Dr Hadwen Trust
Replacing Animals in Medical Research

Briefing on non-animal replacements

All research approaches have *some* limitations. This will apply to non-animal as well as animal research. In medical research, animal experiments can have serious scientific limitations of particular concern. Species differences in anatomy, metabolism, physiology or pharmacology inevitably will arise, underlaid by further species-specific genetic variations. Even subtle molecular differences can have a significant effect on the validity of results for extrapolation from animals to humans.

With animal experiments providing unreliable and potentially misleading results, it is irresponsible to portray animal research in general as a 'gold standard' and all the more vital that we replace it with more humane and scientifically rigorous techniques.

Cell and tissue culture
Human cells and tissues are available from biopsies, post-mortems, placentas or as 'waste' from surgery. Grown in the laboratory, cell cultures are used in numerous medical fields and have contributed exceptionally to our understanding of the underlying mechanisms of cancer, arthritis, Parkinson's disease and AIDS. Cell cultures are also routinely used in vaccine production, safety testing, drug development and to diagnose disease.

Three dimensional cell culture surrogates of human diseases such as cancer are increasingly being studied instead of growing cancers in animals. Using cells donated by patients, scientists can now grow complex microstructures combining different cell types to better mimic the tissues in the human body. This helps scientists to understand the role of each cell type, and investigate the cellular processes that underlie diseases.

A recent development has been the application of silicon chip technology to cell culture. The "biochip" comprises different types of cells on a silicon chip, connected by a network of tiny channels. Cells from vital organs, such as the liver, brain and heart are grown on the same chip, and fluids flow around the circuitry carrying test chemicals to all the cells. This approach could be used to rapidly test chemicals for safety or screen new medicines, helping to replace animal tests in the early stages of drug development.

It is essential that human rather than animal cells and tissues are used for medical research, to avoid the problem of 'translating' results from one species to another.

Molecular methods
Technological advances are resulting in improved molecular methods for analysing and identifying new compounds and medicines. The Dr Hadwen Trust has helped researchers to acquire essential analytical equipment to identify new anti-cancer and anti-malaria drugs, based on their molecular interaction with DNA, as an alternative to selecting drugs using animal tests.

New methods of rapidly analysing DNA samples from human tissues are now being used to understand the cell processes underlying various illnesses, leading to better treatments. For example, the Dr Hadwen Trust has funded research into genes that predispose individuals to fibrosing lung disease, as an alternative to researching the illness in animals such as genetically modified mice.

The latest analytical technology called MALDI-TOF-MS has been applied by a Dr Hadwen Trust grant-holder to identify infectious microbes without animal tests, as a humane alternative to the classical tests that relied on rabbits and guinea pigs.

Microorganism studies
Tests with simple microorganisms, such as bacteria, fungi, yeasts and algae are being used as early indicators of chemicals likely to be harmful, and are frequently faster, cheaper and more humane than animal tests. Bacteria can be genetically modified to manufacture useful products previously obtained from animals, such as insulin and antibody fragments.

Computer modelling and bioinformatics
Computers are increasingly being used to model the structure and modes of action of new drugs, and to predict their safety. High-powered computer models are used to study molecular interactions and to simulate human tissues and organs. Computer simulations enable ‘virtual experiments’ to be conducted, for example to test reactions to medicines and chemicals, as alternatives to experiments on animals. Advanced computer programs are used in the new field of systems biology, which looks at all the complex interactions in biological systems. This new bioinformatics perspective helps to integrate different components of the body to provide a realistic picture of the whole organism.

The Dr Hadwen Trust has helped develop computer simulations, including a model of the human placenta and fetus which assisted the treatment of problems affecting unborn babies; and a model of the human heart for cardiovascular research. These models are based on relevant human data and can be used to carry out simulated experiments, in place of experiments on animals. We have also supported work using computer modelling to improve cancer treatments, and to explore illnesses of ageing.

Volunteer studies
One of the best ways to conduct medical research is by studying human volunteers. New imaging techniques, for example, make it possible to conduct safe and ethical studies of human volunteers where previously animals had

been used. Dr Hadwen Trust projects have used a variety of sophisticated imaging techniques to non-invasively investigate the intact human brain. These include using a MEG scanner to study epileptic patients; investigating pain in patients with functional MRI; and developing a novel technique, TMS, to study localised functions of the human brain in volunteers.

Technical advances are increasing the range of safe, ethical methods for studying volunteers. For example, Dr Hadwen Trust researchers have used fibre-optics to sample airway tissues from the lungs of asthmatic patients and healthy volunteers, and improve the relevance of asthma research without animals. Fibre-optic bronchoendoscopy is a minimally invasive and safe procedure that involves inserting a fine flexible fibre into the lung to sample tiny amounts of tissue.

Human microdosing, in which exceedingly tiny doses of novel medicines are safely investigated in volunteers, has become possible due to the development of ultra-sensitive analytical methods, such as AMS (accelerator mass spectrometry). A microdose is so low that it cannot be toxic to humans, so these studies can be carried out early in the drug development process. Early human trials are important for identifying potentially useful drugs and eliminating those unlikely to work in humans, pre-empting much animal testing. Microdosing would also be valuable in helping to avoid potentially severe or fatal side-effects in clinical trials, such as those experienced in the TGN1412 trial disaster in March 2006. Six volunteers suffered potentially life-threatening unexpected side-effects that had not been indicated by previous tests on rodents, dogs and monkeys.

Population studies
Studying diseases in human populations, including the effects of genes and lifestyle, has been crucial to understanding disorders such as cancer, heart disease, asthma, osteoporosis and birth defects. For example, most of the major risk factors for cancer and cardiovascular disease were identified by human population studies. Such information is vital to improving human health and providing insight into the causes of illnesses. The Dr Hadwen Trust helped fund a large population study into how fetal and infant growth influences the development of heart disease in later life, as an alternative to experiments on pregnant animals.

The '–omics' biology
With the development of new techniques over the last decade, scientists can now study the basic structures of the human body in more detail than ever before using genomics (gene analysis), proteomics (studying proteins) and metabolomics (studying metabolic processes). For example, genomics can be used to locate a human gene on a chromosome, predict its function and anticipate its role in the body, where animal models used to be the main approach. These new fields predict and confirm fundamental human information, often replacing the classical animal-based methods.

Genomics is the study of all the genes that make up a person. A relatively new field, it aims to identify and understand an organism's genetic code. In combination with computer predictions, genes can be located and identified without using animal tests. Knowing more about our genetic make-up will help us understand why some people become sick while others don't, and to find ways to improve health and prevent disease.

Proteomics is an analysis of all the proteins in an organism. Our genes instruct the making of proteins which in turn direct the activities of our cells and the functions of our bodies. Proteomics helps us to understand the molecular processes underlying disorders and diseases.

Metabolomics is the study of the unique chemical fingerprints of cells. It is complementary to genomics and proteomics since it can give a snapshot of the activity going on in particular cells and tissues. With genomics and proteomics, metabolomics it is an essential tool to obtain a more complete picture of living organisms in health and disease.