies in this field are followed by animal experiments and since few animals spontaneously develop DIVD it is artificially induced. The LDF team believe that such experiments contribute almost nothing to the understanding of DIVD. They aim to establish whether IL-1 has the same effects in whole tissue as in cell culture. To do this they are developing the first tissue culture system that uses human tissue to study DIVD. The new system mimics the forces and pressures within human discs, rather than those of animals which do not share our posture.

Professor Freemont and Dr Hoyland comment: *"We believe that our loaded disc system could have so many advantages over the animal models because it employs human tissue, works under human spinal loading conditions and the experimental conditions can be very closely monitored and controlled – were our research successful, there would be an immediate and significant decrease in animal experimentation in this field of research."*



LDF

Using tissue culture to battle back pain at the University of Manchester.

Summary of Research

Education

A reusable learning objects approach to stimulating the use of alternatives in higher education

For almost 20 years, the LDF has been working with Dr David Dewhurst of the University of Edinburgh to develop programmes replacing animals in university practicals, saving countless animals all over the world.

In November 2003, Dr Dewhurst's team concluded a three-year project developing computer-based learning materials in biomedical sciences as alternatives to animals in undergraduate teaching. The LDF then began funding a new three-year project to create a package that would enable teachers to assemble personalised teaching and learning materials replacing animals in higher education.

The impact of alternatives such as CAL (computer-assisted learning) programmes on replacing animal experiments depends upon the willingness of academics. Academic diversity and institutional conservatism are often barriers to new learning materials – if a learning aid does not meet all the needs of an institution it will be rejected. This may lead to continued, and clearly unnecessary, use of animals in teaching.

Teachers have indicated that they would like to use certain components of the CAL programmes but would like to be able to customise them. For example, they may need a facility for drugs to be added to, or deleted from, a pharmacology programme, add different videos or translate from English.

Another problem is that, typically, all the components of a multimedia CAL are locked into the application and linked intrinsically to its delivery mechanism. Also, changes in technology (such as the change from DOS to Windows) may result in the delivery mechanism becoming obsolete.

This project is developing a workable solution to these problems. This has

now become possible with developments in Internet technologies and the concept of digital reusable learning objects (RLOs) and repositories. Thus, it is possible to give teachers the building blocks (digital RLOs) and tools to create their own learning resources. The RLOs are stored in a digital repository which can be searched and suitable RLOs can be downloaded. These can then be aggregated using tools and learning design templates. Teachers would be able to combine selected RLOs with new components of their own. They will have a choice between the existing CAL programmes developed with LDF funding, or they can create their own from these.

The project is also revitalising components where necessary and producing different languages, storing components in a readily available on-line repository; developing a simple to use authoring or reaggregation tool and learning design templates to enable teachers to reassemble assets, add new ones etc., as well as developing new learning objects.

Dr Dewhurst says: *“Once initiated it is anticipated that this project will involve and benefit all teachers wishing to use alternatives both as donors and users of RLOs. It would overcome language problems and stimulate the introduction of alternatives into many new curricula with a consequent saving of animals and animal suffering. The potential for saving animals in education worldwide would be greatly increased by having different language versions which would work across any technology platform.”*

Alternatives in higher education lecture tour of Brazil

In 2004, the LDF sponsored a lecture tour of Brazilian universities by Dr David Dewhurst to promote computer based teaching packages replacing animals.

Dr Dewhurst and Professor Elaine Del Bel visited departments at the Universidade de São Paulo in São Paulo and Ribeirão Preto, the Universidade Federal de Mato Grosso do Sul in Campo Grande, the Universidade Federal do Rio de Janeiro, and the Universidade Federal de Santa Catarina, Florianópolis. They also met staff from the Universidade Católica Dom Bosco.

Dr Dewhurst found that there was already a move away from animal use in physiology and pharmacology and a willingness to use alternatives. However the cost of programmes is a problem and Portuguese language versions are clearly desirable. The Universidade Federal do Mato Grosso do Sul is a non-research university, yet it used more animals in teaching than facilities undertaking more research. Here over 600 rats are used annually for neurology, cardiology, endocrine and reproduction teaching; 20 frogs for neuromuscular and neurophysiology; 160 chickens in necropsy classes; and 2-3 chickens for veterinary science. At the other facilities much of this animal use had been abandoned.

The tour re-emphasised the importance of the current LDF project to improve delivery, availability and different language versions of alternatives.

Dr David Dewhurst addresses the conference for a National Centre for the Replacement of Animal Experiments (see page 11).

Tim Phillips / LDF



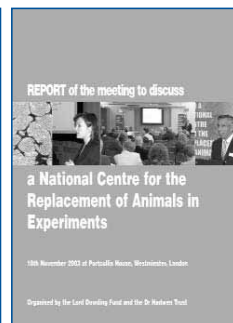
Government rejects call from scientists for National Centre for Replacement of Animal Experiments

In the summer of 2004, the Government caved to interest groups and made the disappointing announcement that it was establishing a National Centre for the Replacement, Refinement and Reduction of Animals in Research (3Rs). Disappointing because the centre will fail to focus on replacing animal experiments but rather will concentrate its efforts on tinkering with existing animal methodologies, through “refinement” and “reduction”. This in the face of strong calls for a centre committed to driving forward “replacement”.

The LDF had promoted the concept of a National Centre for the Replacement of Animal Experiments (NCRAE) to the House of Lords Select Committee on Animal Experiments in 2002. A joint proposal by the LDF and Dr Hadwen Trust (DHT) was then extensively circulated and promoted.

In November 2003, the LDF and DHT staged a conference in Westminster to discuss a NCRAE. The event was addressed by leading scientists and attracted about 80 participants including politicians, government officials, scientists, and funding bodies.

The conference was opened by Joanna Lumley OBE, and the first session discussed the “*Political arguments for a National Centre*” with Ian Cawsey MP (Labour) and Norman Baker MP (Liberal Democrat). Session two covered “*Scientific perspectives on the need for a National Centre*” and was addressed by Prof. Haroun Shah (Head, Molecular Identification Services, Health Protection Agency) and Prof. Paul Tofts. Session three considered “*Organisation and funding of a National Centre*,” with Dr Samantha Orr (Director, UK Human Tissue Bank) and Dr Paul Furlong (Neuroimaging Research Group, Aston University) as speakers. The final session examined “*Training and*



Photos: Tim Phillips / LDF

economic benefits of a National Centre” with Dr David Dewhurst (Founder, Sheffield Biosciences & Director, Learning Technology, Edinburgh University) and Andrew Davidson (Chair, Xceleron Ltd, York University).

The speakers agreed that replacing animal experiments cannot be left to chance. By drawing together scientists across different disciplines, a centre could encourage the collaboration and cross fertilisation of necessary ideas.

The meeting discussed practical issues, for example the shortage of human tissue. A National Centre could help to co-ordinate supply and access and provide guidance and training in handling human tissues. Neuroscientists using imaging techniques to replace animal experiments have experienced difficulty in raising funding for the latest technologies, leaving the UK behind other countries. A National Centre could help focus funding strategies.

The meeting heard how animal testing is a poor predictor of human responses: around one third of drugs fail in the first human trials. There is a need for more relevant testing and the public wants safer drugs, but industry and regulators are resistant to change. Accelerator mass spectrometry (AMS) is an analytical tool of unprecedented sensitivity. It can be used to study samples from human volunteers given harmless ultra-low doses of drug candidates. Such emerging technologies have many advantages – speeding development and improving safety. There is just one AMS machine being

used to study biosamples in the UK, whilst Japan has many.

The meeting considered that a NCRAE could identify upcoming methods; give status to scientists developing replacement methods, and attract other scientists to do so; develop dialogue and collaborations; promote new expertise (e.g. human tissue handling); develop a national strategy and provide funds to advance this.

The proceedings of the meeting were published and distributed to scientists, MPs, Lords and various government departments. Later in the year, a compromised 3Rs centre was confirmed

Refinement and reduction take place within animal laboratories, but replacement requires original thinking and a cross-disciplinary approach, scientifically. There appears to be no logic in binding “Replacement” to “Refinement and Reduction” apart from the fact that they begin with the same letter!

A centre for the 3 Rs might save money, but it will dilute the commitment to replacement. A Centre for Replacement would have a vast task; so, apart from an animal experimenter or a government wishing to save money at the expense of progress, who would wish to triple the workload, and cut the financial commitment to replacement by a third?

Much was said in the media about this being a centre for alternatives, but the fact is that the public’s perception of “alternatives” is “replacement”. Anything else is misleading.

Leading scientists address the conference for a National Centre for the Replacement of Animal Experiments (clockwise from top left):

Dr David Dewhurst (Founder, Sheffield Biosciences & Director, Learning Technology, Edinburgh University);
Dr Samantha Orr (Director, UK Human Tissue Bank);
Prof. Haroun Shah (Head, Molecular Identification Services, Health Protection Agency);

Joanna Lumley OBE and Dr Paul Furlong (Neuroimaging Research Group, Aston University);
Andrew Davidson (Chair, Xceleron Ltd, York University).

