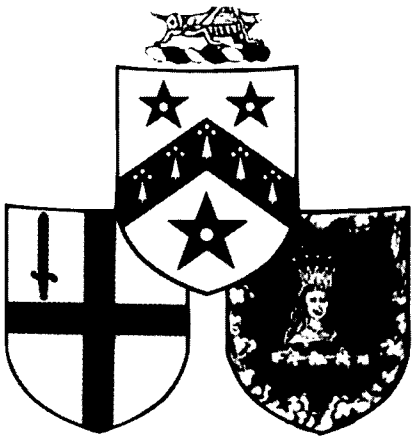
G R E S H A M

COLLEGE



MEDICAL RESEARCH: HOW FAR SHOULD WE GO?

Three lectures by

PROFESSOR FRANCIS COX PhD DSc
Gresham Professor of Physic

Lecture 1 - 1 November 1994
HUMAN GUINEA PIGS

Lecture 2 - 15 November 1994
HUMAN EMBRYOS

Lecture 3 - 22 November 1994
ANIMALS AND ALTERNATIVES

Gresham College was established in 1597 under the Will of the Elizabethan financier Sir Thomas Gresham, who nominated the Corporation of the City of London and the Worshipful Company of Mercers to be his Trustees. They manage the Estate through the Joint Grand Gresham Committee. The College has been maintained in various forms since the foundation. The one continuing activity (excepting the period 1939-45) has been the annual appointment of seven distinguished academics "sufficiently learned to reade the lectures of divyntye, astronomy, musicke, and geometry" (appointed by the Corporation), "meete to reade the lectures of lawe, phissicke, and rethoricke", (appointed by the Mercers' Company). From the 16th century the Gresham Professors have given free public lectures in the City. A Mercers' School Memorial Chair of Commerce has been added to the seven 'ancient' Chairs.

The College was formally reconstituted as an independent foundation in 1984. The Governing Body, with nominations from the City Corporation, the Mercers' Company, the Gresham Professors and the City University, reports to the Joint Grand Gresham Committee. Its objectives are to sponsor innovative research and to supplement and complement existing facilities in higher education. It does not award degrees and diplomas, rather it is an active collaborator with institutions of higher education, learned societies and professional bodies.

Gresham College, Barnard's Inn Hall, Holborn, London EC1N 2HH
Tel no. 0171 831 0575 Fax no. 0171 831 5208

Human guinea pigs

Earlier this month the Royal Society of Tropical Medicine and Hygiene celebrated the 150th anniversary of the birth of its founder, Sir Patrick Manson, universally regarded as the 'father of tropical medicine' and it is one hundred years ago that Manson first suggested that mosquitoes might transmit malaria. For over 2500 years physicians and scientists had speculated on the nature of this disease and Manson's theories set in train a series of further investigations that have been so successful that today we know practically everything that there is to know about malaria. Most of these discoveries have been made over the last 15 years. I make no excuses for digressing from the topic of medical research and how far we should go and musing about my favourite subject because malaria is a microcosm of medical research as a whole.

One hundred years ago, physicians had virtually no weapons in their armouries with which to combat infectious and nutritional disorders whereas today these offer few threats, at least in the developed world, and the only constraints on their potential elimination is time and money. Surgical procedures unthought of 25 years ago are now commonplace and unsolved problems such as cancer, AIDS and mental disorders are gradually being resolved. However, this progress has its price and the advances of the past decade or so have taken place at such an astronomical rate that scientific knowledge has far outstripped the capacity of those providing health care, clinicians and the general public to comprehend, let alone implement, the potential that has been unleashed.

In a recent press release, the World Health Organization stated that 'With scientific and technological advances, there is an ongoing debate on the legal, human rights and bioethical issues raised by human experimentation; discrimination in access to health care; death and dying; genetic technology; the patenting of human cells; mental health; embryo research; organ and tissue transplantation; HIV/AIDS; reproductive health, including artificial reproductive technologies; and patient's rights'. In my last series of lectures, I considered some of the implications of genetic technology and in the next I shall have something to say about AIDS. In this series, I am going to discuss two of the topics highlighted by the World Health

organization, human experimentation and embryo research, and a third topic, that underpins all biomedical research, the use of animals.

The recent outbreak of plague in India has rekindled some of the horror of the great diseases that devastated the world in the dark and middle ages but are today no longer regarded as serious threats to health. Of these diseases, probably the most feared of all was leprosy and the debt the we owe to those who worked with this disease and unravelled its nature is incalculable. Foremost among these scientists and physicians were two Norwegians, Daniel Danielssen and Armauer Hansen, who, at the end of the last century, transformed our understanding of leprosy, which had hitherto been determined by the attitudes of the Church, from folklore and fear to the realisation that the disease was caused by bacteria and could thus be treated and prevented. However, Hansen was responsible for one unforgivable outrage which resulted in his being banned from medical practice in Norway for the rest of his life. What did Hansen do and what did he do wrong? Before I answer this question we need to look into the context of the times and to consider the circumstances which led to his actions.

From the earliest recorded times, humans have been aware of the various diseases that have afflicted our race and many great Greek, Roman, Arabic, Chinese and Indian physicians and scientists have striven to understand their causes against a background of ignorance and prejudice. Among these giants and standing head and shoulders above them is Hippocrates whose influence on human experimentation is the basis of all modern medical research. This is no time to go into the history of medicine but briefly our concepts of disease have ranged from manifestations of the wrath of the gods to humours, the airs that surround us particularly those rising from the marshes or from decaying material. From the eighteenth century, it had been suspected that the lesions of sick people, such as those with plague or leprosy, contained malign agents but it was not until 1865 when Pasteur demonstrated that many diseases were caused by microorganisms that the science of medicine truly began. Central to this new era were the postulates laid down by the German microbiologist, Robert Koch, which, briefly, state that in order to incriminate a microorganism in any infectious disease it is necessary to find that organism in the diseased person (or animal) and to transmit the same disease to another person (or animal) with the organisms isolated. These

postulates are still accepted today.

Now let us return to nineteenth century Norway. In 1856, Danielssen had considered the possibility that the cause of leprosy resided in the nodules of the victims and set out to investigate this by injecting material from such nodules into himself and into his colleagues who insisted on being injected in the same way. None of them developed any disease. It was not until 1873 that Hansen discovered the organisms that cause leprosy and was also frustrated in his attempts to transmit the disease to such an extent that he decided to inject leprous material into the eye of a female patient. This so angered the Norwegian medical community that Hansen was subjected to a public trial and his subsequent removal from medical practice.

I have stressed this fragment of medical history because it makes two very important points. Firstly, medical understanding has developed from heroic experiments in which physicians and scientists have used either themselves or willing colleagues for experimental purposes. Secondly, when they deviate from this acceptable type of experimentation and involve others who are unaware of the consequences, the medical profession will show its disapproval and do all in its power to protect the victim. Essentially, this is what human experimentation, or what is commonly called the use of human guinea pigs, is all about.

Let us consider another well documented example. Nearly two hundred years ago almost a century before Pasteur's discoveries, on May 14th 1796, Edward Jenner, a Gloucestershire doctor, hypothesised that cowpox would protect people against the deadly disease, smallpox. In order to test this hypothesis, he injected cowpox material into the arms of a boy, James Phipps. He records what happened

'I selected a healthy boy, about eight years old, for the purpose of inoculation for the Cow Pox.'

On July 1st the same year, Jenner injected the boy with smallpox material and did so again on twenty other occasions. James Phipps survived and has entered the annals of medical history. Not so lucky was Jenner's experiment with another child, five year old John Baker from the local poor-house. John

Baker died, according to Jenner, the result of '...a contagious fever in the workhouse...' Despite this and other setbacks, Jenner had invented vaccination and had set in train a series of events which led to the total elimination of smallpox from the world in 1979.

This episode illustrates a number of the problems inherent in human experimentation, the ethics of Jenner's experiments, the use of children in experiments and the balance between the risk to few and the benefits to many. James Phipp's life was put at risk but he was thereby responsible for saving millions of other lives. Here is the dilemma, weighing the risks to the few against the benefits of the many.

I have used the word experiment here but a scientist would not consider this to be an acceptable experiment. Experimentation has taken on a very precise meaning. Scientists do not set out to prove a hypothesis but set up a hypothesis and devise ways to disprove it. This is, in the words of Karl Popper, probably the greatest scientific philosopher of the twentieth century, who died recently, is the principle of 'falsifiability'. Essentially, the objective of scientific research is to propose a hypothesis and to devise ways to test it, in other words to falsify it. In this way a hypothesis can stand or fall on a single observation no matter how many other observations point in another direction. Scientific experiments, therefore, have to include many controls to ensure that the results obtained really mean what they seem to indicate. Jenner, for example should have included boys and girls, younger and older children, adults and in all cases should have infected with smallpox some who had never received cowpox. In addition, he should never have 'selected' an individual, he should have chosen one randomly. Of course, he could never have done this and should never have done this. This is something that continually faces those involved in human experimentation, the need to perform a properly controlled scientific experiment balanced against the need to protect individuals against undue risks.

Jenner could not have performed a perfectly designed scientific experiment because as a doctor his hands were tied by his Hippocratic oath though whether he paid much attention to it is debatable. The Hippocratic oath is pagan in origin and contained three sections; Invocation of the gods, the physician's duties to his teachers and patients and the duties of patients. The oath is

long and the important element as far as human experimentation goes is the one that states 'I will never use treatment to injure or wrong. I will not give poison though asked for nor will I suggest such a plan. Over the years the oath has been modified and Christian and Muslim adaptations have been introduced and, in 1948, the Declaration of Geneva rephrased the oath in an entirely secular way and introduced the phrase 'The health of my patient will be my first consideration.

The realisation that experimentation is a integral part of medicine and must be controlled is contained in the statement by Claude Bernard, widely regarded as the founder of the science of experimental medicine, who wrote in 1856

'...never performing on a man [and presumably a woman] an experiment which could be harmful to him in any degree whatsoever though the result amy be of great interest to science, that it, of benefit to the health of others.'

It should be obvious that Jenner and Hansen (and virtually every other physician attempting to move the science of medicine forward) have paid scant attention to either the oath or the injunction but some deviations from the norm have been more outrageous than others. We can dismiss the distant past in which life was short and brutish and practitioners were bewildered about the causation of disease and concentrate on what has happened in this century. The most notorious abuses occurred in Germany from 1930 until 1945. The conflict between the ideals of the Hippocratic oath and National Socialism began with the conception of the policy of euthanasia and once this had been accepted there was nothing left and a rapid slide into totally unacceptable behaviour had begun. Easy access to slave labour and the inmates of concentration camps led to a host of medical investigations of doubtful value. The brains and other tissues of euthanasia victims were used for medical research, sterilization was introduced often without the knowledge of the victim, septicaemia was induced in adults and children, children were infected with tuberculosis, twins were infected with such diseases as typhoid and gas gangrene was induced as a preliminary to treatment with sulphonamides.

The Hippocratic oath had crumbled and medical experimentation had drifted into war crimes. The various war crimes commissions had to take action and the result was a series of Codes and Declarations which for the first time

considered medical research outside the Hippocratic concept of patient care and recognised that there is something fundamentally different between medical procedures carried out on a patient in order to alleviate symptoms or cure disease and similar procedures in which the outcome is simply the acquisition of medical knowledge. The Helsinki codes of 1965 and 1975 were the first to cover medical research and the gist of these codes is that medical progress is desirable and doctors have a duty to improve their treatments while at the same time protecting their patients from any undesirable consequences. The codes also state that scientific advance always includes some experimentation. The Helsinki Code of 1975 lists twelve basic principles including the following:

Voluntary consent is essential and includes freedom of choice.

Experiments must yield fruitful results for the good of Society that cannot be obtained in any other way.

Experiments must be based on animal experimentation and knowledge of the disease.

Either the subject or the experimenter should be able to bring the experiment to a conclusion.

For the first time scientists and physicians knew that experimentation was not only permitted but was encouraged and also knew the parameters within which they had to operate. Before discussing these principles further it is necessary to discuss what actually constitutes a medical experiment. This is not actually as easy as it seems. Most experiments are concerned with drugs. There is always a need for new and better drugs and pharmaceutical companies are always eager to identify a niche and to fill it. The aim is not always profit, it is usually the recognition that a new drug is needed to replace an older one or one with more side effects. No drug is perfect and the Helsinki codes recognise the duty of a doctor to improve the treatment of his or her patients.

In this area, we are all, knowingly or unknowingly, human guinea pigs because every drug we take is being continuously monitored and adverse effects of

minor alterations in the formulation are not necessarily evident even to the practitioner prescribing it until they become apparent and the drug has to be modified again or withdrawn. There are some conditions for which no acceptable drugs are available, most cancers, for example, and many tropical diseases. Vaccines are also continuously being developed and there will be about another ten or so available by the end of the decade. Drugs and vaccines are assessed in the same kind of way. First the drug is tested for efficacy in a variety of ways and then for safety and efficacy in animals. This is currently a legal requirement in many countries. If the drug is found to be both safe and effective in the laboratory it has to be tested in humans. This testing takes place according to well established and well controlled guidelines. Essentially, the drug is given to healthy volunteers in whom any possible side effects will be picked up. Then it is given to volunteers under modest threat of infection and if promising is then given to volunteers under heavy threat of infection. If all these trials are successful, more extensive trials are conducted until the pharmaceutical company can persuade the various bodies concerned with safety and efficacy that the drug is both safe and effective. It is then registered. Registration in one country does not necessarily mean registration in another so a drug may have to be tested in several different countries before it gains worldwide approval.

The Helsinki principles are useful guidelines but are very difficult to implement and are subject to numerous interpretations. Let us consider voluntary consent. This is now enshrined in the phrase 'informed consent' and seldom has any phrase been more widely interpreted or its principles been more difficult to enforce. Obviously, the further along the path to drug registration that one goes the more difficult it is to obtain fully 'informed consent'. Those involved in the preliminary trials, often students, are usually very well informed and monitored but this process becomes more difficult as one moves along the path and more individuals become involved. There is also the added complication that when populations naturally exposed to an infection or at risk from a cancer are involved the decision is not simply to see whether the drug works but to see if it works better than the one already being used.

Realistically it is almost impossible to obtain informed consent because very

few individuals are able to understand the complexities of drug action and the best that can be hoped for is some sort of informed but uneducated consent. Being informed is not the same as being told about the possible consequences of any particular course of action or of alternative treatments and doctors are not legally bound to tell their patients the whole truth about the programmes into which they are being enroled. In fact, thousands of patients enter clinical trials without making any decision about whether to join it or not.

So far, I have been mainly concerned with rational and educated adults. It is not possible to obtain informed consent from children, those with mental disabilities or those so seriously ill that they cannot make decisions on their own. I do not intend to comment further on this area but, in the past, and probably in the present, it is one of the areas of greatest potential abuse.

Informed consent is an ideal but one that, in the words of Hamlet is 'a custom more honoured in the breach than the observance.' It is only when things go wrong that such breaches come to the attention of the public and there have been a number of such cases. The one that has received the most attention in the United Kingdom is that of Mrs Margaret Wigley who in 1981 was operated on for bowel cancer and enroled without her consent or knowledge in a clinical trial for a new drug the effects of which she died from two weeks later. Thalidomide and Opren are other well publicised examples.

So what went wrong in these cases? It is not at all easy to organise a clinical trial that is both scientifically and medically sound. The gold standard at present is the Randomised Clinical Trial in which subjects are randomly allocated into different groups. This kind of trial is very old and was originally devised by Sir Ronald Fisher for studies of various effects on agricultural crops. In 1946, this kind of trial was introduced into medicine by Sir Austin Bradford Hill for trials on the efficacy of streptomycin against tuberculosis and all that has happened since then is that the statistical methods used to compare differences between the various groups have been improved and speeded up.

Let us consider the simplest example. Subjects are divided into two groups,

one given a drug and the other not and the number dying from an infection are compared. Obviously, this is unacceptable so it is necessary to use at least four groups. (A) New drug, (B) Old drug, (C) Placebo and (D) No drug. Again, the last is unacceptable so already the results are becoming difficult to interpret. In such trials, there are two additional possibilities, the blind trial in which the subject does not know whether he or she is being given an established drug, a new drug or a placebo. In double blind trials, neither the doctor administering the drug nor the subject knows which individual is in any particular group. The problems inherent in this kind of trial are these. The patient cannot be really informed so cannot realistically give informed consent and the doctor surrenders his or her relationship with the patient to a statistician or a computer. There are a number of examples of over-optimistic interpretation of the data on the part of the pharmaceutical company involved, failure to conduct the trial properly and even deception on the part of the doctors involved. As doctors are paid for conducting such trials, the temptations to cut corners must be enormous.

In order to avoid some of the problems, the Zelen modification of the Randomised Clinical Trial has been introduced. In this, the patients are randomised before the trial begins and divided into two groups, (A) the best available treatment and (B) the new treatment. Only those in the second group are told about the nature of the trial and are informed and free to enter it or to decline to do so.

There are all sorts of problems with these kinds of trials. In 1971, in San Antonio, Texas, all the women on a trial for a new contraceptive pill thought that they had been given the pill with the obvious consequences. In this country, a Medical Research Council trial to test the efficacy of vitamins for the prevention of spina bifida was badly flawed. Women who have had one child with spina bifida have a 1 in 20 chance of having another. It was known that both vitamin B and folic acid lower this chance and the researchers wanted to know what these two substances would do together. The subjects at risk were divided into four groups of 750, one was given folic acid plus vitamin B, others were given either folic acid or vitamin B and one group was given nothing. As a scientific investigation, this would have been satisfactory but, although 750 women had the chance of 100% protection, 1500 only had a 50% chance of protection and 750 were entirely unprotected.

Another major problem is the placebo. Until about 100 years ago, all that physicians could offer in most cases was a placebo and this practice served medicine reasonably well. Placebos are now a burning issue in the pages of The Lancet. Placebos are essential parts of any properly conducted clinical trial provided that ethical considerations are not compromised. Essentially, in a randomised trial one group is given an experimental treatment and a comparable group what seems to be the same treatment but with no effect. It has been widely held that placebos lack any medical effect but it is now clear that they can act directly or indirectly. In numerous trials, over 70 of patients given placebos record feeling good, are reassured by the treatment or simply have faith in it. Such patients are likely to respond better to any treatment thus invalidating, or at least throwing doubt on, the results of a trial.

It is difficult, therefore, to argue that there is anything that is really a randomised clinical trial and, even if there was, such trials could not approach the rigour of scientific experiments expected by scientists. Human experimentation is not an exact science and, not being an exact science, things can and do go wrong.

At the beginning of this lecture I referred to the unethical experiments involving humans carried out in the last century and the first half of this century and, given changes in attitude and increased restriction, it would be reasonable to assume that such experiments are a thing of the past. However, unethical experiments have been performed relevantly recently and are probably still being carried out. There are a number of examples that have only come to light because of the publicity that they have engendered. The most notorious is the so called 'Tuskagee experiment'. Tuskagee is a small town in Alabama which was, and still is, populated mainly by poor blacks descended from slaves. In 1932 the population had a very high incidence of syphilis and the authorities decided to study untreated syphilis in this population and a year later a decision was made to follow these untreated cases to death. Some 400 individuals were recruited into the trial under the pretext of free treatment which, however, was not given and all the patients received was aspirin and tonic. For forty years, the victims continued to present themselves for blood tests without any useful treatment despite the fact that arsenic had become available in the late 1930s and penicillin in the 1940s.

At the beginning of the experiment, most, if not all, of the cases would have been treatable. Despite the availability of satisfactory treatments, the Tuskagee group was excluded from therapy, their names were removed from treatment lists and those reporting for military service were returned to Tuskagee. In 1952, the United States Public Health Service decided to continue the experiment and in 1953 it was decided that these patients should not receive penicillin for any other infection. In 1969, a decision was made to continue the experiment which was not, in fact, terminated until 1972 as a result of massive publicity. $10 million was give to the survivors and the families of victims who still did not understand what had happened to them and thought that the money was in appreciation for their cooperation.

This is a particularly disturbing example of a conspiracy between State and medical practitioners but the lessons of Tuskagee do not seem to have been learned. Between 1945 and 1975, in the United States, over 800 subjects including service personnel, adults with mental handicaps and children were exposed to radiation without their consent and the results were monitored by such institutions as Harvard and the Massachusetts Institute of Technology. In the United Kingdom, service personnel have been exposed to low levels of nerve gas but, despite the fact that these experiments involved volunteer subjects that had been medically screened and briefed, details have not been made public because, in the words of the Director General of Chemical and Biological Defence Establishment near Salisbury, it was 'not in the national interest to publish details of volunteer studies'.

These three examples illustrate some of the problems inherent in human experimentation, the use of uneducated and uninformed individuals and the use of service personnel. Service personnel, prisoners, medical students, the mentally ill and children do not really have the freedom to chose whether or not to take part in a clinical trial and the pressure being put on both parents and children in the current measles vaccination programme suggests that processes bordering on the unethical are still taking place and that various authorities are aiding and abetting such procedures. Whether we know it or not, we are all probably taking part in some kind of medical investigation.

So what of the future. Theoretically, the public is protected by the 1993

World Health Organization's International Ethical Guidelines for Biomedical Research involving Human Subjects but progress in medical understanding is being made at a phenomenal rate and procedures that were unthought of a few years ago are now commonplace. In particular, the impact on the development of drugs and vaccines and the possibilities of correcting genetic disorders have not been fully appreciated nor has the fact that there is now virtually nothing that cannot be done and that only the availability of skills, time and money is holding up even further progress. Biomedical scientists can now offer anything but, at the same time, the public is becoming increasingly well informed and anxious to benefit from any newly promised advances. Scientific progress must be tempered with reality and so must the public perception of what can and cannot and what should and should not be done. Pressure groups are now demanding treatments that have not been fully evaluated and nowhere is this more apparent than in the case of AIDS. Interested individuals scan the literature, go to meetings and apply pressure in all directions. AZT, the Wellcome anti-AIDS drug, reached the market prematurely and was over-prescribed largely because of pressure from the AIDS lobby. The WHO has just approved the trial of a new vaccine against AIDS in developing countries despite the fact that it has only limited efficacy and has not been approved by the National Institutes of Health who decided not to proceed with the testing of this vaccine in the United States. The use of both the drug and the vaccine can be defended on the grounds that AIDS is such a dreadful disease that some short cuts must be taken. Given the progress of medicine, and the anticipation of rapid advances, human trials will continue to be necessary but it is also important to consider the human guinea pigs who might become involved at a much earlier stage that is desirable.

Human experimentation has played, and will continue to play, am essential role in the advancement of medical knowledge but the medical profession, the public, the pharmaceutical companies and the lawyers are confused about their particular roles. Working against each other is not going to help the World Health Organization in its aim of achieving health for all by the year 2000.

Human embryos

In my first lecture, I suggested that the acquisition of scientific knowledge had taken place at such an astronomical rate over the past decade or so that it had outstripped the capacity of clinicians and the general public to comprehend what was happening let alone to know what to do with it.
In no area are the problems greater than in the field of embryo research.
Since prehistory it has been known that certain disorders run in families but it was not until the beginning of this century that the concept of inherited, or genetic, disorders became widely accepted. In 1900 the infant mortality rate in England and Wales was 154 per thousand of which 4.5 per thousand were due to genetic disorders. By 1980 the infant mortality rate had fallen to 12 per thousand but the numbers dying from genetic disorders remained the same. Thus, the percentage of deaths from such disorders had risen from nearly 3% to 37%. Genetic disorders had become, and remain, the major cause of mortality not only in the United Kingdom but throughout the developed world. Currently, about 10% of live births have some kind of genetic abnormality ranging from serious to inconsequential. One quarter of all children in hospitals are there because of some genetically related disorder as are one in eight adults. Genetic disorders therefore represent the greatest medical problem of the twentieth century and are likely to remain so into the next millennium. The consequences of the existence of these disorders are tremendous both at a personal level, affected couples have a one in two to one in four chance of producing afflicted offspring, and at the level of the State as the burden on hospital places and after-discharge care is incalculable. However, genetic disorders could be eliminated by the application of the techniques and discoveries of molecular biology but the constraints here are not scientific but ethical and in the public perception and fear of the unknown.

As I said in my previous series of lectures, everything we are or do is written in our DNA. The instructions in our DNA are encoded in a 3 billion letter sequence and a single mistake can lead to disastrous genetic consequences. Over 5000 genetic disorders can be attributed to defects in single genes, for example cystic fibrosis, and many others to defects in combinations of genes. In addition, many genetic disorders predispose individuals to other conditions such as susceptibility to infections, cancers

or allergies like asthma.

Until a decade ago, there was little that could be done about these disorders and the most that could be hoped for was early diagnosis, with the possibility of an abortion, or counselling of affected couples. Now there is much more that is possible and the question being asked is not what can be could be done but what should be done. This is where embryo research comes in.

In order to understand the current dilemma it is necessary to consider the background to the present situation and some of the ethical problems that are restricting further progress. Our present state of knowledge has arisen as a merger from two disparate fields, the introduction of in vitro fertilization (IVF) and the techniques of genetic engineering. IVF is commonly referred to as the production of 'test tube babies' thus creating emotive overtones and references to Mary Shelley. In fact, IVF, which was pioneered by Patrick Steptoe and Robert Edwards in the United Kingdom in 1978, is a very straight forward and, to most people including religious bodies, an acceptable process. Essentially, when a couple who are infertile but have nothing wrong with them except possibly a simple blockage, undergo IVF, eggs harvested from the woman and sperm from the man are mixed together in a laboratory for 2-3 days and the fertilised eggs replaced into the woman. There are a number of minor variations on this pattern such as introducing harvested eggs and sperm together into the woman, a procedure favoured in Ireland. IVF is, of course, not as simple as this and does involve a number of procedures that are not entirely without risk and are not necessarily acceptable. Hormones or drugs have to be given in order to stimulate ovulation and harvesting the eggs can be dangerous and deaths have occurred. The failure rate is also relatively high, up to 80% in some of the best clinics and even more in smaller ones.

Nobody will deny that IVF is an important medical achievement but that it can be improved and this is one of the basic aims of embryo research. Gradually the success rates are increasing and the use of drugs and dangerous procedures are being reduced. However, IVF has two important spin-offs. Firstly scientists now have an endless supply of embryos with which to experiment and, secondly, the possible misuses of IVF are becoming apparent. Let us consider this second aspect first. The original aims of IVF were laudable and Louise Brown born in England 1978 and Candice Reed born in Melbourne in 1980 must

have given as much joy to the scientists and clinicians who engineered their births as they did to their parents.

Inevitably, however, someone somewhere will step beyond the mark and if this happens insidiously it is difficult to see where acceptable conduct ends and unacceptable conduct begins. In 1983 a woman whose eggs had been fertilised by her partner allowed her embryos to be implanted in her sister and this was the first surrogate mother. Following this there was a spate of surrogacy first on an altruistic basis and then on a commercial one. Commercial surrogacy has now been banned but so have a lot of other things like driving over 70 miles per hour on a motorway. IVF also opened up the possibility of women conceiving children fathered by unknown men. This was particularly attractive to lesbian women who could then bear children without having to indulge in sexual intercourse or admitting any reliance on a man. The possibility of a woman giving birth to a child resulting from the egg and sperm of unknown donors is but a tiny step along the same path and reports that post menopausal women can now conceive and a woman can give birth to a child of a different colour from herself or her partner create problems for future generations. In addition, IVF is expensive and this effectively means that babies can be bought. The legal and social aspects of all levels of IVF and surrogacy constitute a minefield through which I am unqualified to tread. I do not wish to make any moral judgements but the point I wish to make is that the best intentioned medical advances can, and do, have unforeseen consequences and that once the roller coaster has started there is no stopping it especially where money and human self-interest are concerned.

The most interesting, important and controversial spin-off from IVF has been the availability of an endless supply of eggs and embryos. When a woman is treated with hormones prior to IVF she superovulates and produces up to 40 eggs. Many of these can be fertilised but only the best ones are implanted. The others can be frozen indefinitely so that subsequent attempts at implantation can be made if the first fails. What happens to the remaining eggs of which there are now thousands or even millions stored all over the world? This is a question at the heart of embryo research. Some scientists argue that they should be destroyed and others that they should be used for research purposes.

Before I go one and discuss this problem it is necessary to say something about the development of the human embryo. A few years ago any discussion about what constitutes an embryo was largely academic and mainly confined to what various religious groups thought about abortion and when it should or should not be carried out. The accumulation of molecular biological knowledge has made this kind of argument redundant and has focused attention onto the fundamental question of what an individual is and when it begins to exist as an entity.

My first introduction to embryology came from a brilliant embryologist, David Newth, then at University College London and later at Glasgow, who showed me the development of a snail. The development of a snail is peculiar in that after fertilization the egg divides and one half of the egg is destined to become one half of the snail and the other the other half. At each division, a hierarchy of development occurs and each cell gives rise to a particular structure. If a single cell is removed then none of the structures resulting from that cell line will develop. This permits very accurate mapping of the developmental patterns of the snail and the origin and fate of every single cell can be traced. The crucial point is that the fertilised egg contains all the information necessary for the development of a whole snail and that development proceeds, the fate of each cell becomes more and more restricted. This is not that these later cells do not contain the information required but it is because their ability to develop along anything other than their determined routes is sequentially switched off. Convincing evidence that this is the case comes from elaborate experiments using frogs. If a nucleus, containing the DNA, is removed from a skin cell and injected into an egg from which the original nucleus has been removed, the egg develops into an embryo and thence into a whole tadpole. This indicates two things, that fertilization is not necessary and that a skin cell contains all the genetic information necessary for producing an entire individual. During human development cells can be removed without detriment for about 14 days and this is the last point at which monozygotic twins (twins derived from a single egg) can develop. Nevertheless, as in the snail and the frog, every cell has the potential to develop into a complete individual.

The logical conclusion from these observations is that the egg, even if unfertilised, is a potential individual and, in the case of humans, a

potential human. This is a long way from what one normally considers an embryo to be so it is necessary to look at human development more closely. After fertilisation, the egg containing a mixture of genetic material from both the father and mother divides to form 2, 4 and 8 cells and by day 5 it consists of a hollow ball containing about 100 cells called the blastocyst. At this stage it begins to burrow into the wall of the mother's uterus, a process that is complete at 7 days after fertilization. At this stage about 99% of the cells are involved in this support system which nourishes the embryo while the remaining 1% go on to form the embryo proper. At 14 days the basic form of the embryo is established and at 56 days a recognisable foetus can be seen for the first time.

The development of a human embryo is a continuum and it is therefore impossible to draw hard and fast lines that clearly determine when an embryo actually begins to exist as a individual when it can no longer be used for research purposes. This was the problem that faced the Warnock Committee in the 1980s and proposals submitted to them ranged from unfertilised egg (effectively meaning no embryo research) to the clearly recognisable foetus at 56 days or even the 26 week foetus after which independent survival becomes possible. They eventually agreed on 14 days. In the United Kingdom, human embryo research is now regulated by the Human Fertilization and Embryo Authority, set up in 1990, a statutory licensing authority which has impressive powers and inter alia regulates embryo research. It is illegal to perform experiments on embryos more than 14 days old unless frozen for part of that time. In other countries, such as Germany, embryo research is even more restricted while in others, including Denmark and Spain, it is prohibited altogether.

Why should one want to do research on human embryos? Partly because of the need to discover more about the causes of infertility and to improve IVF but mainly to find ways of eliminating or ameliorating genetic disorders. Having access to a plentiful supply of embryos means that molecular biologists should be able to determine the precise causes of the 5000 or so single gene genetic disorders. Already considerable progress has been made. It is now possible to detect genetic abnormalities by amniocentesis (sampling the amniotic fluid) at mid-pregnancy or by chorionic villus sampling at 3 months. Unfortunately both of these procedures have inherent dangers and the only outcome of an

adverse finding is an abortion or the mother carrying what she knows will be a defective child. The techniques of IVF offer a more acceptable alternative, preimplantation diagnosis. In this procedure, eggs from a mother, who suspects that either she or her partner or both are carrying the genes for a genetic disorder, are removed after 60 hours at the 8 cell stage. Single cells can be removed safely and examined for defects, a procedure that takes only 2-3 hours, and, if healthy, the embryo can be replaced. This procedure would prevent the trauma of abortion and, if carried out on a world wide basis, could lead to the elimination of the more serious genetic disorders.

As with IVF, the benefits of early diagnosis are obvious but the disadvantages are less easy to gauge. Firstly, what constitutes a genetic character sufficiently important to justify discarding the embryo carrying it? Some, such as cystic fibrosis, are obviously serious defects, others like predisposition to breast cancer, which develops after 40 or more years and might by then be curable, are less obvious. Many genetic disorders are X-chromosome linked and occur only in males so it might be justifiable to reject male embryos where the risk is certain or very high. Some characters are trivial such as height, eye or hair colour and there is no justification for rejecting such embryos. Or is there? Once a procedure has become available it is going to be used and, if there is the demand, someone, somewhere will provide the service. Already, there is a trend towards sex selection. In India, female infanticide is not uncommon and, if more acceptable methods became available the selection of male children would increase particularly among educated people. This could also happen in China, by 1981, following the introduction of the 'one child rule', the percentage of surviving male infants which had been about 50% had increased to 58%. Presumably many Chinese who would not consider infanticide might well accept selective embryo destruction. South Korea is already concerned about the trend towards more male children than females and even in the United States, parental preference for male children is 10% higher than for females. At the other extreme, in the same country, lesbian women are seeking ways to avoid bearing male children. It is not beyond the bounds of possibility that some parents might like to select tall, blue-eyed, fair-haired children and Hitler's dreams would have been fulfilled with clear consciences and eugenics will have entered the world on the coat tails of responsible science.

This is not idle speculation. In 1985, Lee Kuan Yew, the Prime Minister of Singapore stated that '...we must expend our limited and slender resources (on naturally superior individuals) in order that they will provide...the catalyst which will ensure that Singapore shall retain its pre-eminent place in South East Asia...' and offered financial and other incentives to graduate women to have more children and for uneducated ones to have fewer. Singapore is unlikely to go all the way towards the elimination of those it considers undesirable but the procedures are in place for other States to do so.

Another unfortunate spin-off from IVF is the possibility of breeding babies for spare parts. From 14 weeks, the ovaries of female foetuses contain viable eggs and the use of these to alleviate a shortage of donor eggs has already been suggested. It is argued, logically, that if the foetus is to be destroyed, it would be a pity to waste such valuable material. The possibility of a child the same age as its mother is a daunting one. Relying on the same logic, foetal tissues have also been used for other purposes, pancreas for the treatment of diabetes, brain cells for the treatment of Parkinson's disease and bone marrow for transplants. The British Medical Association's response is that only material from therapeutic abortions should be used in these kinds of ways but there is already a chink that leaves the door open for real abuses, the deliberate conception of infants for spare parts. There have already been reports that women have been prepared to conceive infants for kidneys or bone marrow for transplantation to other children and even themselves. The possibility of a trade in spare parts by surrogate mothers (whose own genetic make up is irrelevant) is not a totally remote one; Guatemala makes $20 million each year from the export of children. Money can buy practically anything.

The general title of this series of lectures is 'Medical research: how far should we go?' I must admit that I do not know how to answer this question. Biomedical scientists today stand where the physicists involved in the Manhattan project stood fifty years ago. They had at their fingertips all the potential of atomic energy yet they saw that in the hands of politicians it had literally become a bomb. The difference is that, whereas there were only a handful of physicists with the ability to harness atomic energy and only a few laboratories where it could be done, today there are thousands of competent molecular biologists capable of performing the most elaborate

genetic engineering techniques in virtually every major laboratory in the world. There will always be rogues and there will always be those prepared to profit from the misfortunes of others. However, I do not think that we, as scientists, should cease in our efforts to make the world a healthier place and should strive to prevent disease using every means at our disposal. It is up to society as a whole to ensure that what we discover is used for the general good and that excesses are curbed. The Human Fertilization and Embryo Authority is a worthy and sensible safeguard and it is worth looking at some of its clauses:

1. It is illegal to create an embryo outside the human body.
2. No embryo to be used in unlicensed research.
3. No embryo to be used after 14 days.
4. No human embryo to be implanted into an animal.
5. No animal embryo to be implanted into a human.
6. No nuclei to be replaced.
7. No transgenic hybrids (genes inserted into the germ line).
8. All frozen embryos to be destroyed after five years.

This is a compromise but one that tells us clearly how far we should go. If public opinion can be massed behind these restrictive but sensible proposals then there is no need for concern. However, if public opinion is against even these proposals then it would not be surprising if scientists felt that they might have to over react which would be disastrous for us all. There have already been serious confrontations at clinics carrying out IVF and laboratories engaged in embryo research and there are parallels with the activities of pressure groups opposed to animal experimentation. However, there are rational arguments for and against research on embryos as there are for research involving animals. What is needed is serious dialogue and this is something I shall be talking about in my next lecture.

Animals and alternatives

Gresham College is currently holding a series of seminars concerned with old age, a topic that has not been seriously discussed during the 397 year history of the College. The reason for this is that we are all living longer and a child born in Europe or North America today can expect to live for 80 years, about twice as long as one born a century ago, and can also expect to live a healthy life compared with that of his or her ancestors whose whole lives were dogged by illness.

However, this is not true everywhere, particularly in the tropics, but even here rapid progress is being made and the problems for the future will be overpopulation rather than the containment of disease. The World Health Organization has set itself a mission, 'Health for all by the year 2000' and although this is now thought to be over-optimistic there is little doubt that health for all is a realistic aim and one that can be achieved before the middle of the next century. Smallpox has been eradicated, guinea worm will be eradicated in the next year or so, river blindness and leprosy are on their way out.

Every single stage of this progress from total ignorance to total control over certain diseases, and the probability of control over others, has resulted from meticulous research and the application of research findings. Let me define research, a word that has been corrupted by sociologists, politicians and pollsters. Research is the process of investigation leading to the discovery of new facts. It is concerned with what is not yet known and the possible outcome of the investigation must include both the expected and the unexpected. Most scientists place more reliance on the unexpected than the expected and this is something that puts scientists apart from the general public who, in general, draw comfort from the fact that everything is predictable.

In the biomedical sciences, the questions being asked are what causes disease, how it can be prevented and how this knowledge can be applied. In the past there have been numerous examples of scientists who have pursued their discoveries to the end but today most scientists are more interested in making new discoveries than in the application of their findings. Manuel Patarroyo,

the Colombian biochemist who devised the vaccine against malaria that has hit the headlines recently, is leaving the clinical trials to others while he returns to more basic research on tuberculosis.

Much scientific research tends to be polarised with the scientists on one side and their opponents on the other. Classical examples are Galileo and Darwin where the opposition came from the entrenched views of the Church. In Darwin's time this debate was informed and healthy. There was little research going on, there were few researchers and those that were involved in research disseminated their findings widely in popular publications. At the end of the last century serious scientific magazines, such as Nature and The Lancet, were widely read by the educated public which, by and large, was well informed even if little the wiser. Today, things are different. There are many scientists and these publish their findings in learned specialist journals to which the public have neither physical nor mental access. The public has to rely on the intermediary of the press, radio and television for information thus the gulf between scientists and the public has never been wider.

I have introduced my topic today at some length because I believe that the cause of the present controversies concerning biomedical research have their roots in the twin vices, arrogance and ignorance.

Medical research has always been controversial and distasteful. Prohibition of the use of dead bodies has been a major constraint in the past as has the use of human subjects and animals. Until fairly recently, much basic medical research was carried out by zoologists. Fruitflies, butterflies, snails, roundworms, starfish, fish and birds have all provided important clues about the ways in which humans work and how things can go wrong. Fruitflies have provided much basic information about genetics, butterflies and snails about inheritance, and birds about immunity. The massive field of immunology has its roots in Elie Metchnikoff's observations on phagocytic cells in starfish and the human genome project used as its prototype a humble roundworm called Caenorhabditis.

Most advances, however, have come from the use of mammals. Our earliest records of the use of animals in medical research date from the second century

AD and the work of Galen of Pergamon (129-200 AD) whose influence extended into the Middle Ages and who was known as the 'Prince of physicians'. Galen made numerous discoveries including the role of arteries in the flow of blood and the nature and functions of the nervous system. Previously it had been thought that the arteries contained air, a reasonable speculation based on post mortem studies, but Galen discovered that they contained blood and that it was pumped there from the heart. He also differentiated between nerves and tendons and demonstrated that certain functions were controlled by nerves. Galen could not have made these observations on humans so he used pigs and Barbary apes (not really apes but macaque monkeys). Since then virtually no major medical discovery has been made without recourse to observations and experiments on animals and the macaque monkey has been extensively used.

It is important at this stage to say something about medical research in general and the use of animals in particular. The use of animals is a stage through which most investigations go before any findings are applied for the benefit of humans. The length of this phase varies according to the nature of the investigation, it might be transient or it might be prolonged. Nobody wants to prolong this stage and it is in everyone's interest to get to the end-point of the investigation, that is the application of the findings to human health or welfare, as quickly as possible. Unfortunately, this cannot happen until the investigators are as sure as they can be that they have established that their findings are valid and that no foreseeable harm will come to the human subjects in the next stage of the investigation.

Animals are used for several different kinds of investigation, the treatment and prevention of diseases (including drugs and vaccines), the nature of genetic disorder, fundamental research, diagnosis of infections and diseases, the preparation of natural products and safety. In the United Kingdom about 3 million animals are used every year, half of which are used for investigations into the treatment and prevention of disease and about a quarter for fundamental research. The numbers used for the preparation of natural products, safety and diagnosis are declining as non-animal techniques are being gradually introduced. For example, it used to be necessary to produce antibodies (against tetanus toxins, hepatitis and measles, for example) in animals but this can be done more cheaply and with purer products using cell cultures in laboratories using a technique for the production of

what are known as monoclonal antibodies which are now used for a variety of different purposes including the preparation of diagnostics. Insulin, which used to be produced from the pancreas of animals, has now been replaced with a human form produced by cells grown under laboratory conditions.

The increasing use of cell culture methods is an example of what I meant by the progress that can be made by passing through a phase of animal use to the evolution of a satisfactory end product. Having passed through this phase, there is no need to return to it and further modifications need never again resort to animal experimentation. Unfortunately, it has not always been as simple as this and in the evaluation of drugs and vaccines, and in some kinds of fundamental research, the use of animals is still thought to be necessary. Nevertheless, past experiences indicate that gradually the use of animals can be reduced and eventually discontinued altogether. Let us consider some examples which can be regarded as 'case histories'. Currently there is discussion about the possibilities of relaxing our very stringent rabies laws which were drawn up when rabies, which is a very nasty disease and from which recovery is very rare, could not be controlled. Now there are good vaccines. In 1885, material for a vaccine had to be prepared from the spinal cords of infected rabbits, in the 1960s duck embryos replaced rabbits and by the 1980s the virus could be grown in a human cell line and the potency of the virus can now also be tested in cell lines. The use of animals is no longer necessary. The development of a human vaccine against rabies has also had an important spin-off. In continental Europe, meat containing the vaccine is dropped in areas inhabited by foxes and this has had the result of protecting not only humans and dogs but also wildlife including rabbits. It is worth speculating on how many wild rabbits have been saved as a result of the pioneering work done by Louis Pasteur using laboratory rabbits.

Poliomyelitis, which was a major threat in the 1940s and 1950s, is now virtually eliminated from Europe, and was entirely eliminated from North America in 1991, mainly as a result of the widespread use of vaccines. In China, where poliomyelitis was endemic, 100 million children were vaccinated in two days and there have only been 2 cases this year. The virus used for the vaccine was initially maintained in monkeys and is now grown in human cell lines and also tested in cell lines thus reducing the numbers of monkeys used in the United Kingdom from an average of 5000 each year to 1000, a number

which will gradually decline. The tetanus anti-toxin, which used to be tested in mice from 1890 until 1980, can now be tested using a simple immunological assay that does not involve any living cells at all.

The reason that I have stressed vaccines is that in this field lie both the greatest hopes for medical advances towards the goal of 'health for all by the year 2000' and for the total elimination of the use of all animals. The World Health Organization's global immunisation programme against tuberculosis, poliomyelitis, diphtheria, typhoid, paratyphoid and measles has now reached 80% of the world's children, compared with less than 10% in 1977, and is estimated to have saved the lives of 3 million children every year. New vaccines against diseases such as pneumococcus, cholera and meningitis are on their way and old ones against tuberculosis, tetanus, typhoid, measles and whooping cough are being improved. Most of these vaccines are based on the new technologies of molecular biology and require very little, if any, animal involvement.

At this point I must digress in order to destroy a commonly held myth, that the diseases that have been eliminated would have disappeared altogether because of improvements in hygiene. There is no doubt that many common diseases were declining before the advent of vaccines particularly in the richer parts of the world, but there is equally no doubt that, taking into account the law of diminishing returns, vaccination has played a major part in the final elimination of these diseases. One cannot be complacent and it would appear that the decline in vaccination compliance has been responsible for recent increases in the incidence of tuberculosis, measles and whooping cough in this country. In the United States, where vaccination is compulsory, there have been no such episodes except in certain minority groups, who decline vaccination, which still experience infections with these common childhood diseases. The seeming paradox that poliomyelitis is no longer a problem in Europe despite the fact that many children are not vaccinated or revaccinated is due to the fact that vaccinated individuals excrete the virus used in the vaccine and this tells us more about our hygiene than about the efficacy of the vaccine. In the developing world, the situation is very different and vaccination has had to be used for the improvement of the overall health of the various populations involved before the implementation of improvements in hygiene and sanitation in order to

ensure that the population was sufficiently educated, prepared and able to respond to sanitary reforms.

The development of drugs has progressed in the same kind of way as vaccines but here there are some major problems. In the first place, the use of a drug admits some sort of defeat on the part of prevention but there are many conditions for which drugs are required and without which the patients involved would either die or have their quality of life seriously impaired. There are a lot of drugs in use. In the United Kingdom, their use is staggering, 50 million prescriptions for antibiotics each year and 30 million for asthma, for example.

The advantage of drugs is that they offer easy solutions but the disadvantage is that they are all toxic and that toxicity is difficult to evaluate except in whole animals in which all the body activities are functioning together. The acceptability or otherwise of a drug is based on the ratio of its efficacy to its toxicity. Despite their differences, all mammals are basically very similar and some time during their development, new drugs are routinely tested in animals. One of the difficulties here is that different species of mammals respond to drugs in different ways so several species have to be used. Currently, there seems to be no real alternative and all the drugs in use today have at one time or another involved animal trials. In general, these have been useful and informative although occasionally they have been misleading.

In this context, there are a number of myths about the conclusions drawn from drug testing in animals. It has been stated that penicillin kills guinea pigs, that the sedative morphine actually excites cats and mice, that aspirin causes birth defects in cats. In fact, it is only with excessively large doses never used in humans that these effects are seen. Similarly it has been argued that Opren (an anti-arthritis drug) and the sedative, Thalidomide, were found to be safe in animals although they produced harmful effects in humans. However, the fact is that these drugs did produce adverse effects in animals but these were actually missed; Thalidomide, for example, was so toxic that the foetuses died and were resorbed thus obscuring the gross abnormalities later so tragically seen in human foetuses. Overall, those involved in medical research are agreed that, at least for the present,

observations on animals do provide useful and relevant clues about what is likely to happen in humans and must be incorporated into any procedure for the development of new drugs.

Why do we need any more drugs? Firstly, there are many conditions for which there are no drugs or where the existing drugs are less than 100% effective, toxic, unstable or too expensive. AIDS, cancers and viral infections immediately come to mind but there are also very few satisfactory drugs against any of the tropical diseases that together affect some 1000 million people. There is also a second problem and this is that bacteria and parasites that cause disease rapidly develop resistance against drugs so there is a need to keep one step ahead.

So far, the emphasis has been mainly on infectious diseases about which a great deal is known and where research is largely directed towards the refinement of existing preventative measures and treatments. There are, however, a number of conditions for which the causes are unclear and treatments are unknown. The causes of genetic disorders are gradually being unravelled and the possibilities of eliminating these diseases is something I have discussed in previous lectures. This leaves the mental disorders about which we know very little and the only solution will lie in years of extensive research some of it inevitably involving animals.

The point that I have been trying to put across is that animals have made a major contribution to medical progress and will continue to do so. The discoveries of 60 of the 90 Nobel Prize winners for Medicine were based on experiments involving animals. On the other hand, it is clear that the use of animals is only part of this process, that there are many objections to using animals, both from a scientific viewpoint and an ethical one, so there must be other alternatives. First, however, it is necessary to put the use of animals into context. In the United Kingdom, the use of animals is carefully regulated by Home Office Acts and the restrictions placed on researchers are among the most stringent anywhere in the world. The first Act dating from 1876 served both the public and the scientific community well for over 100 years but concern from many quarters resulted in the present Act which dates from 1986. The provisions are numerous but essentially no experiment or any other procedure can be carried out on an animal without a

Home Office Licence. Every individual and every procedure must be licensed and licences are not given unless the Home Office inspectors are convinced that the potential use of the experiment is important enough to justify the use of an animal and that the experiment cannot be carried out in any other way. There are also stringent regulations on the care and treatment of laboratory animals which must be specifically bred for the purpose (the kidnapping of pets is another myth). We have precise figures on the numbers of animals used for medical purposes and in 1992 (the last year for which complete data are available) 2.9 million animals were used of which 2.4 million were rats and mice. These figures may seem large but, in context, 600 million animals are killed for meat every year, 8 million rats are killed as vermin and 2 million cats and dogs are abandoned. In the human context, one mouse is used for every 23 men women and children.

Nevertheless, the use of nearly 3 million animals is unacceptable. Scientists do not like working with animals, with which they often form close bonds, nor does the informed public so what are the alternatives. There are a number so it is easiest to list them.

1. Cell and tissue cultures. Many human cell lines can now be grown in cultures and these have been very useful. However, human cells are not easy to grow and very few reliable long term cell lines are available and many that are have been derived from aberrant cells such as tumours that grow quickly in cultures. Cell and tissue cultures also suffer from the disadvantage that the cells exist in isolation from other kinds of cells and it is now clear that virtually all body functions, particularly those involving the immune system, are part of a network of activity that cannot be mimicked under laboratory conditions. Nevertheless, cell culturing techniques are improving all the time and the prospects for their more extensive use are good.

2. Quantum pharmacology (Quantum structure-activity relationships [QSAR]). This involves the use of high technology employing the latest techniques in chemical analysis for the investigation of drugs and metabolites and, in particular, the relationships between drugs and their receptors. This is an extremely powerful tool and has proved invaluable in detecting minute changes in the interactions between molecules.

3. Computer modelling. This is also a very powerful tool that enables a scientist to see exactly how a particular molecule binds to another for example a receptor. This permits the modification of existing drugs or the design of new ones. Computer modelling is also being used in the design of vaccines, for example, the recently developed vaccine against malaria.

4. Molecular biology. The tools of molecular biology can be used to detect the genes responsible for the expression of various molecules and for the prediction of molecular structures that might serve as targets for vaccines or drugs. These techniques can also be used to detect damage to DNA caused by drugs.

5. Genetic screening. It is now possible to read what is written in our genes from single cells and this information can be used to predict susceptibility to, outcome of and even likelihood of effective drug therapy.

6. Non-invasive observations on humans. The use of ultrasonic techniques and CAT scans has revolutionised diagnosis of diseases particularly in the brain. These techniques can also be used to provide vital information about brain and other disorders by comparing healthy and unhealthy individuals without recourse to invasive techniques and these techniques can also be used by those working with animals.

7. Epidemiology. Epidemiological studies can be used to detect and map the occurrence of diseases thus pinpointing their possible causes and predicting their spread.

In an ideal world, a drug would be designed by a computer and tested against an infected or tumour cell in culture. This is, in fact, what happens, but at the present time these various techniques are only adjuncts to observations using animals. Nevertheless, they have already reduced the use of animals massively and as these techniques become more sophisticated they will increasingly reduce the needs for animal experimentation.

What of the future? The arguments for and against the use of animals in medical research is an old one. In 1831, the physiologist, Marshall Hall, clearly set out his beliefs which are almost parallelled by the 1986 Home

Office Act. Hall stated, inter alia, that no experiment should be performed (1) without a clear objective, (2) if any other alternative was available, (3) that caused suffering or (4) needlessly confirmed previous results. Most scientists today would not disagree with Hall.

Perhaps the most important contribution to the discussion on animal experimentation comes from the British Veterinary Association which recognises 6 'Rs', Refinement, Reduction, Replacement, Respect (for animals), Recognition (of the suffering of animals), and Relief (from pain). Other organisations broadly opposed to animal experimentation, including the Universities Federation for Animal Welfare (UFAW), the Fund for Replacement of Animals in Medical Experiments (FRAME) and the Royal Society for the Prevention of Cruelty to Animals (RSPCA) are broadly in agreement and openly embrace the first three 'Rs', Refinement, Reduction and Replacement, terms that have now entered the literature of the subject.

The major problem is that some people on either side of the animal experimentation argument take extreme views ranging from banning all experiments involving animals to complete freedom to use animals in any way they like. The two feed off each other, one sees the others as sadists and the other contemptuously regards the others as fanatics and these, in turn, respond to secrecy and contempt with frustration and violence, thus clouding the middle ground. Probably the most useful contribution to the debate comes from Franklin Loew, Dean of Tufts University in Boston, who argues that laboratory animal research causes less pain and distress than implied by the animal protection literature but more pain and distress than claimed by research advocates. In March this year Loew suggested a Humane Forum Society of the United States. Unfortunately, Europe is currently taking a less conciliatory approach.

There has in recent years been a sea change in attitudes to the use of animals in medical research. In the United Kingdom, the restrictions placed on scientists has reduced the numbers carrying out such experiments to those who really care about the health and welfare of humans and who now show greater respect for the animals they use and, overall, there has been the realisation that animals do suffer pain and distress and that treating them well is the responsibility of all those concerned. At one time it was thought that the

suffering of animals could be justified by the possible advances that might be made; now it is realised that the outcome of many procedures can be predicted and suffering avoided or ameliorated.

It has also been recognised that unnecessary suffering or distress can never be justified either ethically or legally. As a consequence, the numbers of animals used, according to Home Office figures, has declined sharply, from 5.5 million in 1974 to 3.5 million in 1975 and less than 3 million in 1992 (a figure somewhat inflated by the fact that this refers to procedures rather than actual numbers of animals). In the United States the decline has been about 25% since 1985. There are also other moves to improve the lots of animals, for example The European Union is now breeding the primates that are regarded as essential for medical research and this will prevent the importation of animals from countries where the regulations governing the breeding and handling of animals are less restrictive than ours.

In the United Kingdom, the Home Office has total control over what animal experimentation can be carried out, where and by whom. It has the final sanction of refusing or withdrawing licences, a right that it uses and is seen to use. A scientist involved in animal experimentation without a licence is like a heavy goods vehicle driver without a driving licence and an institution without a licence will be unable to attract research workers or research grants even for those who seldom or never use animals but who feel that they might need to keep a few animals sometime. Currently, the greatest pressure for changes in the use of animals is coming from the Home Office itself which is now canvassing for research projects that reduce the severity and numbers of experiments on living animals.

However, I do believe that, given the necessity for some animal experimentation, even more could be done to reduce the number of animals used and that the scientific community owes it to the public to demonstrate that it is serious in its attempts to do so. There is one simple way in which this could be done. The reward a scientist seeks is not financial but recognition by his or her peers. This is achieved by publishing research in a prestigious journal. Editors of biomedical journals are beginning to ask referees to satisfy themselves that certain criteria are met before recommending publication and pose questions such as whether the experiments

were compatible with the alleviation of human disease, were they performed humanely and were the numbers of animals used the minimum that were statistically acceptable. As an editor of a major journal, and an avid reader of the scientific literature, I see too many manuscripts describing trivial experiments, repetitive experiments and use of excessive numbers of animals. Unethical experiments on humans have now been virtually eliminated and now is the time to eliminate such experiments using animals by making it clear that certain things are just not acceptable.

In this series of lectures, I set myself the question 'medical research how far should we go?' in the context of human experimentation, embryo research and the use of animals. The simple answer is that respect for all forms of life must be our guiding principle and that if we even consider abandoning this principle we have gone too far.