

VICTIMS OF CHARITY...



A REPORT ON THE CRUEL AND
SCIENTIFICALLY INVALID
EXPERIMENTS FUNDED BY MEDICAL
RESEARCH CHARITIES

CANCER RESEARCH UK

BRITISH HEART FOUNDATION

PARKINSON'S UK

ALZHEIMER'S SOCIETY

Researched and written by
Dr Adrian Stallwood & Andre Menache

www.animalaid.org.uk

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INTRODUCTION

The medical research charities that are the focus of this report are well-regarded British institutions, charged with seeking remedies for health problems that devastate millions of lives every year. As well as laboratory research, they devote a proportion of their income to providing practical support for affected patients and their families.



Marmoset monkeys in neurological research

Animal Aid's interest in Cancer Research UK, the British Heart Foundation, Parkinson's UK and the Alzheimer's Society relates to the animal experiments they fund. The appalling suffering meted out in the course of such experiments – to mice, monkeys, goats, pigs, dogs and other animals – is sufficient reason for them to be stopped. Animals' brains are deliberately damaged with toxic chemicals, or their hearts are slowly and systematically destroyed. Animals are tormented in water mazes, injected with cancerous tissue and subjected to breeding programmes that produce weakened, disease-prone, mentally deranged 'mutants'. The agonies they endure are described – in cold, arcane prose – in the published scientific papers that serve as the raw material for our report.

Necessary evil?

Some people argue that, though regrettable, such suffering is justified because significant health benefits accrue to people. The core of our report assesses the validity of that claim. Researched and written by a hospital doctor and a veterinary surgeon, the authors examine past and contemporary accounts of experimental procedures by the researchers themselves; as well as scientific reviews in leading specialist journals. They conclude that animal-based research into cancer, dementia, heart disease and Parkinson's has been a wasteful and futile quest – one that has failed to advance the cause of human medicine.

We have identified 66 charities that use public donations to fund animal research (and nearly 80 that forswear the use of animals). We focus on Cancer Research UK, the British Heart Foundation, Parkinson's UK and the Alzheimer's Society because they are bodies of some standing and authority. Their collective annual income is currently more than £710m, with Cancer Research UK taking £515 million of that total. At the other end of the scale is Parkinson's UK, which draws £17 million.

Policy of concealment

How much of their respective research budgets goes into funding animal experiments? We asked the charities directly but received, in response, rhetoric rather than

detail. They would not say how many animals – and of which species – they use. Or how they are used. Through intense burrowing into specialist scientific libraries we did eventually find a good deal of information, and this forms the backbone of our report. But that material was more difficult to obtain than it should have been. Occasionally, code numbers and phrases were favoured in place of straightforward terms such as 'non-human primate', or 'dog'. Deliberate obfuscation? We cannot know, but what is clear, is that the four charities concerned are loath to reveal to the general public details of the scale and nature of the animal research in which they are engaged.

Animal Aid believes that transparency and accountability are vital. The public gives huge sums of money to these charities. In return, they should be told what they are paying for. They should have available to them details of the torments the animals experience, and also be offered verifiable information about the alleged fruits of such activities.

The immune-deficient 'mouse model'

As we have seen, the largest of the four charities is Cancer Research UK (CRUK). It currently spends more than £300 million on research (of all kinds; not just that which uses animals), even though it is widely recognised that cancer is largely preventable – lifestyle and environmental factors being responsible for more than 90 per cent of new cases. CRUK, however, continues to fund dozens of animal studies, mostly on mice, at academic and research institutions throughout the UK and overseas.

Animal researchers have struggled for decades to mimic human cancer in mice. The 'triumph' of all this activity is strains of mice who have been stripped of their immune defences and into whom are introduced human cancer cells. Researchers often do no better than deposit this alien material (the 'xenograft') under the mouse's skin, thereby producing a 'subcutaneous xenograft'. The result is an unconvincing 'model' of the human condition. People with cancer generally have an active immune system that affects the way their cancer develops, whereas the mice are immune-deficient. And the introduced human tumour is deposited at a site from where, it is reported, it almost

never spreads to other parts of the body – this spreading (metastasis) being the factor that decreases a patient's chances of survival.

A large percentage of the immune-deficient mice die in the womb or perish soon after birth from conditions that leave them unable to breathe or feed properly. Those who do survive face considerable challenges. Some develop (unplanned for) tumours and degenerative diseases. Others suffer anxiety – made evident through frenetic plucking of hair or whiskers from cagemates or from themselves. They are also susceptible to stress-induced circling, pacing, jumping or back-flipping.

Destroying the hearts of dogs and pigs

For heart disease research, healthy animals have often been grievously injured to produce a condition that is markedly different from those found in human patients. Dogs have had their hearts systematically destroyed over a period of months by the injection of polystyrene beads into their coronary arteries. With pigs, the favoured method is to place constricting rings around those same arteries. These narrow gradually over a period of weeks, resulting in a heart attack. The British Heart Foundation (annual income £213.7 million; expenditure on research £48 million) funds highly invasive experiments involving dogs, goats, pigs and rabbits. More recently, large numbers of fish have been the victims of their laboratory activities.

Many people will have seen the BHF's 'Mending Broken Hearts' advertising campaign, aimed at raising £50 million for heart failure research. It has featured talking zebrafish – a luckless minnow whose regenerative powers are claimed to offer hope for heart disease sufferers. Zebrafish have already been subjected to years of mutilating experiments. The BHF plans much more of the same. This report debunks the 'science' behind the BHF hype.

Forced to swim in a water maze

Equally unconvincing are the 'animal models' of Alzheimer's disease. Neurotoxins have been injected directly into the brains of rodents and monkeys, while rabbits have been poisoned with a diet of cholesterol and copper. The current fad is for genetically manipulated mice, some of whom are forced to swim around a pool of water from which they cannot escape or touch the bottom (mice are scared of being in water). Their task is to find a small platform on which they can rest. In later tests, the torment is increased when the platform is submerged.

A recent article in *Nature* magazine sums up where such activities have brought us. '...In recent years, and especially for neurodegenerative disease, mouse model results have seemed nearly useless.'*

Injecting poison into the brains of monkeys

Even more conspicuously vicious is the history of animal use for Parkinson's Disease research. In contrast to the positive steps achieved as a result of studying human Parkinson's sufferers, we show that animal research into PD has failed to deliver. Researchers, nonetheless, continue to 'model' the disease by injecting poison into the brains and circulation of primates and other animals.

For example, research funded by Parkinson's UK led on to a 2004 experiment in which 12 monkeys each suffered 18 separate brain injections 'in the hope of achieving longer-lasting behavioural deficits', with needles being left in their brains for two minutes after instillation of poison. Recipients of such treatment are likely to be left so severely disabled that they have to be hand-fed. They will suffer rigidity, poor coordination and loss of balance.

And highly toxic pesticides have been injected into the abdomens of mice, in order to kill or severely incapacitate them.

Valuable work

It is important to make clear that much of the educational and patient-support work done by the four charities under review does merit strong public backing. In the case of the Alzheimer's Society, more than 70 per cent of its nearly £60 million budget is devoted to 'care services', with 'just' £2 million spent on research. Substantially the largest share of Cancer Research UK's income, by contrast, goes on research (at the heart of which is a fixation on the 'mouse model'). What all four bodies have in common is a determination to conceal the nature and extent of the animal suffering for which they are responsible.

Research relevant to people

Our objective is to expose what is currently hidden, and thereby show an unsuspecting public just what their generosity is paying for. Beyond that, we want to press the four charities concerned (and others that fund animal experiments) to reappraise their research agendas. We wish to see them recognise that their animal research is as medically unproductive as it is cruel, and that they should be directing the funds bequeathed to them by the public into modern, non-animal research methods (a number of which are outlined in this report) that are directly relevant to people.

Andrew Tyler, Director Animal Aid

* (Schnabel J (2008). *Neuroscience: Standard Model. Nature. 454:682-685*)



VITAL STATISTICS: THE STORY OF FOUR CHARITIES IN FIGURES

CANCER RESEARCH UK

Annual Income: £515 million (2009/10)

Expenditure on Research: £308 million

Expenditure on Information and Advocacy: £14 million

Staff Employed: 3,500

Headquarters: Moving from eight London-based offices to one new site, the Angel Building in Islington, in autumn 2011

Mission Statement: 'We are the world's leading charity dedicated to beating cancer through research... Our aim is to ensure more people survive cancer.' It launched 10 goals in May 2007 to be achieved by 2020, which included educational goals (for example 'to make the public aware of the main lifestyle choices they can make to reduce their risk of getting cancer').

Original Aims/History: Formed in 2002 as a research initiative, following the merger of the Cancer Research Campaign and the Imperial Cancer Research Fund. Now the biggest single independent funder of cancer research in Europe.

BRITISH HEART FOUNDATION

Annual Income: £213.7 million (2009/10)

Expenditure on Research: £48.4 million

Expenditure on Prevention and Care: £37.2 million

Staff employed: 2,000

Headquarters: Head Office in Central London, regional offices across the country

Mission Statement: 'Our mission is to play a leading role in the fight against disease of the heart and circulation, so that it is no longer a major cause of disability and premature death.' Aims embody both research and education.

Original Aims/History: Founded in 1961 by medical professionals concerned about the increasing death rate from cardiovascular disease. Its aim was to raise money to help fund extra research into causes, diagnosis, treatment and prevention of heart and circulatory disease. In 1986, it became more involved in public education. In 1990, it moved into rehabilitation.





PARKINSON'S UK

Annual Income: £17.1 million (2009)

Expenditure on Research: £4.8 million

Expenditure on Care, Nursing and Service Provision: £10.8 million

Staff Employed: 250

Headquarters: Head Office in Central London, local groups across the country

Mission Statement: 'Our vision – our ultimate ambition – is to find a cure, and improve life for everyone affected by Parkinson's.'

Original Aims/History: Founded in 1969 as the Parkinson's Disease Society, to help patients and their relatives with the problems arising from Parkinson's, to collect and disseminate information on Parkinson's and to encourage and provide funds for research. Today they focus on research in addition to support, and want to improve services for people affected by Parkinson's through campaigning and education and training for professionals.

Note: Parkinson's UK has the UK's largest human brain bank dedicated to the disease. One of the group's strategic priorities is to develop new animal models of Parkinson's because the current ones 'don't recreate the changes that happen in the human brain'.¹

ALZHEIMER'S SOCIETY

Annual Income: £58.7 million (2009/10)

Expenditure on Research: £2 million

Expenditure on Care Services: £42.4 million

Staff Employed: 1,200

Headquarters: Head Office in Central London, services across the country

Mission Statement: 'We exist to champion the rights of everyone with dementia and those who care for them.' One of their goals is to 'galvanise investment for research into the causes, prevention, treatment and care of people with dementia'.

Original Aims/History: Formed in 1979 as the Alzheimer's Disease Society by two people who recognised the need to raise awareness of dementia and to improve the quality of care, support and information for people with dementia and their carers.



THE USE OF ANIMALS IN CANCER RESEARCH



Incidence and mortality

Cancer incidence has reached epidemic proportions. Around 300,000 new cases are diagnosed each year in the UK, and more than one in three people will develop some form of the disease during their lifetime. Between 1978 and 2007, incidence rates increased by 25 per cent, with a 14 per cent increase in men and a 32 per cent increase in women. Cancer is not a single disease. There are more than 200 different types, four of which – breast, lung, large

bowel (colorectal) and prostate – account for more than half of all new cases. In 2008, there were around 156,000 deaths due to cancer.²

The increase cannot be explained simply in terms of an ageing population. Not only are rates of juvenile cancer increasing but, in May 2009, an eight-month old baby boy became the youngest individual to be diagnosed with prostate cancer in the UK. In 1960, one hundred children per million were diagnosed with cancer. By 2005, this figure had increased to 138 per million.³ Cancer is now the most common cause of death in children aged 1–14 years.⁴ It is commonly acknowledged that cancer is largely preventable. Lifestyle and environmental influences are responsible for 90-95 per cent of the incidence, while genetic predisposition accounts for between 5 and 10 per cent.⁵ The recognised risk factors include smoking, obesity, a diet high in saturated animal fats and low in fibre, excess alcohol consumption, environmental pollution and over-exposure to sun and radiation.

What is cancer?

Cancer is uncontrolled cell growth, beginning at the level of a single cell. Normal, healthy cells multiply in a controlled fashion, governed by cellular mechanisms, which are in turn controlled by proteins, which are encoded by genes. If a cell becomes stressed or damaged for any reason (e.g. through exposure to toxic chemicals), it will normally stop multiplying and try to repair the damage. If the cell is unable to do so, it will commit suicide ('apoptosis') in order to preserve the integrity of surrounding cells.

Cells have a wide array of mechanisms to protect them from the effects of stress and DNA damage. But these can be overcome by, for instance, a highly toxic chemical

Note on Prevalence and Incidence

Prevalence measures how much of a given disease or condition there is in a population at a particular point in time. Incidence measures the rate of occurrence of new cases of a disease or condition. Simply stated, prevalence is *how many people have the condition at any given time* and incidence is *new cases in a given time (usually a year) in a given population*.

or a cancer-causing virus. Equally, excessive hormonal stimulation (caused, for instance, by hormone replacement therapy or hormone-mimicking chemicals such as pesticides) can lead to uncontrolled cell multiplication – breast and prostate cancer being the most common examples of this.

History of cancer research

The father of 20th-century cancer research is Sir Richard Doll, whose pioneering work firmly established a link between smoking and lung cancer, based on epidemiological (human population) studies. He also did pioneering work on the relationship between radiation and leukaemia, as well as that between asbestos and lung cancer,⁶ and alcohol and breast cancer.⁷

Despite his success, attention since the 1990s has turned increasingly from epidemiology towards the molecular approach to cancer, using biotechnology. Much of this research is currently being conducted using animals – most frequently, mice.

Animal models in cancer research and their historical failure

From 'nude' to 'SCID' to transgenic mice

Animal researchers have struggled for decades to mimic human cancer in mice. They have failed for a variety of reasons. Their biggest initial obstacle was that when human cancer cells were transplanted or injected into mice they were rejected by the mouse's immune system. In an attempt to overcome this problem, an immunodeficient mouse was developed – known, because they were without fur – as the nude mouse. Bred specifically to lack a gene (FOX1) that is critical for the proper development of the thymus, researchers could engraft human cancer cells into the nude mouse that

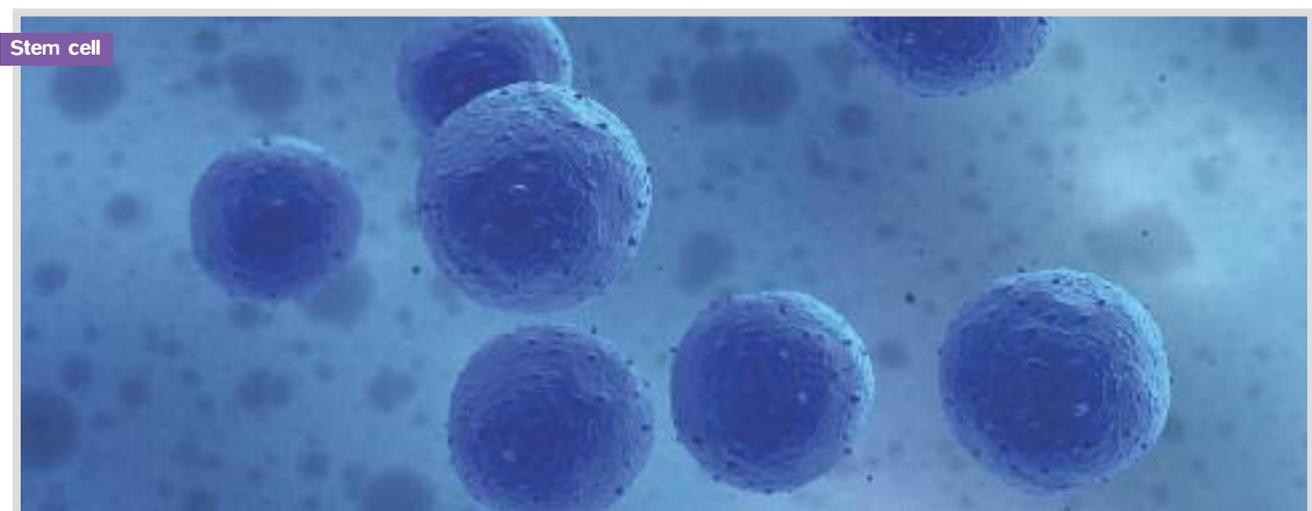
would not be rejected.⁸ However, because some important immunity function remained, not all cancers grew well.⁹

And so a new type of mouse was bred – known as SCID (severe combined immunodeficiency) – that was, as the name implies, even more immune-deficient than the nude variety. The SCID mouse soon became a favourite of pharmaceutical companies. Cancer researchers could take an established human cancer cell line and insert it under the skin of the SCID mouse – producing what is known as a subcutaneous xenograft – then test the mouse's response to an experimental cancer drug.¹⁰

Over the years, researchers continued to genetically manipulate the SCID mouse, knocking out more genes to further disable its immune defences. But then came an important realisation: eliminating more and more of the mouse's immune system might let an experimenter introduce foreign cancer tissue and see it 'successfully' grow but that is not how cancers work in people. Most human cancer sufferers have a functioning immune system, which interacts with the cancer throughout its development, changing the course and outcome of the disease.

The multiple failings of the mouse model... by a scientific expert

In fact, there were several ways in which the SCID and nude mice fell short of providing a solution to the problem of 'modelling' human cancer. An article in a leading cancer journal summed up the multiple problems: 'The subcutaneous xenograft is clearly better than nothing, but its drawbacks are well known. The mouse has no functioning immune system; something rarely seen in human cancer, and the tumor is growing in an artificial site. Xenograft tumors almost never metastasize [spread to other parts of the body and thereby decrease the patient's chances of survival]... Finally, the tumor does not develop naturally in the mouse. Instead, it is transplanted from the



cell line of a fully-grown human tumor – another divergence from the human situation. When you consider that drugs behave differently in mice than in humans, it's not surprising that the subcutaneous xenograft is a poor predictor of success. In general, it's much easier for a drug to shrink a tumor in such mice than in humans.¹¹

There is now acceptance within the cancer research community that the mouse xenograft model performs very poorly when it comes to developing useful therapies. The US National Cancer Institute conducted a retrospective analysis for 39 drugs in 2000. It compared their performance in xenograft testing and Phase II human clinical trials. Only 45 per cent of compounds with anti-tumour effects in xenografts showed benefit in human trials. In addition, drugs that worked in a particular fashion in tumour cells that had been transplanted into mice could not be relied upon to work in the same way in human patients with the same type of tumour.¹²

A 2003 study compared the value of three cancer models in predicting drug effects in humans. The models were: mouse xenografts of human cells, mouse cell tumours grafted into mice, and human *in vitro* cell lines. The researchers concluded (rather timidly) that the human cell model was 'of at least equivalent usefulness to mouse xenografts'.¹³ In fact, it is clear from the report that it was more predictive for a greater variety of malignancies. Further, the study makes clear that the mouse-cell tumour models were useless.

Two US researchers in 2006 offered further explanations of why the mouse xenograft model bears such a 'questionable relation to the naturally occurring human disease'.¹⁴ They pointed out that the living matrix with which implanted tumours interact is fundamentally different in mice than in people. There are also 'intrinsic differences between mouse and human toxicity features', which in practice mean that doses of a candidate drug in people cannot be increased to levels tolerated in mice.

Despite these fundamental drawbacks, subcutaneous xenograft studies still provide the most common 'proof-of-concept' data for new cancer therapies submitted to the Food and Drug Administration, the world's most important drug authorisation body. And most drugs released to date were 'likely originally tested on SCID mice'.¹⁵

CRUK's use of mouse models – inherently contradictory

Cancer Research UK is clearly aware of the shortcomings of mouse xenografts. A promotional poster¹⁶ for genetically modified mice, produced by its Cambridge Research Institute in 2007, had this to say: 'Although initially useful, xenograft models of human cancer do little to replicate the real disease and are essentially an *in vivo* Petri dish... It is

An illustration of breast cancer



therefore not surprising that xenografts have an altered response to chemotherapeutic drugs. The time for reliance on such models to determine the response to a new therapy has passed.'

And yet CRUK researchers at the same institute are committed to the continued use of xenografts for 'the tumours of major interest'.¹⁷ Bafflingly, these researchers are working on experimental therapies that they hope can move from the laboratory to use in human patients. The contradiction between word and deed is obvious.

Failings of the genetically engineered mouse models

Meanwhile, the long-suffering mouse continues to be subjected to all manner of genetic experiments aimed at producing a reliable surrogate for human cancer – a quest that remains as elusive as ever. Rather than having cancer cells engrafted, these mice are designed to develop cancers spontaneously. Genes are deleted (creating 'knockout' models) or human genes are added (producing 'transgenic' strains). According to official Home Office statistics, more than one-and-a-half million genetically engineered mice (GEMs), including those suffering 'harmful mutations', were bred and killed in 2009. The majority of these mice were used in cancer research, immunology and genetics.

Cancer Research UK currently funds dozens of studies that use such mice at academic and research institutions throughout the UK and overseas. With more than 7,000 publicly available mouse strains from which to choose, each containing 24,000 genes,¹⁸ researchers can always find something new and 'interesting' to study, even though it is difficult to find evidence of how human patients have benefited from all this elaborate and costly activity.

It is important to remember that the use of GEMs is still in its infancy. So far, they have proved eminently suitable for cruel tinkering, but far less useful in actually bringing cures to patients. The following inherent flaws may well mean their predictive value ends up no better than mouse xenografts:

- Like subcutaneous xenografts, GEMs are not good at replicating advanced cancer, particularly metastasis. This often makes them clinically unhelpful, and in some cases essentially valueless in treatment development. For example, the clinical problems associated with prostate cancer are largely restricted to its dissemination throughout the body.
- Mouse models have been bred without genes that, in people as well as in the mice themselves, have been identified as tumour suppressors. However, the type of tumours that arise in people lacking these suppressor genes are often different from those developed by the gene-deficient mice.¹⁹
- Transgenic GEMs develop cancer through the expression of 'foreign' inserted genes, which means 'disease evolution is unlikely to be similar to that of their human counterpart.'²⁰
- GEMs use artificial gene promoters [DNA segments that regulate how genes work], which themselves can influence how the resultant cancers originate, progress and spread.²¹
- Perhaps the most fundamental problem lies with oversimplistic models, which involve turning off certain abnormal biological pathways (or key chemical reactions). In fact, cancers are usually caused by multiple mutations in co-existent cells, and are critically dependent on a highly individualized cellular environment. Many researchers are now coming to terms with the fact that human cancers are far more complex in behaviour and genetics than was previously thought. Last year, US scientists discovered a staggering 1,700 gene mutations in the cancer genomes of just 50 breast cancer patients. Most were unique to individual patients' tumours, and only three occurred in 10% or more of the cancers studied.²² Such complexity is not feasibly reproduced in mice, despite researcher's attempt to 'humanise' them with genetic alterations.

An American cancer biologist commented in 2008 with reference to GEMs: 'If one wants to know whether a patient's tumor will respond to a specific therapeutic regime, one must examine the response of that human tumor, not a mouse tumor, to the therapy.'²³

New cancer models, old cancer failures

Even though there is a wealth of evidence in the scientific literature pointing to the deficiencies of the mouse models, a 2004 review expressed surprise at the 'discouragingly low' success rate for new cancer therapies. This was despite the fact that 'many trials are now conducted using novel agents with specificity for molecular pathways and cellular components', and that 'curing experimental cancer in mice is a relatively easy process'.²⁴ Since that time, the lack of progress in this area is even more glaring, with a stream of high-profile and costly failures. In the last two years alone, phase III clinical trials have failed for iniparib (being tested against breast cancer), AS1413 (against leukaemia), figitumabab (against lung cancer), zibotentan (against prostate cancer), recentin (against colon cancer) and patupilone (against ovarian cancer).

The words of Dr. Irwin Bross, former director of Sloan-Kettering, the world's largest cancer research institute, delivered in 1981 in evidence to the US Congress, still ring true: 'While conflicting animal results have often delayed and hampered advances in the war on cancer, they have never produced a single substantial advance either in the prevention or treatment of human cancer.'²⁵

His views were echoed 23 years later in a Fortune magazine article entitled 'Why We're Losing The War On Cancer'. A research fellow at drug company Eli Lilly declared: 'If you look at the millions and millions and millions of mice that have been cured, and you compare that to the relative success, or lack thereof, that we've achieved in the treatment of metastatic disease clinically, you realize that there just has to be something wrong with those models.'²⁶ **A.M & A.S**



ANIMAL SUFFERING IN CANCER RESEARCH

A daunting list of stresses and hazards

Some techniques for producing genetically altered mice involve genetic manipulation of DNA, using a virus as a vehicle to insert a gene. With other methods, programmed stem cells obtained from embryos or from skin cells are used. Alternative techniques rely on the effects of toxic chemicals that are injected directly into the abdominal cavities of young mice.

Such chemicals include N-ethyl-N-nitrosourea (ENU). Where ENU impacts on non-target genes, serious malformations can result. They include cleft palate, which can leave the newborn pups in a desperate condition, unable either to feed or breathe properly.²⁷ But with all the above-described methods of genetic alteration, the chances of achieving the desired outcome are in the range of just 1-2 per cent. This means that the vast majority of progeny die either as embryos or shortly after birth. The mice who do survive face a daunting variety of stresses and hazards, according to a report published by a key government-appointed laboratory welfare organisation.²⁸

Immune-deficient mice, such as the SCID and nude strains, will have a susceptibility to infection. Some develop [unplanned for] tumours, degenerative diseases or other dysfunctions. Genetic alterations can also cause increased anxiety, frustration and heightened aggression. In addition, genetically altered mice may be prone to frenetically plucking hair or whiskers from cagemates or from themselves. They are also susceptible to 'stereotypies' – stress-induced repetitive movements, such as circling, pacing, jumping or back-flipping.

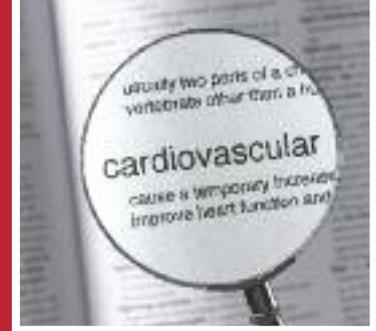
An example of an animal experiment funded by Cancer Research UK

As to the experiments themselves, typical is a 2009 project funded by Cancer Research UK, in which nude mice were injected with human cancer cells and then force-fed, via a tube from the mouth to the stomach, an experimental anti-cancer drug.²⁹ There were daily force-feedings over a ten-day period. This was in addition to painful daily injections, via the tail vein, of a radiotracer chemical to study the cancer's development. At the end of the ten-day trial, the mice were killed and their organs studied. A.M



'... while conflicting animal results have often delayed and hampered advances in the war on cancer, they have never produced a single substantial advance either in the prevention or treatment of human cancer...'





THE USE OF ANIMALS IN HEART DISEASE RESEARCH



Incidence and mortality

Coronary heart disease (CHD), which is characterised by a narrowing of the coronary arteries due to a build-up of fatty deposits, is the most common cause of death in the UK, killing 80,000 people in 2009.³⁰ It accounted for approximately one in six male deaths and one in eight female deaths in that year. Other forms of heart disease affect many thousands, but cause significantly fewer deaths.

Death rates from CHD have been falling in the UK since the late 1970s. For people under 75, they fell by 75 per cent between 1985 and 2009. The majority of the fall between 1981 and 2000 has been attributed to reductions in major risk factors, principally smoking.³¹

These figures, however, mask a disturbing recent trend. The fall in death rates has been slowest in younger age groups (35-44 years), especially among women.³²

The epidemiologists who uncovered this trend concluded in 2009 that it could be 'the first warning sign of worsening lifestyle choices and behaviours rather than deterioration of medical management of coronary heart disease'.

The prevalence of CHD is extremely high. The most recent data from the British Heart Foundation (BHF) shows that around 3.4 million adults in the UK report angina and/or a heart attack.

Heart failure – in essence, the failure of the heart to pump properly – is now at epidemic proportions in the UK, and the prognosis remains dismal. Data from the London Heart Failure Study show that around 40 per cent of people die within one year of an initial diagnosis of heart failure, which is worse than expected survival rates for breast, prostate and bladder cancers.³³ Prevalence and incidence (see page 6) are both increasing, and do so steeply with age. Around 750,000 people lived with the disease in 2010, compared with just 100,000 in 1961.³⁴

The commonest cause of heart failure is damage due to CHD. More patients are surviving the acute phase of a heart attack, and so the decreased mortality from CHD parallels the increasing prevalence of heart failure.

History of heart disease research

The BHF claims that 'without animal research, many of today's life-saving treatments for heart and circulatory disease could not have been developed'. This categorical assertion is impossible to prove or to disprove retrospectively. It is certainly the case that treatments in use today have employed surgical experimentation or drug trials on animals. Whether the use of animals was essential, however, is mere speculation. We cannot know whether the use of non-animal techniques instead may have brought benefits of equal or greater medical value. Nor is it known how many potentially useful treatments have been lost due to misleading animal data.

Undoubtedly, many surgical techniques developed during the last century involved animal experimentation during their development. But it is striking how often the first *human* trials led to a dramatic acceleration in progress, in a way that cannot simply be ascribed to technological improvements.

The history of heart transplants provides a telling example.³⁵ Alexis Carrel first experimented with transplanting dogs' kidneys into their necks in the 1890s. In 1955, Demikhov transplanted the hearts removed from 22 dogs into the chests of others, and none lived longer than 15 hours. Many experimenters performed dog heart transplants during this decade, and survival rates were universally poor. A group of US researchers concluded, by way of explanation, that 'there is a specific adverse effect

Obesity is a risk factor for heart disease



of severing the heart from the body'.³⁶ In 1964, a team from Mississippi transplanted a chimpanzee's heart into a human recipient – the patient died shortly afterwards, as the 'donor's' heart was too small.

In 1967, Professor Christiaan Barnard performed the first human heart transplant, with ten more by Denton Cooley and associates during the following year. In response, transplant programmes developed 'seemingly overnight'.³⁷ By 1974, Shumway's Stanford team had performed 59 human heart transplants, with a three-year survival rate of 26 per cent. It was careful clinical studies and follow-up of their patients that was crucial to this progress, something not possible with short-term animal procedures.

A similar time line can be mapped out for coronary artery bypass grafting: the first animal procedures took place in 1910, but it needed human success in 1966 before rapid progress was made.³⁸ And the same pattern can be seen with regard to interventional cardiology: biventricular catheterisation of a live horse was first performed in 1711, but the technique only became successful in humans after Forssmann guided a catheter into his own right atrium in 1929.³⁹

There are also instructive historical examples in which researchers have discovered unacceptable side effects of new treatments in animal subjects, but forged ahead regardless, with subsequent human benefit. The first Starr-Edwards heart valves, when transplanted into dogs, were plagued by fatal thrombus (blood clot) formation, and the necessary post-operative anticoagulation caused many dogs to bleed to death. Modifications to the design improved canine survival figures – but it was the original, simpler design that was chosen for placement in people. The researchers knew that humans were much less likely to develop thrombi than dogs; one commented: 'humans will tolerate this surgery much better than dogs... dogs, for some reason, don't like to have their blood bubbled through a pump oxygenator'.⁴⁰

Animal models in heart disease research and their historical failure

Crude, cruel and irrelevant

The use of animal 'models' – dogs, pigs and rodents are commonly used – to mimic cardiovascular disease has always been striking for its crudity and cruelty. For research into heart attacks and heart failure, healthy animals are usually grievously injured to produce a disease that is markedly different from those found in human patients. Notwithstanding, experimenters have devised many ways to destroy the circulatory systems of animals in laboratories:

- Dogs have undergone appalling procedures in the quest to damage their hearts. They are naturally resistant to heart attacks, having a rich collateral coronary circulation, and cannot be induced to develop heart disease with an artificial fatty diet. Instead, their hearts are systematically and gradually destroyed over a period of months by injecting polystyrene beads into their coronary arteries.⁴¹ The mortality rate after such treatment can approach 30 per cent.⁴² Tying off the coronary arteries of dogs is also common, although half of the victims die acutely – not by design – of malignant ventricular tachycardias. A leading US veterinarian, Dr. Holly Cheever, observes:
- As pigs do not possess such an extensive cardiac blood supply as humans, a favoured method of damaging their hearts is the placement of constricting rings (ameroids) around the coronary arteries, which narrow gradually over a period of weeks resulting in a heart attack.⁴⁴
- Millions of rodents have been victims of crude surgical mutilations to induce heart attacks and resultant heart failure. 'Aortic banding', in which a stricture is placed around the ascending aorta of weanling rats, is widely employed. The stricture gradually blocks the blood flow out of the heart as the rats grow and, by 18 weeks of age, they are breathless and swollen with fluid collecting in their lungs and abdominal cavity.⁴⁵ Mice are increasingly used to model heart attacks (MI, myocardial infarction) by tying off their coronary arteries, with up to half the subjects dying within the hour.⁴⁶



- Other methods of injury include freezing the hearts of animals with liquid nitrogen, poisoning them with known cardiotoxins, or electrically forcing their hearts to beat so fast that they fail.⁴⁷

The mouse has clearly emerged in the last decade as the most favoured laboratory species for cardiovascular experiments. This is largely due to researchers developing transgenic varieties programmed to be born with or to develop diseases. These lines include mice liable to die spontaneously due to rupture of their major vessels, or who will develop dilated and dysfunctional heart muscle.

The shortcomings of the ‘animal model’ as acknowledged by the research community

Whether surgically or genetically created, the research community readily admits that these models do not accurately reproduce human pathology. The animals used are unlike humans in their basic physiology and anatomy. Rodents, for example, have a resting heart rate five times higher than humans, with different electrical impulses and muscle composition.⁴⁸

In addition, the damage ‘induced’ in healthy animals is fundamentally different from the diseases found in humans. A 2010 review from the National Institute for Medical Research (NIMR) noted the obvious: ‘[in the animals] heart failure occurs suddenly post-surgery in the context of a relatively young heart, whereas in humans, the onset may be insidious over several years in the context of comorbidities and age-related changes... The major disease burden of heart failure in the future is expected to come from patients with the complex phenotype cluster of hypertension/hyperlipidaemia/obesity/diabetes... it is not obvious how closely [it] resembles the current animal models’.⁴⁹

Researchers have, however, always justified their use of animals by claiming that it has led to novel observations that can then be explored in humans. In many instances, this claim is spurious as data from the animal experiments only confirm what is already known to occur in patients. One paper from 2009 credits a rat myocardial infarction model with ‘ground-breaking’ significance in the use of ACE inhibitors.⁵⁰ A quote from the original paper reveals otherwise: ‘In the present study, the chronic administration of captopril [an ACE inhibitor drug] to rats with myocardial infarction and failure yielded hemodynamic results similar to those noted above in patients with congestive heart failure.’⁵¹

Neither can it be said that the models are reliably predictive of human outcomes. The same rat model suggested that endothelin receptor antagonists would give similar positive results to captopril but, in fact, patients with heart failure got worse.⁵² Mice engineered to overproduce a chemical

suspected to worsen heart failure (TNF-alpha) unsurprisingly improved when the receptors to this chemical were blocked. However, a human drug trial using the same substance failed, leading researchers to caution that ‘positive results in preclinical rodent studies do not necessarily translate to clinical benefits when applied to non-uniform heart failure populations’.⁵³ Such examples of non-correlation are the rule rather than the exception.



During the last 30 years, hundreds more heart failure drugs have been developed using animal models, with very few making it to clinical trials on patients. A particularly wasteful 20-year obsession has been the search for antioxidants that could slow cardiovascular damage by neutralising free radicals, presumed to be toxic. Despite many studies (often involving rabbits being poisoned with cholesterol), which showed ‘proof of principle of the efficacy of antioxidants in animal models of atherogenesis, atherosclerosis regression, and reperfusion injury’, randomised trials in humans have been ‘disappointing’.⁵⁴

Shockingly, BHF researchers have now announced that a new transgene mouse model shows why this is the case – free radicals can be cardioprotective.⁵⁵ This casts enormous doubt on the validity of the previous models, or suggests that the animals were manipulated to produce desired but erroneous conclusions. It is likely that a slew of animal experiments will now take place to ‘validate’ the new preferred hypothesis.

Curiosity-driven experiments

Experimental cardiothoracic surgery on animals continues today, and a good deal of it is funded by the BHF. Even a cursory probe into the scientific literature reveals that the charity has funded thousands of terminal experiments in the name of ‘basic’ research. This Home Office category refers to speculative, ‘blue skies’ procedures that may or may not lead to medical advances in the future. One of the most damning, though by no means isolated, examples of BHF-supported research is the long-running series of dog

Heart attack



experiments carried out at Leeds Medical School. The repetitive and self-justifying programme has been roundly condemned by cardiologist and former dog researcher John Pippin.⁵⁶

Some current trends in heart research

Regenerative medicine – the new Holy Grail of cardiology

With the epidemic of heart failure showing no signs of abating, the last decade has seen an explosion of interest in 'regenerative' cardiac strategies – in essence, helping the heart to repair itself with functional tissue rather than scarring. Despite experimenters' best efforts, 'significant cardiac regeneration of any form has not been reported in mammals after multiple modes of injury, including ischaemic infarction, burning, freezing, mechanical injury, chemical injury, etc'.⁵⁷ This regenerative ability – if it ever did exist – has disappeared over millions of years, suggesting that its loss conferred a survival advantage. Nonetheless, researchers have been trying to challenge evolution with stem cells and genetic manipulation, so far with little success.

a) Stem cells

These are immature cells with the ability to evolve into various kinds of specialised tissues. Pluripotent stem cells, which have the potential to develop into many cell types, can be found in human embryos or can be induced in the laboratory, starting, for instance, with skin cells. Adult tissues such as bone marrow harbour a lesser number of differentiated lines, whilst a still more limited variety (known as progenitor cells) is found in highly specialised organs such as the heart. Stem cell research and trials have involved transplanting cells into animal or human recipients. There is also ongoing work exploring gene-based strategies, with the aim of inducing indigenous tissues to re-acquire a degree of 'stemness'.

Stem cell therapies for heart disease are highly controversial, with numerous unique methodological and clinical problems. However, it comes as no surprise to discover that stem cell trials on animals generated a mass of 'positive' data that was not replicated in human trials. Heart-damaged rabbits, for example, showed improvements when injected with bone marrow or muscle stem cells. Human trials with these cells have been universally disappointing. Irrelevant experiments have also been conducted on rabbits using fibroblasts.⁵⁸ These are not even stem cells and are not able to change into specialised cardiac tissue. Mainly for this reason, this is not an approach that has been pursued in humans.

Skeletal myoblasts (SMs) are muscle-derived stem cells. Trials directly injecting SMs into patients' hearts during bypass surgery were curtailed when subjects experienced life-threatening arrhythmias (irregular heart rhythms), although 'previous extensive animal experiments provided no hint of an arrhythmogenic risk'.⁵⁹ A later trial in 2007, in which all patients had defibrillators implanted along with the SMs, was also a failure. The lead researcher has commented: 'Once again in medicine, clinical outcomes have not matched the hopes raised by the animal data'⁶⁰ and he called the animal models 'suboptimal'.⁶¹ Since then, there have been numerous further trial failures of stem cells, using both SMs and bone marrow cells to treat heart attacks, heart failure and chronic angina.⁶²

Guidelines issued in 2008 for stem cell trials sensibly recommend that 'participants should appreciate that researchers may not know whether or not the stem cell treatment will be beneficial, that animal studies might not

predict effects of the cells in humans, and that unexpected adverse events may occur'.⁶³

Leading researchers in this field are now stressing that human trials, not further animal experiments, will be key to progress. A European Society of Cardiology task force made the following recommendation in 2005: 'No matter what animal experiments are undertaken, the mechanisms that may be deduced from them may not be the actual mechanism pertaining to benefit in the human clinical situation... We believe that sufficient animal experiments have been performed in this area to allow clinical studies to continue'.⁶⁴

b) Gene therapies

These therapies usually employ viruses to deliver DNA that codes for desired proteins into target cells. Administration of these vectors in heart research is highly invasive, commonly via the coronary arteries.

Fibroblast growth factor – FGF – helps blood vessels to develop in humans. When FGF gene viruses were injected into the hearts of ameroid-constricted pigs, they showed evidence of improved cardiac blood flow. However, a Phase 3 clinical trial in humans with angina was forced to stop recruiting in 2004 due to lack of efficacy.⁶⁵

Dr Paul Williams, a BHF Clinical Researcher, commented in 2010: '... despite a huge amount of basic science research, promising animal studies, and numerous clinical trials, to date no gene therapy has demonstrated unequivocal benefit in the clinical setting... is all the hype and research expenditure unwarranted?'⁶⁶

Part of the reason for this dismal performance is the use of laboratory-based physiological outcomes that are derived from animal trials. This data can be carefully selected to demonstrate benefits that do not translate to real-world patient improvements – all too frequently revealed by a Phase 3 clinical trial. The NIMR review referred to above states: 'Many of the clinical end points that are important to doctors, patients and health care systems alike, such as quality of life, exercise tolerance and hospital admission, are unlikely to be modelled adequately in any animal system.'⁶⁷

Obesity research

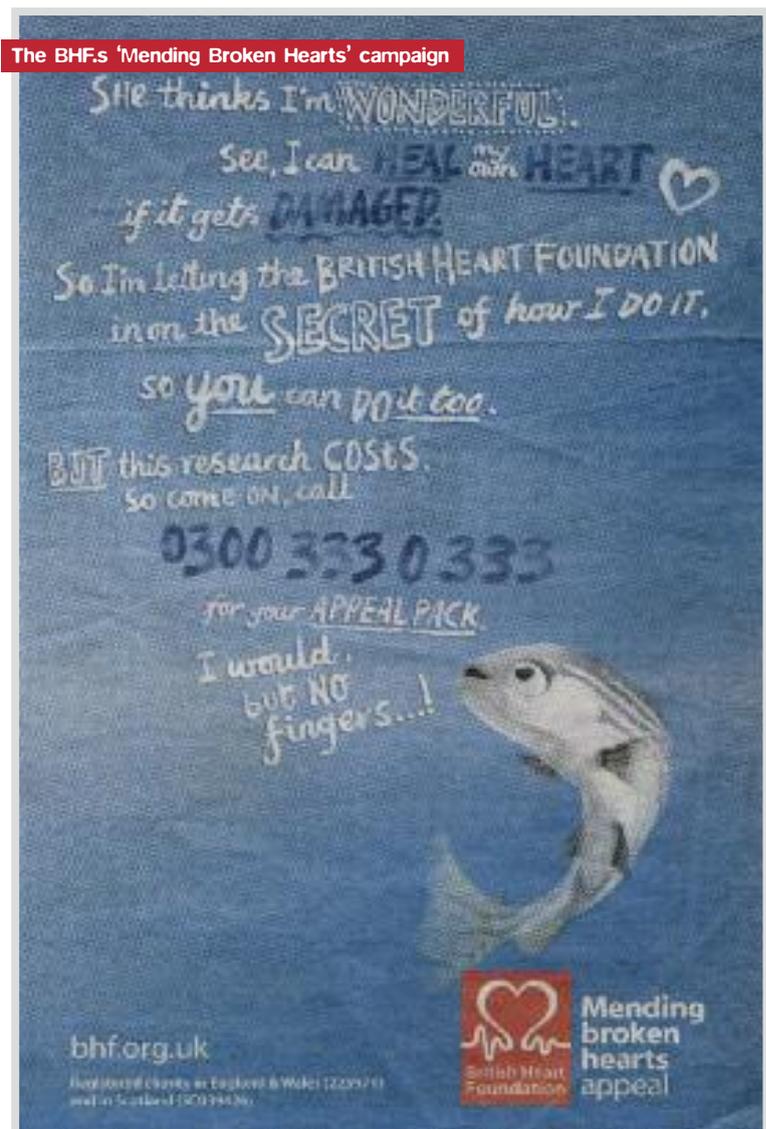
Despite widespread knowledge and acceptance of the causes of human obesity, the BHF is currently funding highly questionable research

that deliberately makes animals ill via dietary modification. In a repellent 2008 series of experiments, researchers fed female rats an 'obesogenic' unnatural diet, and allowed them to mate and give birth. After the females had weaned their pups, they were fasted overnight and 'sacrificed', and their offspring's eating habits studied. Litters of other obese females were decapitated at varying intervals after birth so that their bodies could be dissected. There is no mention of medical relevance at any point in the experimental write-up.⁶⁸

The BHF's 'Mending Broken Hearts' appeal

The therapies described above are key planks of the BHF's current programme for heart failure, upon which the charity 'needs to spend' £50 million. To illustrate the underpinning science, the BHF describes four research examples – all involve stem cells, and two involve their testing on animal models. For example, Professor Andy Baker will use his grant to discover 'how much the stem cell treatment can improve the heart's ability to pump in

The BHF's 'Mending Broken Hearts' campaign



mice'.⁶⁹ Another project will 'use the cells to promote the growth of new heart cells and blood vessels in mice'. Given the above, it is surely legitimate to question the relevance of these experiments to medical progress.

Mutilating zebrafish

The advertising motif of the campaign is a talking zebrafish, said to represent hope for heart failure sufferers. These small minnows have a remarkable regenerative ability – researchers have amputated many different parts of their bodies, and they are able to grow them back. This ability is not newly discovered, and zebrafish have been studied for many years. They are increasingly popular as 'models' because they are cheaper than mammals, reproduce quickly in large numbers, are transparent when young, and have had their genome sequenced.

In a series of mutilating experiments over the last decade, anaesthetised zebrafish have had their scales pulled off with forceps and portions of their heart chopped out with scissors. The fish were returned to water after the procedure. Unsurprisingly, they 'appeared less active and less co-ordinated while swimming' before recovering over a few days.⁷⁰ They were later killed and their hearts removed for study. Fish are capable of feeling pain and possess, in addition to a central nervous system, pain receptors all over their bodies – it is hardly surprising that they did not look well after such brutal surgery.

Last year, experimenters performed similar partial heart amputations on one-day-old mice and removed their hearts three weeks later. They found that the organs had regenerated without scarring. The surgery was also performed on seven-day-old mice but their hearts did not heal, suggesting that the regenerative ability was lost by this age.⁷¹

The BHF claims that these experiments could help develop treatments for human heart failure – an assertion that merits a rigorous and sceptical examination:

- There are a great many fundamental bio-evolutionary differences between zebrafish and humans. Importantly, the former have two-chambered hearts (compared with the four-chambered human organ), with different cardiac muscle, and can grow throughout most of their adult lives. Kenneth Poss, a leading zebrafish researcher, observes: 'It would appear that the teleost heart is better designed for growth and regeneration, while the mammalian heart is better designed for sheer contractile force'.⁷²
- Cardiac progenitor cells are present in mammalian hearts, and it was thought until recently that zebrafish used these stem cells to regenerate cardiac tissue.

However, zebrafish repair their hearts via a different mechanism (dedifferentiation),⁷³ which has no functional analogue in human hearts. After this discovery, researchers stated lamely: 'If we could mimic in mammalian cells what happens in zebrafish, perhaps we could be in a position to understand why regeneration does not occur in humans.' This hardly suggests curative potential.

- It is clear that the American researchers do not know how neonatal mice regenerate their hearts, or how this could lead to human heart failure treatments: '...we can begin to search for drugs or genes or other things that might reawaken this potential in the adult heart of mice and eventually of humans.'⁷⁴
- The BHF's campaign explicitly references stem cell treatments as candidates for early clinical trials within five years. The implication is that these treatments are novel. As described above, stem cell treatments for heart failure have already failed in clinical trials following success in animal models.
- In humans, coronary artery disease is the most common cause of heart failure. It damages heart muscle both acutely and chronically via a lack of oxygen and nutrients. Heart attacks lead to large fibrous scars in an already diseased organ. Heart failure is associated with a complex series of long-term physiological derangements. All these elements are absent in animal models in which the hearts of mice and fish are surgically damaged.

In conclusion, there is no evidence whatsoever that these heart amputation studies will ever translate into clinical benefit for humans. Last year, a group of leading cardiologists using stem cells advised that 'additional safeguards are warranted because of the innovative nature of these treatments, differences between animal and human physiology, limited experience with these cells in humans, and the high hopes of desperate patients for whom no alternative effective treatment currently exists'.⁷⁵ Unfortunately, no such caution is detectable in the BHF's current fundraising drive. **A.S**

ANIMAL SUFFERING IN HEART DISEASE RESEARCH

'The experiments involved opening the chests of anaesthetised dogs, cutting their spinal cords, draining and re-circulating their blood and cutting nerves to the brain, gut and diaphragm...'

The British Heart Foundation funds invasive animal research, involving dogs, pigs, rabbits, goats, rats and mice. Some researchers prefer to use dogs and pigs rather than rats because their heart size is comparable to that of humans. However, heart size is not necessarily a useful parameter when trying to compare human and animal heart function. Other factors play a major role, such as differences in blood clotting mechanisms, and the fact that, in quadrupeds, 70 per cent of the blood volume is at, or *above*, the level of the heart, whereas in humans 70 per cent is *below* the level of the heart. In an experiment using seven healthy dogs, the animals underwent two procedures.⁷⁶ In the first, all of the dogs were anaesthetised and their chests surgically opened. The heart sac (pericardium) was cut open to allow the researchers to inject a damaging nerve toxin (phenol) into one of the main blood vessels supplying the heart, which also damaged its associated nerve supply. The heart sac and chest were then closed with sutures and the dogs allowed to recover. No mention is made by the researchers of the clinical condition of the dogs during this recovery period. Three to four weeks later, the dogs were once again anaesthetised, the heart exposed and a fluorescent dye injected into it to record blood flow, while various measuring instruments were applied to the heart. Once the experiment was completed, researchers killed the anaesthetised dogs by cutting out their beating hearts.

27 experiments involving 100 dogs

In 2005, the BHF ran into serious controversy over a series of 27 experiments that it had funded using more than 100 dogs. The experiments involved opening the chests of anaesthetised dogs, cutting their spinal cords, draining and re-circulating their blood and cutting nerves to the brain, gut and diaphragm.⁷⁷

Former Harvard Medical School faculty member and heart specialist John Pippin MD FACC, who examined the research team's published papers, was scathing. He wrote: 'Very evident in this collection of papers is the characteristic use of one study to justify the next. In many cases, unanswered (usually unforeseen) questions arising from one study produced the rationale for a later study. In several instances, the team invokes conflicting or erroneous results from previous studies (sometimes their own) to justify another study.'⁷⁸ He continued: 'This work provides an exceptional example of a common practice: the manipulation of animal models for convenience and usefulness, regardless of the effects upon the validity of results obtained. This is not uncommon among those researchers who propose and perform studies to satisfy their scientific curiosity and sustain their careers, without sufficient regard for potential applications to humans.'⁷⁹

Given that the BHF continues to fund similar dog experiments, it would seem that it has ignored Dr Pippin's findings. Whilst the dog is a well established model in heart research, those involved are becoming increasingly uncomfortable as public awareness of their activities grows. This could help to explain why the following study was conducted on goats, rather than dogs – even though goats, of course, have the same capacity to suffer pain and stress.

Protracted and ultimately lethal goat experiments

Ten healthy adult female goats were anaesthetised and their blood pressure was measured by an instrument inserted into an artery in one of their limbs for the duration of the procedure.⁸⁰ From the following day, the goats received a heart drug by mouth at different doses for seven days. They were also briefly anaesthetised every day in order for blood pressure measurements to be made while they received an injection of a naturally-occurring chemical that affects blood pressure. Repeated anaesthesia is a stressful procedure for any animal, especially during the recovery phase, in addition to being physiologically demanding on the liver, which is responsible for metabolising the anaesthetic.

A follow-up experiment involved 28 adult goats.⁸¹ All were anaesthetised, while a pacemaker device was implanted via the external jugular vein. The goats were allowed to recover before undergoing the next stage of the experiment, in which the pacemaker was switched on for three continuous 28-day periods, separated by 24-hour rest periods, with the aim of upsetting the natural electrical activity of the heart. Blood samples were taken every few hours for the first week, then once a week until the end of each 28-day period – a series of interventions that would have caused the animals significant pain and distress. At the end of the third 28-day period, several of the goats were anaesthetised for a last time, their chests opened and their hearts examined before being killed. It is unclear from the article what the fate was of the remaining goats.

The researchers concluded that important heart events seen in human patients were absent or difficult to detect in their goat experiments. In particular, left ventricular dysfunction and atrial fibrosis – two key structural heart changes seen in humans – are not replicated in goats. These major caveats are surely sufficient justification for invalidating the goat model.

Eight pigs suffer graft rupture

Researchers at the University of Bristol were funded by the British Heart Foundation to study a new technique for vein grafts in 56 Large White-Landrace cross pigs.⁸²

The pigs were given a general anaesthetic, while a portion of a leg vein was cut out and inserted into the main artery on one side of their necks, in much the same way as a coronary bypass is performed. The veins were then coated with either a low or high dose of an immunosuppressant drug to improve the chances of a successful outcome of the graft. The pigs were allowed to recover from the procedure and kept alive for a few more weeks.

The pigs were subsequently re-anaesthetised either one, four or 12 weeks later (although not mentioned in the study, it would appear that the pigs would have been killed at this stage of the experiment) in order to cut out the graft for microscopic study and evaluation. The researchers noted that the graft appeared healthy at one week but not at four weeks. Increasing the dose of immunosuppressant in an attempt to prolong its effect led to serious problems. For example, there were eight deaths from graft rupture in the pigs who had received the high doses of immunosuppressant drug. These animals would have experienced a traumatic and painful death.

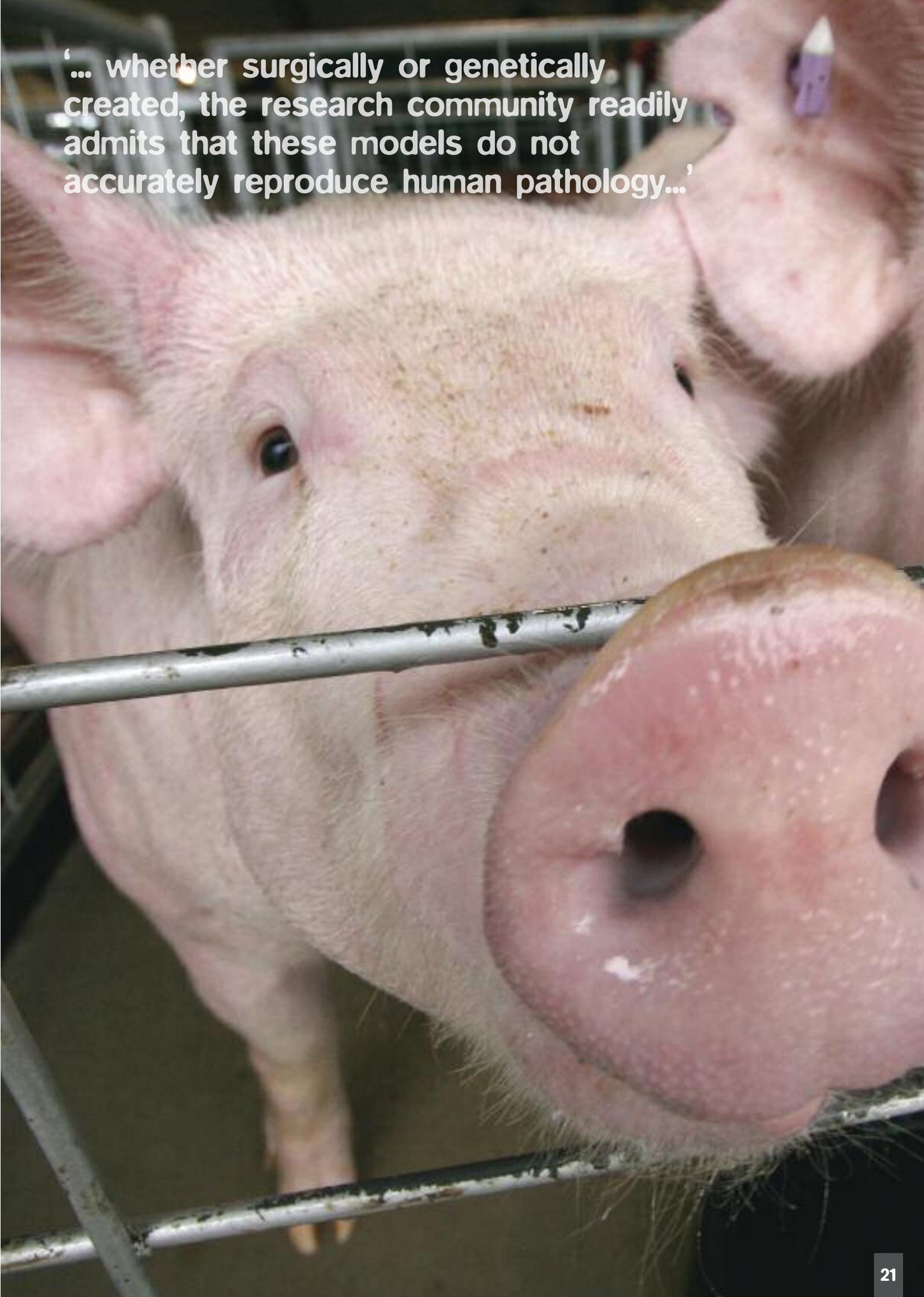
'Heart attack' induced in rabbits

Researchers at the British Heart Foundation Glasgow Cardiovascular Research Centre conducted a study using 27 healthy New Zealand White Rabbits.⁸³ The stated objective was to study the electrical activity of the left ventricle following heart attack. The rabbits were divided into three groups. The first 11 rabbits were anaesthetised and had a major artery supplying their hearts tied off with surgical suture, to mimic a serious heart attack. The second group of four rabbits was also anaesthetised and had their chests opened, but their hearts were not damaged. Finally, the third group of 11 rabbits was not anaesthetised or operated on but kept as control animals for later comparison with the 'heart attack' rabbits.

Eight weeks after surgery, the rabbits' hearts were examined with an ultrasound device prior to them all being killed and their hearts studied in the laboratory. It should be noted that there are some significant differences between rabbit and human hearts. The former is obviously much smaller and also beats much faster (180 to 250 beats per minute, compared with 72 bpm for a human heart). In the rabbit, the right atrioventricular valve of the heart has only two valve leaflets (cusps) rather than three in humans. Conclusions drawn from the rabbit heart cannot be applied predictively to people. A.M



‘... whether surgically or genetically created, the research community readily admits that these models do not accurately reproduce human pathology...’



Parkinson's disease
also called *paralysis agitans* or *shaking palsy*
a form of paralysis causing uncontrollable shaking of the limbs and a mask-like face.
[after *J. Parkinson*, 1755–1824, a British doctor]

THE USE OF ANIMALS IN PARKINSON'S DISEASE RESEARCH

Incidence and mortality

Parkinson's Disease (PD) is a common condition, with both incidence and prevalence being strongly age-related. It currently affects 1 in 500 people in the UK, representing 120,000 people or about 1-2 per cent of the population above the age of 65.⁸⁴ Prevalence increases sharply to 3.7 per cent in those over 75 years, and 5 per cent in those aged 80 years and over. The InfoPark international research project estimates that by 2050, 3-4 million Europeans will have PD as the population ages.⁸⁵

The annual incidence is age-dependent, from 17.4 per 100,000 between 50 and 59 years of age, to 93.1 between 70 and 79 years.⁸⁶

Results of long-term UK studies over the last 40 years suggest a stable prevalence of PD. There is no good evidence that PD sufferers die earlier. The UK rate for mentions of PD on death certificates declined by 22 per cent for males and 32 per cent for females between 1985 and 2004.⁸⁷

History of Parkinson's Disease research

Discoveries about PD during the last half of the 20th century proceeded only very slowly. And whilst the underlying disease process is now clearer, its causes remain uncertain. There is still no cure, only treatments which can alleviate symptoms, and whose efficacy tends to decline over time.

An examination of the major treatment breakthroughs cited by Parkinson's UK shows clearly that they have been due to human studies:

- The drug levodopa remains the single most potent and useful PD drug. The pioneering discoveries in this area were made by Oleh Hornykiewicz in the late 1950s. The breakthrough came when 'rather than trying to use animal models of the disease, like many others did, I felt that the best way to test my idea was to go directly to the human brain and see whether in PD



there was a dopamine deficiency or not'.⁸⁸ Autopsy samples proved Hornykiewicz correct, and his work led immediately to the first successful trials of dopamine replacement – in human PD sufferers.

- Selegiline is a monoamine oxidase inhibitor, and potentiates the effects of levodopa. It was studied first in humans – 47 parkinsonian subjects – by Birkmayer and Riederer in 1975,⁸⁹ and is still in widespread use today.
- Apomorphine is the strongest of the dopamine agonists used to treat PD. Again, its use in this context was pioneered in human drug trials, first by Schwab in the 1950s and later by Cotzias.⁹⁰
- Contrary to a campaign of public misinformation by proponents of animal experiments, deep brain stimulation treatment for PD was discovered in a human patient. The technique was used to successfully treat a series of patients *before* monkey research took place.⁹¹

Animal models in Parkinson's Disease research and their historical failure

An immensely expensive blind alley

In contrast to the positive steps made when studying human Parkinson's sufferers, animal research into PD has proved, especially recently, to be an immensely expensive blind alley. A recurrent theme has been researchers' obsession with creating 'animal models' that purportedly mimic the human disease. PD animal researchers openly acknowledge the numerous shortcomings of these surrogates, but continue to push them as being essential to progress – until the next model comes along.

A variety of methods have been used to artificially generate 'parkinsonism' in animals in laboratories. Researchers continue to inject poison into the brains and circulation of primates, producing a 'toxic' model that is fundamentally different from human PD. Most notably, the brain-damaged primates, unlike people, gradually recover.

Paralysis, ulcers, unable to feed or walk... the suffering of monkeys in PD research

Marmosets are the victims of choice, and have to endure numerous intracerebral injections in order to keep them sufficiently diseased. Research funded by grants from Parkinson's UK led on to a series of appalling experiments on these animals. In 2004, 31 monkeys were used to investigate a therapy that had already failed in human

clinical trials.⁹² The unluckiest dozen suffered 18 separate brain injections 'in the hope of achieving longer-lasting behavioural deficits', with needles being left in their brains for two minutes after instillation of poison. The experimenters concluded that their techniques 'may cause a concern for the safety' of patients – a concern that had already been clearly established in human trials.

Mice are also routinely poisoned with brain-destroying chemicals, or genetically modified to develop certain aspects of neurological disease, none of which have proved scientifically satisfactory. Highly toxic pesticides have been injected into the abdomens of mice, specifically in order to kill or severely incapacitate them.⁹³ One of these was paraquat, a herbicide so hazardous that it causes irreversible organ damage and failure when ingested.

The most widely used brain poison is MPTP, which was discovered when people were accidentally exposed to it. The substance is usually injected into monkeys and rodents, under the skin or directly into blood vessels, for which major surgery can be required. A particularly saddening and callous review by an American experimenter describes how she makes monkeys in her care 'extremely sick'.⁹⁴ As well as parkinsonian symptoms – slowness, lack of movement, stooped posture and trouble walking – the animals can become paralysed, develop ulcers and hypothermia and experience severe weakness. Some are too feeble to eat and require feeding via tubes into their stomachs.

Marmoset monkeys used in Parkinson's Disease research



© BUAV



The extent of the diseased animals' disability is then assessed using various 'Parkinsonian scales'. A badly poisoned squirrel monkey, for example, would 'stay in a confined area of the cage... [make] few or no body movements regardless of provocation... [have an] inability to grab food and may need to be hand fed... [and] fall from the cage with no attempt to move'.⁹⁵

Hung from spinning rods, restrained in tubes, startled with noise... the suffering of mice in PD research

Mice suffering parkinsonian symptoms are forced to endure a battery of manifestly cruel tests – they are hung suspended on wire grids or spinning rods, made to walk on balance beams, startled suddenly with noises, and made to remove sticky labels stuck to their foreheads. In tests deliberately designed to inflict pain or test 'depression', they are restrained in tubes and their tails heated, forced to swim in a glass cylinder for 15 minutes, or hung up on a lever by their tails.⁹⁶ These tests are considered relevant to the testing of PD therapies for humans.

After testing, animals are invariably killed so that their brains can be studied.

Despite the fundamental problem of human Parkinson's irreproducibility, MPTP-damaged animals have been used in hundreds of experiments, which have proved worthless and unnecessary. According to Dr Marius Maxwell, an Oxford, Cambridge & Harvard-trained neurosurgeon: 'There is no evidence to suggest that their overall predictive concordance to human PD treatment... would exceed the best case 50:50 coin toss probability.'⁹⁷

A catalogue of research failures

Several of the most notable failures or delays in PD treatments can be ascribed to the use of misleading animal models:

- There has been a failure to develop neuroprotective drugs that slow the progression of the disease. Many animal drug trials in this area have proved contradictory and unhelpful. Despite 'overwhelmingly positive' animal studies on MPTP-damaged mice, the cholesterol-lowering drugs statins are useless in slowing the disease in humans. According to Benjamin Wolozin, a Boston University Professor of Pharmacology: 'The problem lies with the chasm between experimental work and clinical trials...the

most reasonable interpretation is to accept that the disease is more complicated than reflected in the animal or epidemiological models.⁹⁸

- A review in 2003 found that animal neurotoxin models of PD demonstrated a neuroprotective effect from iron chelators, radical scavenger antioxidants, MAO-B inhibitors, glutamate antagonists, nitric oxide synthase inhibitors, calcium channel antagonists and trophic factors – none of which are useful in humans. The review authors, all prominent pharmacologists and PD researchers, concluded: ‘The animal models of Parkinson’s disease may not be totally reflective of the disease and, therefore, the chemical pathologies established in the animal models may not cause, or contribute to, the progression of the disease clinically.’⁹⁹
- One of the latest drugs to be touted as a neuroprotector is exendin-4. However, the most recent results of trials in rats do not even match those of earlier rodent research.¹⁰⁰
- Evidence suggests that animal research confused the issue of cell transplant surgery for PD. In the 1990s, transplants of foetal nerve cells into the brains of PD patients were halted after disabling side-effects relating to the donor tissue became apparent. Animal trials had not indicated the risk, which researchers have suggested was due to ‘differences between the non-human primate and human putamen [a structure located at the base of the forebrain]’.¹⁰¹ A revisiting of this research in 2010 was mainly stimulated by brain imaging of two PD patients who had received transplants. This study demonstrated an excess of serotonin-producing cells in the grafted area,¹⁰² which could be damped down by drug therapy.
- Gene therapy for PD (see below) is a relatively recent development, but, true to history, animal models are once again proving useless. In 2006, a gene encoding the growth factor neurturin was introduced into the brains of MPTP-poisoned rhesus monkeys, using a viral vector. They demonstrated a dramatic improvement in their parkinsonian symptoms. In human clinical trials, however, neurturin gene treatment was no better than sham surgery¹⁰³ (whereby the same procedure was performed but without introducing the ‘active ingredient’ – i.e. the sham group act as controls).

Contemporary research into Parkinson’s Disease

Parkinson’s UK has identified four priorities for their latest research programme. Alongside finding biomarkers to help diagnose PD earlier, and a greater understanding of nerve

cell death, developing new animal models for both research and drug testing are also key objectives.

In support of these, the organisation quotes Professor J Timothy Greenamyre, a US-based PD researcher: ‘Current animal models mimic some of the symptoms of Parkinson’s but they don’t recreate the changes that happen in the human brain. To do this, we need better models, where the nerve cells die slowly and develop characteristic features of Parkinson’s, such as Lewy bodies. We need to be able to look at the gradual development of the condition in animals as they age.’¹⁰⁴

It is hard to see why any emphasis should be placed on developing ‘ageing’ animal models when human studies and modern technologies offer a wealth of appropriate and ethical research options. The crudity of such ‘new’ animal models (and their striking similarities to the failed old ones) is revealed by the latest Parkinson’s UK-funded experiments. For example, in 2009, scientists poisoned rats with the pesticide rotenone, already implicated in causing PD in humans.¹⁰⁵ The chemical had been used years earlier to induce parkinsonism in rats and primates. Thus, in a baffling reversal of good science, researchers are using pre-existing knowledge about a likely cause of human PD to create disease parodies in animals – over and over again.

Genetic research and treatments now form a major part of PD activity. Large-scale human population studies are revealing a complex interaction of genetic susceptibility and environmental factors in PD causation. However, despite the failure of transgenic rodent models to deliver medical progress,¹⁰⁶ Parkinson’s UK intends to use these new genetic discoveries to develop more of the same. In a parallel development, Japanese scientists are developing genetically altered marmosets who can pass their altered genome to their offspring.¹⁰⁷ They intend to create colonies of animals born with a PD-type disease for research purposes. However, marmosets are genetically more distant from humans than macaques, the non-human primate of choice until recent years. Marmosets fail many cognitive ability tests that are used to assess treatments for neurodegenerative disorders, and their brains are too small to study with positron emission tomography scans, which are an important element in human trials.

With regard to contemporary PD research, there are striking historical echoes. Even though promising avenues of human-based research are being pursued, there remains a strong reliance on animal models, a reliance that could delay – and possibly derail – progress being made by the human-centred investigations. **A.S**

ANIMAL SUFFERING IN PARKINSON'S DISEASE RESEARCH

Examples of animal experiments funded by Parkinson's UK

Parkinson's Disease is not known to occur naturally in any species other than humans, which is why researchers resort to deliberate brain-damaging interventions in order to produce Parkinson-like symptoms in animals. While there may be similarities between the brains of human and non-human primates, monkeys' brains are not scaled-down versions of the human organ. Their brains are the result of unique evolutionary biology, moulded over millions of years in response to environmental, social and genetic influences. While macaque and marmoset monkeys are often used in Parkinson's Disease research, it is rats who are used more than any other species.

Monkeys severely disabled

In two experiments funded by Parkinson's UK (formerly Parkinson's Disease Society), 26 and eight marmoset monkeys were used, respectively.^{108, 109} They received daily injections of the chemical MPTP for five consecutive days, which rendered them so severely disabled that they were unable even to feed themselves and had to be hand-fed. Over the following eight weeks, the monkeys exhibited rigidity,

poor coordination, loss of balance and an inability to vocalise. Only at the end of the eight-week period were some of the monkeys given treatment to alleviate their symptoms. These 'lucky' animals received different chemical cocktails by gavage (force feeding), while others were left untreated to endure the full effects of MPTP poisoning. The behaviour of the treated and untreated monkeys was then compared and rated.

In another study, 25 female macaque monkeys were used.¹¹⁰ Five were killed at the beginning of the study so that their brains could be kept for comparative purposes with those of the monkeys undergoing the actual experiment. The remaining 20 monkeys received daily injections of the same severely disabling chemical, MPTP, until they too were killed. Their behaviour and ability to move were monitored by videotape recordings. Fruit 'rewards' were used to manipulate the monkeys into doing the researchers' bidding. This may sound benign but such 'rewards' are often provided against a background of food and water deprivation. Five of the monkeys were killed after six days, five at day 12 and five at day 15. The monkeys in the day 15 group exhibited early symptoms of brain damage (loss of coordination) due to MPTP toxicity. All animals were killed with an overdose injection of anaesthetic. Their brains were removed after death for laboratory study.



Rats brain-damaged

Inflammation in the brain is thought to play a significant role in PD. In this experiment, researchers injected two destructive chemicals directly into the brains of rats. One chemical triggered PD-like symptoms, while the other caused inflammation in their brains.¹¹¹ In people, inflammation of the brain can cause symptoms ranging from headaches and visual disturbances to convulsions and coma.

A week later, the rats were injected with an experimental drug directly into their abdomen. Although the drug appeared to protect the brain against inflammation, the authors could only hypothesise as to whether the effect would also occur in PD patients. The injections, which were given twice a day for seven days, would have been particularly painful, since they penetrate muscle as well as skin. These were followed by behavioural tests in which the rats were placed in a circular test arena for up to 60 minutes and observed to see whether they had sufficient coordination to perform tight turn-arounds when changing direction. For animals who may be suffering pain and disorientation, this is likely to have been an ordeal. Later the same day, the rats were anaesthetised while samples of brain chemicals were measured. They were then killed and their brains studied. Although the authors do not mention how the rats were killed, there are several common methods in use today: anaesthetic overdose by injection; carbon dioxide inhalation; cervical dislocation (breaking the neck without anaesthesia); or decapitation (using a guillotine, with or without prior anaesthetic).

A total of 44 male rats were used in another study.¹¹² The animals underwent major head surgery to implant small tubes directly into their brains, secured in place with an apparatus fixed to the skull (dental cement cap) and metal screws. After a 10-day 'recovery period', during which the rats received no painkillers, brain damaging chemicals were administered to the fully conscious rats through the tubes implanted in their brains, in order to replicate PD symptoms. No mention is made by the authors of how the animals reacted. One hour after the procedure, the rats were killed by decapitation and their brains examined. A.M

‘... several of the most notable failures or delays in PD treatments can be ascribed to the use of misleading animal models...’



THE USE OF ANIMALS IN ALZHEIMER'S DISEASE RESEARCH

Incidence and mortality

Dementia – a progressive loss of cognitive function and memory – is caused by various diseases and conditions. In 2007, dementia affected a little more than one per cent of the UK population, and was predicted to rise by 154 per cent in the next 45 years.¹¹³ Dementia is strongly age-related, with one in six people over 80 having a form of it. Alzheimer's Disease, a physical brain disorder, is the most common cause of dementia, affecting around 465,000 people in 2010.¹¹⁴

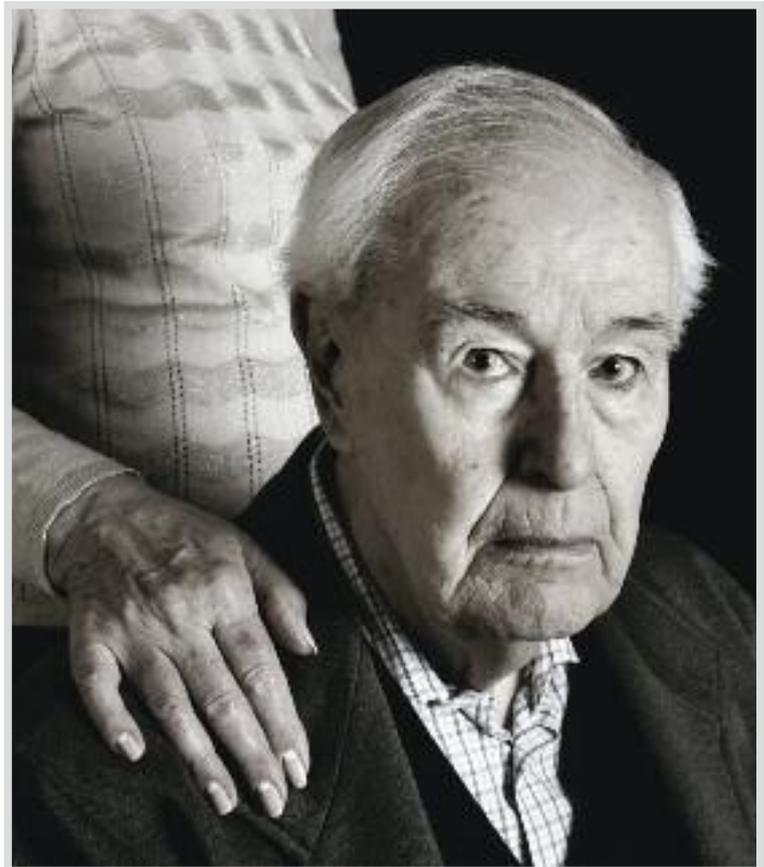
For people over 65, 15 per cent of deaths in women and ten per cent of deaths in men are attributable to dementia. Delaying the onset of dementia by five years would halve the number of UK deaths due to dementia to 30,000 a year.¹¹⁵

What is Alzheimer's Disease?

Alzheimer's Disease changes the chemistry and structure of the brain, causing brain cells to die. The other hallmarks of the condition are the development of plaques and tangles in the brain. The plaques are composed largely of a protein called amyloid-beta, which is cut from a naturally occurring precursor known as APP. Tangles are made up of a protein known as tau, which is produced in an abnormal form. The causes of Alzheimer's Disease are believed to be multiple, with age, genetic inheritance, environmental factors, diet and health all implicated.

History of Alzheimer's Disease research

The Alzheimer's Society, in a sweeping statement that credits animal research for almost all medical therapies ever discovered, claims that it is essential for 'understanding the biology' of dementia and for testing new drugs and treatments. In fact, the biological discoveries are usually



made in humans, with subsequent attempts made to mimic them in animals, the data obtained from which are inadequate and misleading. If animal models had produced a plethora of effective therapies, the position of the charity would be more defensible. In reality, the failure to translate results from animal tests into clinical progress is perhaps most dramatic in the case of Alzheimer's Disease.

Animal models in Alzheimer's Disease research and their historical failure

Chosen for convenience and economics rather than for their predictive value

According to a 2008 article in *Nature*, the research community is now worried that 'it may be unrealistic to

think of modelling the full complexity of ageing-related human brain disorders in mice whose disease course is usually accelerated by a single crude genetic modification'.¹¹⁶ This worry is entirely legitimate.

The 'experimental Alzheimer's Disease' that researchers produce in animals is emphatically not the same as the human variety. Although some aged primates and dogs develop a disease with similarities, no animal species suffers from the same condition. Thus, researchers have had to produce laboratory facsimiles, with what their creators admit have been 'partial and unpredictable' results.¹¹⁷

Their methods include injection of neurotoxins directly into the brains of rodents and primates, and poisoning rabbits with a diet of cholesterol and copper. However, by far the most popular 'models' of recent years have been transgenic mice, whose genetic make-up has been altered. These transgenic models have been instrumental in developing a whole range of ineffective drugs for Alzheimer's.

Alzheimer's in humans leads to complex, progressive structural brain changes and cognitive losses. Despite years of tampering with rodents' genetics, the models produced have not accurately reproduced these features:

- Some mice with mutant tau genes failed to show any sign of altered neurological function. Others formed

more Alzheimer's-like tangles but developed lesions in the spinal cord and brainstem that left them effectively disabled. They were therefore unable to properly carry out tests of cognition and memory that required them, for instance, to run about in a maze.¹¹⁸ More recently still, mice have been created with tangles in the 'right' areas – but they do not form amyloid plaques.

- Many transgenic animals accumulating amyloid plaques display only subtle effects, and do not develop tangles or suffer from significant neurodegeneration.¹¹⁹
- Many APP over-expressing mice 'do not develop pathology at all, probably due to insufficient APP/amyloid-beta expression'. Models that did show either plaques or cognitive impairment did not demonstrate any cell death.¹²⁰

Only very recently have mice been created with amyloid-beta and tangles together. There is no reason to suspect that they will be any more predictive of human success than their forebears. The researchers are not blind to this problem: 'The relevance of... an artificial model to an aged, non-mutant human brain is potentially problematic. Furthermore, there are additional factors that play a role in triggering a disease and its progression, such as diet and



the environment... the impact of these factors have (sic) not been addressed.'¹²¹

In any case, these animals are chosen for convenience and economics rather than for their predictive value – mice 'are relatively cheap to maintain, fecund and have a short life span; they are easy to manipulate genetically and they respond reasonably well in cognitive tests.'¹²²

The irrelevance of animal memory tests

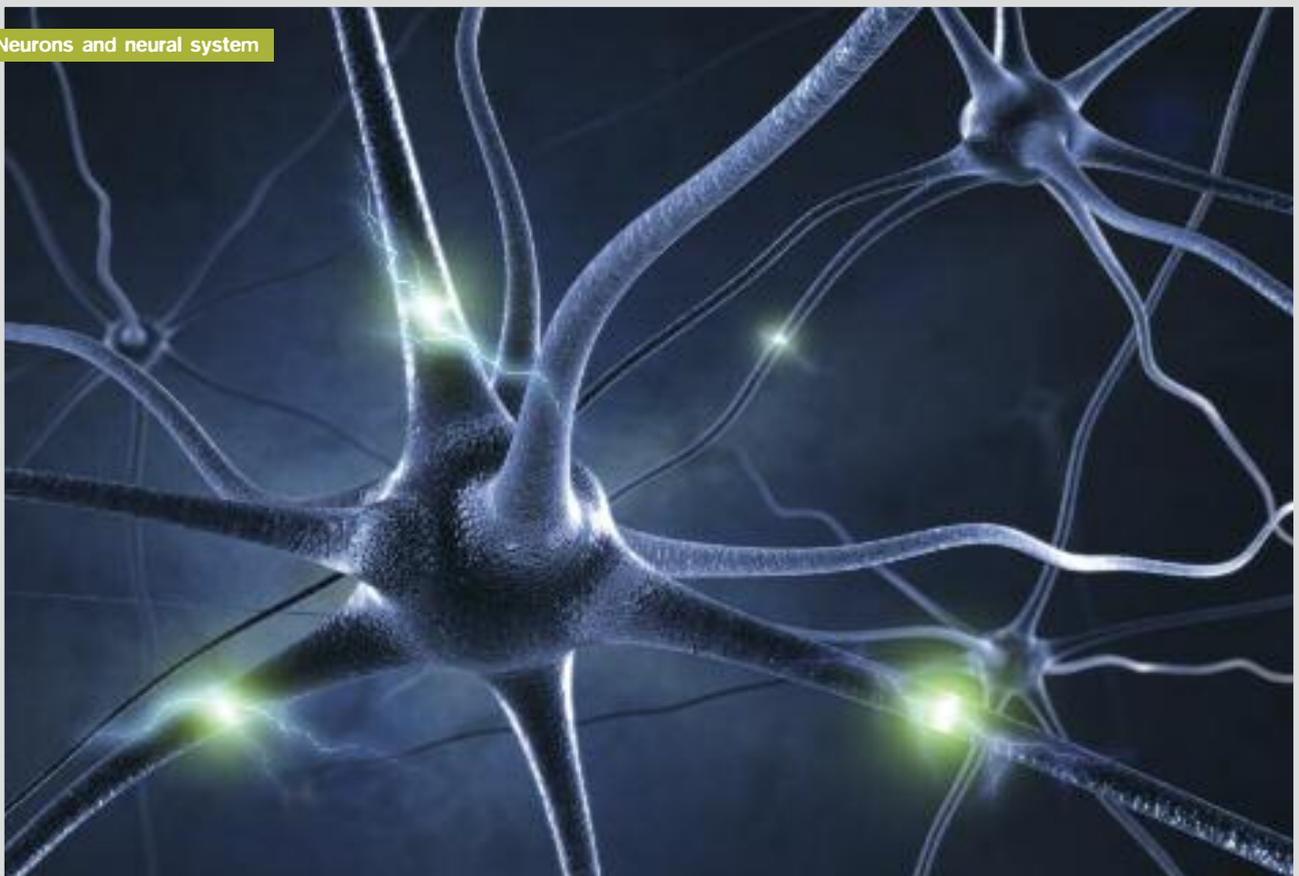
The aforementioned tests, supposedly relevant to Alzheimer's in humans, are extremely crude and reductionist. Some of the most facile – not to mention cruel – include:

- *The active avoidance task.* This is described as 'a fear-motivated... test based on electric current as a source of punishment'.¹²³ In other words, mice are scared into remembering when and where they will receive an electric shock.
- *Y-mazes and T-mazes.* Rodents are placed into these very simple structures, often after having been starved or deprived of water, and are forced to make choices between routes. Experimenters used a T-maze to discover that 'for a thirsty rat the rewarding effects of drinking water are very much greater than those of airlicking.'¹²⁴

- *Isolation-induced aggression testing.* Mice are forced to attack each other, after being held in solitary confinement for prolonged periods.
- *Morris water maze.* This widely used test forces rodents to swim around a pool of water in order to find an escape route. The procedure is highly operator-dependent with myriad variables; standardisation is difficult.
- *Step-down avoidance.* Rodents are dropped onto uncomfortable vibrating platforms, which they can switch off by stepping down onto a grid with a built-in sensor.

A wryly humorous internet column by a US-based pharmacologist, in which 'Alzheimer's rodents' are nominated as the 'worst animal model', effectively sums up the state of the 'art': '...the disease is affecting higher brain functions that are very poorly modelled in any of the small animals... When I used to work in the field, I would occasionally wonder about the relevance of watching a rat run into one half of his cage or another to a person forgetting an important appointment... the infamous Morris Swim Maze... needs its own special room, full of special equipment, and a full-time person trained in its complications to generate the data that you still don't quite trust.'¹²⁵

Neurons and neural system





Expensive and time-consuming flops

The failure of Alzheimer's animal models in drug development:

Time and time again, drugs that seemed powerfully effective in animal Alzheimer's models have failed in clinical trials. Experts have suggested many reasons for this mismatch – the almost ubiquitous poor design of animal trials, the obvious differences between animal models and human pathology, and a dramatic proven publication bias (see page 39) in favour of 'positive' results from animal experiments.¹²⁶

There is a large and growing list of highly expensive drug failures for Alzheimer's. The following are all recent and represent only the tip of the iceberg:

- Dimebon was found to be useful in avoidance experiments in brain-poisoned rats,¹²⁷ but useless in humans. (Phase 3 clinical trial failed 2010.) The pharmacology of the drug was always unclear, and it actually *increased* levels of amyloid-beta in mouse brains. The Alzheimer's Society called the research 'head scratching', but still saw fit to claim Dimebon could be available as a treatment within three to five years.¹²⁸
- Tarenflurbil was shown to improve memory and behavioural performance in transgenic mice, but was totally ineffective in patients with mild Alzheimer's. (Phase 3 trial failed 2008.)¹²⁹
- Tramiprosate significantly reduced amyloid-beta in the brains of transgenic mice, but was ineffective in mild to moderate Alzheimer's sufferers. (Phase 3 trial failed 2007.)¹³⁰
- Semagacestat reduced levels of amyloid-beta in plasma, cerebrospinal fluid and the brain in a dose-dependent manner in animals. However, it worsened cognition and the ability to perform activities of daily living in mild to moderate Alzheimer's patients. (Phase 3 trial failed 2010.)¹³¹

- Bapineuzumab is a monoclonal antibody to amyloid-beta. Such drugs given to transgenic mice cleared some of their brain deposits with 'cognitive benefit'.¹³² The drug failed to improve cognitive function in a Phase 2 trial of 234 Alzheimer's patients in 2008.¹³³
- AN-1792 was a vaccine to amyloid-beta, designed to stimulate patients' own immune systems to destroy the protein. In mouse trials, this immunotherapy was successful at clearing amyloid-beta with no obvious side-effects. It was also found to be 'safe' in monkeys, rabbits and guinea pigs. Yet Phase 2 clinical trials were terminated in 2002 when patients developed serious brain inflammation, and there were no significant cognitive benefits.¹³⁴ Clinical trials of a supposedly safer 'second-generation' vaccine were suspended in 2008, again due to unforeseen side-effects. The AN-1792 researchers later reported postmortem data on some of their patients, all of whom had died of severe dementia. Some had no amyloid in their brains, casting doubt on whether its removal from animal models was of any relevance.¹³⁵
- Nerve Growth Factor (NGF) was shown to safely prevent the death of nerve cells in various strains of rats, and in ageing rhesus monkeys. In the earliest human trial, NGF was infused into the brain ventricular system of three patients, but it caused severe side-effects. Following further research, Phase 2 trials are ongoing, led by the same company that used similar failed techniques for Parkinson's disease.¹³⁶
- Finally, some recent animal experiments proved unhelpful in illuminating epidemiological data. A link between Alzheimer's and type 2 diabetes, for example, has been known for some time. Metformin, a commonly prescribed anti-diabetic drug, has been shown to *increase* the formation of amyloid-beta yet *decrease* the formation of tau in rodents.¹³⁷ The doses used for recent animal studies were much higher than those used in human diabetes, which casts doubt on whether this drug could ever be safely employed in people due to side-effects.

The 2008 *Nature* article points out what is now obvious – 'in recent years, and especially for neurodegenerative diseases, mouse model results have seemed nearly useless'.¹³⁸

Contemporary Alzheimer's research – more of the same

Many questions relating to Alzheimer's remain unanswered, with crucial links in the chain of causation still missing. Heated debates are ongoing – in particular, there is the vexed question of whether amyloid-beta is a cause or a consequence of the disease. It is clear, however, that many 'amyloid-busting' drugs developed and tested using simplistic animal models have been a failure. The obsession with mimicking a disease in animals, without first understanding it in humans, has cost Alzheimer's patients dearly.

However, the Alzheimer's Society remains committed to animal-based research. Many of its current projects are still ploughing the same infertile furrows, with mouse models of Alzheimer's being used to test stem cells, amyloid-reducing antibodies and new drugs. Patently pointless experiments, such as demonstrating that rat nerve cells do not function well if deprived of oxygen, are also funded.

Shockingly, the society is funding several studies on animals that investigate therapies that have already failed in humans. For example, it has granted more than £200,000 for a researcher to investigate the mechanism of Dimebon in mouse models. Another is injuring mice to study the effects of the anti-inflammatory drug Ibuprofen on their memory, despite numerous clinical trials showing these drugs do not help in Alzheimer's and have too many dangerous side-effects.¹³⁹

Equally wasteful and pointless is a series of animal brain damage experiments. It is known from human studies that severe head injury is a risk factor for Alzheimer's, and postmortems in these patients have revealed some of the disease's structural changes. Certain chemicals associated with trauma were also first identified in the brains of Alzheimer's patients. Despite continued human studies in this area, one researcher is destroying the brains of mice, either by tying off their cerebral arteries or by direct trauma to their heads to see if the same findings occur.¹⁴⁰ **A.S**



ANIMAL SUFFERING IN ALZHEIMER'S DISEASE RESEARCH

Examples of animal experiments funded by the Alzheimer's Society

The search for an animal model for Alzheimer's Disease began in earnest in 1980.¹⁴¹ Some of the earliest attempts involved injecting aluminium chloride – a chemical so corrosive that people dealing with it should wear safety glasses and gloves¹⁴² – directly into the brains of developing rabbits.¹⁴³ Today, mice, rats, marmoset monkeys and mouse lemurs are the animals of choice.

Animal researchers have not only developed various techniques to cause brain damage, they have also devised extremely cruel methods to assess brain function afterwards. Transgenic mice are now used to mimic the excess protein deposition in the brain. These mice are bred with a defective human gene associated with AD. However, they often do not develop the desired pathological damage or else display it in the 'wrong' areas.¹⁴⁴

In an experiment funded jointly by the Alzheimer's Society, the Alzheimer's Association, the Alzheimer's Research Trust and the Medical Research Council, transgenic mice containing the defective human gene were crossed with another strain of transgenic mice containing a protective gene. The aim of the research was to see whether the protective gene could block or neutralise the effects of the defective gene, and



so provide leads to the development of therapeutic drugs for AD.¹⁴⁵

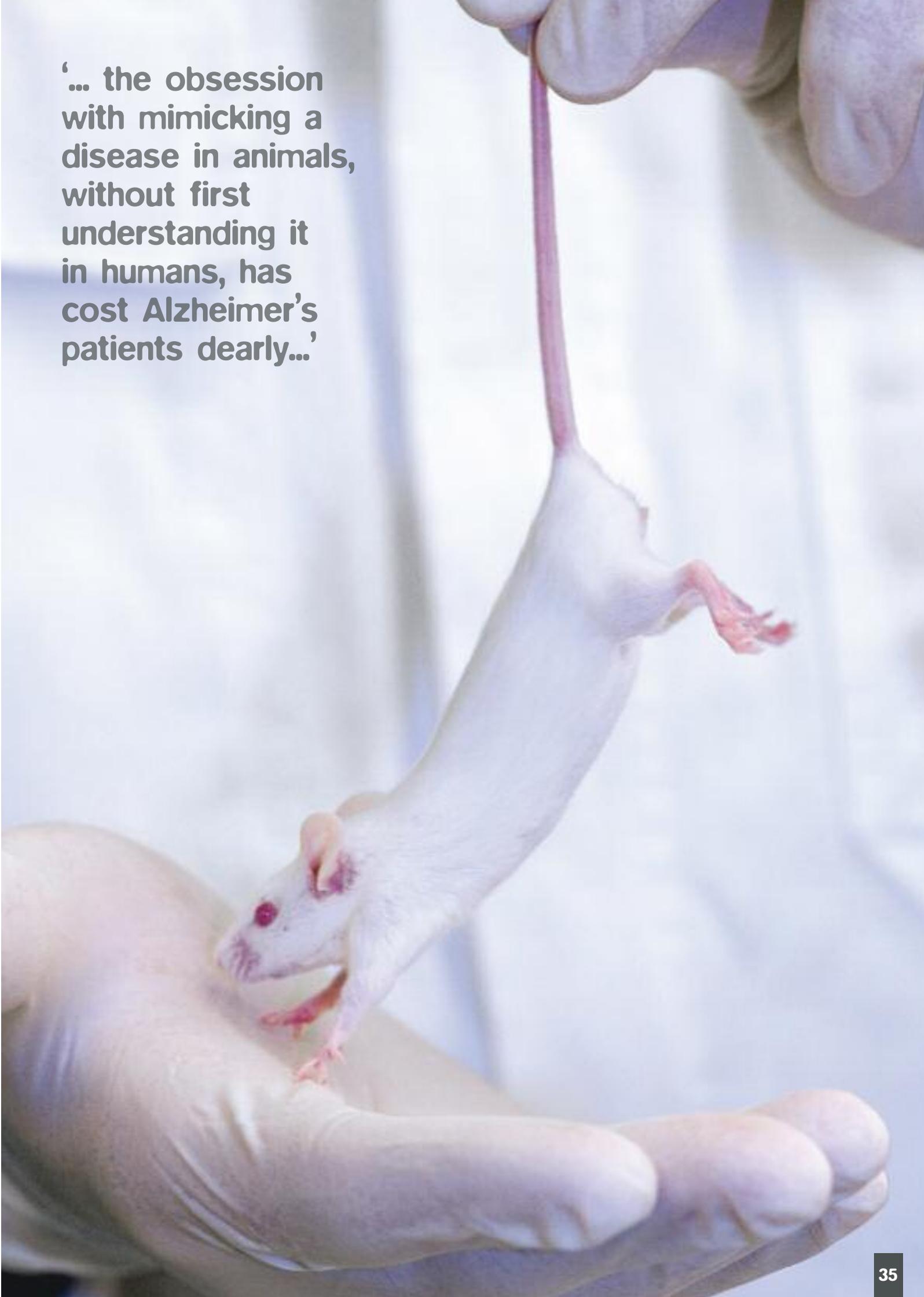
The crossbred mice were subjected to various memory and behavioural tests as a means of gauging the overall effectiveness of the protective gene. As would be expected when two different strains of mice are crossbred, some littermates were born with the protective gene, while others were not. The physical abilities of all the mice were assessed using the Morris water maze, a technique developed 30 years ago. Although mice are scared of being in water, they are put into a small round tank from which they cannot escape or touch the bottom. The water in the tank is deliberately cold so as to provoke frantic swimming, which can lead to exhaustion and to some animals drowning when not kept under careful observation.

In this test, mice were forced to swim until they located a small platform on the surface of the water on which they could rest. Once they had been trained to do this, the platform was submerged so that it was no longer visible on the water's surface. The declared object was to test the spatial memory of the animals. Mice with the protective gene performed slightly better than those without and could locate the hidden platform sooner. At the end of the tests, all the mice were killed and their brains examined.

A similar experiment was funded by the Alzheimer's Society, this time aimed at determining the effect that stress might have on the production of 'bad' protein in the brain.¹⁴⁶ Twenty adult male rats were divided into four groups of five animals: a 20 days stress group, a 10 days stress group, an acute (1 day) stress group and a control group.

Stress exposure was achieved by placing the rats on an open elevated platform for 60 minutes. While free-roaming rats may choose to climb to an elevated level, locating them off the ground in an exposed position in a laboratory environment is highly stressful, as indicated by the immediate rise in levels of stress hormones in their blood. This response decreases significantly after 10 to 20 days once the animals become accustomed to the platform, but they were nonetheless subjected to fear and stress for a long period. All rats were killed 24 hours after their last stress exposure to measure the impact on their brains of what they had endured. The researchers concluded that stress may have an effect on 'bad' protein production in the brain but that further studies would be required to determine the exact mechanisms. A.M

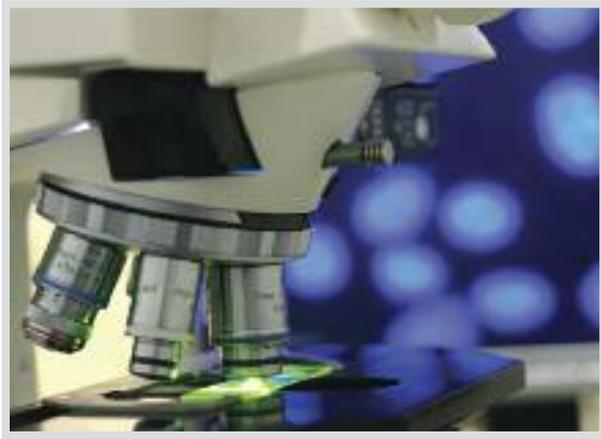
'... the obsession with mimicking a disease in animals, without first understanding it in humans, has cost Alzheimer's patients dearly...'



NON-ANIMAL MEDICAL RESEARCH

The evidence presented in this report demonstrates that proponents of animal research are bringing false hope to millions of patients affected by the medical conditions examined. They have also diverted funds, donated by the public in good faith, away from methods of non-animal testing that are relevant to the species in question – humans.

**Non-animal medical
research: humane, effective
and commercially-sound**



There are many well-established non-animal research techniques that already play an important role in developing therapeutic interventions.

In fact, the medical charities studied in this report all, to a greater or lesser extent, employ such methods. However, they still insist that this work is complementary to animal research, and that some animal suffering will always be necessary to find cures for human disease. The results-based analysis we present demonstrates that animal research does not complement good science – it confounds it.

The options for studying human disease in humans are growing all the time, and are supported by solid science and, increasingly, commercial and government funding. Next to these effective and efficient technologies, animal tests look cruder than ever.

Scanning technologies

There is a wide range of scanning technologies that can reveal processes in living humans. The images produced are now truly remarkable and are especially useful in neurodegenerative conditions like Parkinson's and Alzheimer's.

Human-derived raw materials

Human-derived raw materials can be obtained and used in a range of ways. From donated human cadavers down to human DNA, all levels of tissue sample can be gainfully employed. Intact slices of human tissue, ethically obtained from patients who undergo operations or biopsies, can be maintained in the laboratory so that they retain their function. Tumour biopsies, for example, can be used to see whether a drug has bound to its intended molecular target. Comparing healthy and diseased donated organs can provide important information on disease processes. Stem cells of human origin also have enormous utility.

Human tissues or organ systems

Human tissues or organ systems can also be recreated in laboratories. A Cardiff University team led by cell biologist

Dr Kelly Bérubé has grown human lung cells in the laboratory to form three-dimensional tissue-like structures. These can be used to test substances for the potential to cause damage if inhaled.¹⁴⁷ Human lymph nodes have been created in the laboratory, and can be employed to test vaccines and biologically-based drugs, like the TGN1412 monoclonal antibody, which – having been passed as safe on the basis of tests on monkeys – went on to cause catastrophic injuries to human trial subjects.¹⁴⁸

Computer programs

Human systems, from individual organs to the whole body, can be simulated using highly sophisticated computer programs. These are created using data obtained from people. Computer simulations have been developed, for example, to predict the behaviour of a drug in the digestive system. These simulations are likely to predict such effects in humans more accurately than animal models, and in a much more efficient way.

Microdosing

Microdosing involves giving a tiny amount of a substance – less than one hundredth of the quantity expected to have a noticeable effect – to a volunteer or patient. This dose is sometimes labelled with a safe amount of a radioactive chemical. Body fluids are then analysed to see how the body has responded, or PET imaging is employed to ascertain how the substance behaves in specific organs. This technique has already been used successfully to test drugs for cardiovascular disease, pain, Alzheimer's disease and gastrointestinal disorders.

Microarray

Cell components, including DNA, RNA and protein molecules, can be arranged in a microarray, which is, typically, a tiny chip or slide made from silicon or glass, or it can be a membrane. The signals produced by microarrays are read by scanners and the data generated are analysed by computer. The technology can be used for drug development, both to identify potential drug targets and to test for efficacy and toxicity. Thousands of genes can be monitored simultaneously.

A wholesome diet is a major contributor to good health



Microfluidic devices

Microfluidic devices contain human tissue samples in tiny chambers linked by microchannels. Fluids and chemicals flow in a natural way between different compartments,

simulating conditions in the human body. As with microarrays, microfluidics can produce large amounts of information very quickly. The technology can help scientists to understand how cancers spread, for example. Microfluidics can investigate human tissues and organ systems, with the creation of 'bioreactors' designed to supply nutrients and remove waste products.¹⁴⁹ One team of researchers has developed a system in which human liver, brain cortex and bone marrow are interconnected through a circulatory system mimicking blood flow. These models can be used to predict the effects of substances as they move between these organs.

Epidemiology

Epidemiology involves the study of significant numbers of people over a period of years, comparing their lifestyles, genes, medical interventions, environments, social status, etc. It remains a powerful tool with huge potential, and has already produced enormously valuable findings, including the link between smoking and lung cancer.

Clinical data

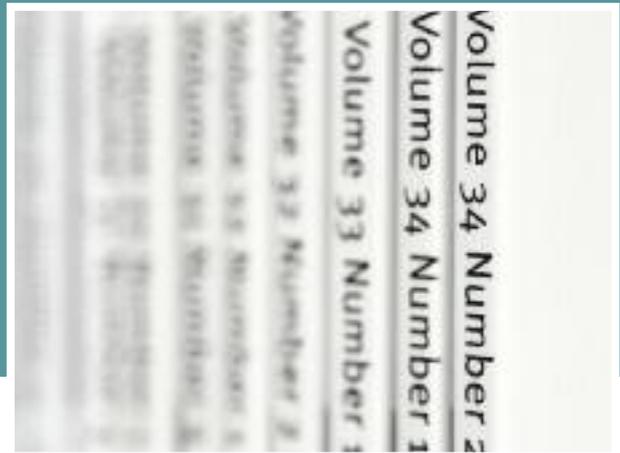
Clinical data and observation are greatly under-used, including the information gathered from minimally or non-invasive procedures (such as blood or urine sampling). Data from this type of benign intervention, undertaken in consenting patients already undergoing procedures, could be collated much more efficiently than is currently the case. **A.S**

Woman receiving CAT scan



PEER REVIEW

The peer review process of approving research is biased, unjust, unaccountable...'



*'We portray peer review to the public as a quasi-sacred process that helps to make science our most objective truth teller. But we know that the system of peer review is biased, unjust, unaccountable, incomplete, easily fixed, often insulting, usually ignorant, occasionally foolish, and frequently wrong.'*¹⁵⁰

Dr Richard Horton, Editor, *The Lancet*

Research for this report has involved analysing and interpreting animal experiments published in leading scientific, peer-reviewed journals. Publication in such august periodicals is often cited as a proxy marker of scientific validity – supposedly, shoddy or poor research does not pass peer review scrutiny and is rejected.

When it comes to animal research, peer review has additional stages. Local ethical review committees have to approve the project and decide whether the experimenters should move to the next stage and submit their proposal to the Home Office. Assuming a licence is granted, a retrospective review is subsequently undertaken by another in-house committee, to scrutinise and check the validity of the work before submission for publication.

Unfortunately, there is evidence that this entire peer-review process is flawed, secretive and biased – at all stages:

- Ethical committees are formed by the same institutions in which the researchers operate. All too often, they simply rubber-stamp the experimenters' proposals after little or no modification. Cardiff University, for example, received 29 applications for project licences between 2006 and 2009. Just one failed to gain approval. The 28 that were approved encompassed nearly 200,000 individual experiments.¹⁵¹
- Despite the ease with which approval is gained, the quality of the experiments is often demonstrably poor. In 2009, the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) commissioned a comprehensive review of research on rats, mice and primates. It found that

the studies 'contained a catalogue of basic and fundamental errors that you would not expect in any properly constructed paper from a practising scientist'.¹⁵² Another recent review also found that 'publication bias'* was prevalent in the field of animal experiments, to a degree that would not be possible with human clinical trials.¹⁵³

- The NC3Rs review additionally found that only 59 per cent of the studies examined stated the hypothesis or objective of the study, and the number and characteristics of the animals used. It must be emphasised that all these experiments had gone through a multi-stage peer review process, and had not been found wanting.
- Institutions often claim that animal research is justified because it has been funded by external grants, such as those provided by the Medical Research Council. However, these bodies are strongly supportive of animal experiments, and often fail to apply the requisite level of scepticism in response to applicants. The MRC, for example, is wholly in favour of 'basic' (or speculative) animal research because 'we don't know where new advances for acquisition of new treatments are going to come into play'.¹⁵⁴ The lack of rigour was highlighted by the Home Office (the government department that grants animal research licences) when it declared that support for animal research by a major funding body 'cannot be taken to guarantee the relevance, importance or scientific validity of any individual experiment'.¹⁵⁵
- Neither the peer review process that takes place within the research institution, nor the Home Office 'cost-benefit analysis' aimed at quantifying animal suffering, is open to public scrutiny. **A.S**

* Publication bias is a tendency on average to produce results that appear significant, because negative or near-neutral results are infrequently published

Cancer, heart disease, Parkinson's and Alzheimer's are conditions that blight the lives of huge numbers of people – both the sufferers and those close to them. We recognise this reality at Animal Aid as much as anyone. And, of course, we are not immune to these diseases and the physical suffering and mental anguish they cause.

If our objection to the animal research funded by the four charities rested exclusively on the brutal treatment inflicted on the animal 'models', we would struggle to win over the public. We do object powerfully, on moral grounds, to what the animals are put through. But we also strongly refute the scientifically flawed proposition that information of direct relevance to human beings can be procured by surgically mutilating and/or genetically manipulating mice, dogs, monkeys, goats, rabbits and other animals. Such research is not only unproductive and therefore wasteful of precious resources offered in good faith by the public, it also uselessly employs scientific minds that might otherwise be directed at producing something of human benefit.

It must be clear from the above that, in rejecting the 'animal model' of human disease, we do not reject the quest, by means of science, for remedies and palliatives. In fact, our report includes a section listing the impressive and growing range of non-animal research methodologies.

Furthermore, we are fully aware that the four charities on which we focus engage in valuable patient support work. Our critique is not intended to damage that work, and need not do so. It is open to anyone who was thinking of donating to one of the four charities but who has decided against doing so after considering our

arguments, to back those charities' work with patients. Parkinson's UK and the Alzheimer's Society, in particular, offer a range of volunteering opportunities. They include help at social events and therapy sessions, as well as one-to-one befriending and support. The British Heart Foundation has nearly 300 affiliated Heart Support Groups that are open to anyone with any kind of heart condition, as well as to their partners and families. Cancer Research UK is much more thoroughly concerned than the other three organisations with research, and therefore directs prospective volunteers to bodies such as Macmillan nurses (Macmillan Cancer Support).

Then there are the scores of medical research charities – no doubt each of them hungry for funds – that cover a vast range of human ailments, and which eschew animal research. Nearly 80 of them are listed overleaf. We would argue that these are the organisations that merit the public's financial support rather than those that use their funds to pointlessly wound, torment and kill large numbers of vulnerable animals.

Such 'research' is a double betrayal – of the animals, and of the human patients in whose name they are made to suffer.

Andrew Tyler

Medical Charities that do not test on animals

This list is correct at the time of printing. For updates, visit www.animalaid.org.uk

- **Action Against Allergy**
- **Action for Blind People**
- **Against Breast Cancer** (also known as Action Against Breast Cancer)
- **Age Care** (formerly Royal Surgical Aid Society)
- **Allergy UK** (formerly British Allergy Foundation)
- **Arterial Health Foundation**
- **The Arthritic Association**
- **Arthritis Care**
- **AVERT**
- **Back-Up Trust**
- **Bath Cancer Research**
- **The Big C**
- **Birmingham Children's Hospital Charity**
- **Breast Cancer Care**
- **Breast Cancer Survival Trust**
- **Breast Friends**
- **British Deaf Association**
- **British Dyslexia Association**
- **British Institute for Brain Injured Children (BIBIC)**
- **British Kidney Patient Association**
- **British Organ Donor Society**
- **British Polio Fellowship**
- **British Red Cross**
- **Cancer Active** (formerly Research Into Ovarian Cancer)
- **Cancer Kin Centre**
- **Cancer & Leukaemia in Childhood (CLIC Sargent)**
- **Cardiomyopathy Association**
- **Caring Cancer Trust**
- **The Children's Cancer and Leukaemia Group** (formerly United Kingdom Children's Cancer Study Group)
- **Christian Lewis Children's Cancer Care**
- **Cleft Lip & Palate Association**
- **Coeliac UK** (formerly Coeliac Society)
- **Colostomy Association** (formerly British Colostomy Association)
- **Down's Syndrome Association**
- **Dr Hadwen Trust for Humane Research**
- **Dyslexia Action** (formerly The Dyslexia Institute)
- **East Anglia's Children's Hospices**
- **Eating Disorders Foundation**
- **Elton John AIDS Foundation**
- **ENABLE**
- **Epilepsy Action Scotland**
- **Epilepsy Society** (formerly National Society for Epilepsy)
- **FORCE Cancer Charity**
- **Greater London Fund for the Blind**
- **Headway – The Brain Injury Association**
- **Heartbeat**
- **The Humane Research Trust**
- **International Glaucoma Association**
- **John Charnley Trust**
- **Laura Crane Trust**
- **Lord Dowding Fund**
- **Lynn's Bowel Cancer Campaign**
- **Macmillan Cancer Support**
- **Michael Palin Centre for Stammering Children**
- **Mid-Kent Breast Cancer Research Appeal**
- **Migraine Action** (formerly Migraine Action Association)
- **Mind, The Mental Health Charity**
- **Myasthenia Gravis Association**
- **National Deaf Children's Society**
- **National Kidney Federation**
- **National Society for Research into Allergy**
- **New Approaches to Cancer**
- **ORBIS UK**
- **The Pain Relief Foundation**
- **Penny Brohn Cancer Care** (formerly Bristol Cancer Help Centre)
- **Quest Cancer Research**
- **Raynaud's & Scleroderma Association**
- **Royal College of Psychiatrists**
- **Royal National Institute of Blind People**
- **SCOPE**
- **Shaw Trust**
- **Spinal Injuries Association**
- **Susan Channon Breast Cancer Trust**
- **Teenage Cancer Trust**
- **Terrence Higgins Trust** (now incorporating CRUSAID)
- **Values Into Action**
- **York Against Cancer**

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