The Genetic Revolution

Genetic engineering is beginning to revolutionise medical (840) and surgical practice (845).However as soon as we put genetic engineering and medicine together we need to make a big distinction between techniques designed simply to selectively identify and abort foetuses simply on the basis of their genetic problems (e.g. Downs babies) and techniques designed to produce cures or treatments for conditions.

Although much embryo research has been labelled as assisting in the prevention of many inherited diseases we have to be honest with ourselves and say that this is only being achieved by mothers consenting to abortions if doctors suspect that the developing child may have an inherited disease.This is "prevention by elimination" or "birth denial" rather than prevention through counselling, education, treatment or cure.

Our understanding of human genetic code means that a vastly increased range of predictions can be made about what an embryo will turn out to be like.In the past such genetic tests were confined to gross problems like Downs Syndrome, where an entire chromosome has been added to the basic number of 46.The defect is obvious with simple observation down the microscope using special techniques.Incidentally, taking a sample from a developing foetus is not without its hazards.The rate of spontaneous miscarriage following the procedure can be as high as one in ten (check figure).It is a procedure to be considered very carefully - whatever your position on abortion - especially where the mother is in her late thirties or early forties and the couple have taken some years to conceive.In this situation it is a particular tragedy to

discover after a doctor-induced miscarriage that the baby developing was completely normal.It may be the only pregnancy the woman will ever have.

An example of the rapid extension of pre-natal screening is that for the polyposis gene which gives rise to bowel cancer at an early age.It is inherited.In one recent care at University College London the woman's father had died from bowel cancer aged 38.The bowel of his daughter had been checked when she was a teenager only to find tell-tale signs of early changes.Almost all her large bowel was removed in an operation which will almost guarantee her freedom from the cancer.The small part remaining is close to the end of the gut and can be easily checked.She almost decided to be sterilised but was referred to a genetic counsellor who informed her that although the precise polyposis gene has not been identified, specific markers near it have been identified allowing the rogue gene to be identified correctly in nine out of ten of those carrying it.She then become pregnant and her foetus was tested at ten weeks.We are not told of the outcome (850).

Incidentally I often wonder about this conflict between the rights of the mother to have a healthy child, and the right of a child with medical problems to be born - whatever the religious or philosophical persuasions of the parents.

A large number of other genes are being pinpointed.For example the gene causing neurofibromatosis which at its most extremeform produced the Elephant man (860).A milder form affects one in 3000 of all babies born.The gene causes symptoms ranging from brown patches on the skin ("cafe au lait") to multiple benign tumours arising from the sheaths of nerves.

Another example is breast cancer which kills 15,000 women a year as the commonest cancer in women, and between five and ten out of a hundred of all cases are inherited.Women with a mother and a sister with breast cancer have more than eight times the risk of developing it themselves.Women with relatives who developed breast cancer after the menopause have only slightly increased risk.The Human Genetics Resources Laboratory in Hertfordshire believes it has located two faulty genes on chromosome 17 - a chromosome already highlighted as suspect by American researchers (870).Researchers are very close of finding genetic markers so that high risk of breast cancer can be detected in the womb or after birth.Examples of such medically important genes are increasing almost every week.A recent addition to the list as we saw in an earlier chapter has been the discovery of the fragile X gene which causes mental handicap (875).

Having worked with those who have sometimes severe disabilities from birth I am very uneasy about the judgments of the nondisabled or "healthy" on the quality of life of all others.It is true that someone - say - born blind or with a likelihood of future disease, might be so depressed later on as to commit suicide, but it is also true that the great majority of those who cannot see or who experience serious illness at some time nevertheless lead full, active, independent and fulfilling lives.Indeed the main handicap if there is one is that society is still very unthinking when it comes to design and the way things are done.One or two wheelchair ramps seems to just about some up the response to the needs of the disabled.Are we carrying out birth denial because we cannot tolerate wheelchairs or brail signs in the lifts?

This whole area is likely to become very complex in the future.Although there are a large number of genetic diseases where the problem is entirely a result of faulty genetic code, it is also emerging that the commonest killers of all: heart disease and other similar problems, also have a genetic component.Doctors have known this for a great many years which is why family history is so important.Doctors in hospital will always ask if your parents are still alive and if not, what they died from.An example is heart disease: a man who's grandfather and father all died before the age of 60 from heart attacks is at high risk for developing diseased coronary arteries.The genetic engineer should be able to help us confirm who in the general population is likely to become ill from particular diseases (880).

For the last ten years we have recognised that if 10,000 adults eat a diet high in animal fats - especially cholesterol - then the number with heart disease is likely to rise.The huge marketing campaigns by margarine manufacturers have been built on this fact.However what is becoming clear is that for the great majority of the population, fat intake is probably almost irrelevant compared to a minority who have a genetic problem which means animal fats in their diet tend to produce damaging changes in the body.

A simple test, taking a couple of hours, could tell us which group we are in - saving dietary inconvenience, expense and enlarging good choice.such genetically influenced diseases affect at least one in ten of the population, including diabetes mellitus, certain types of cancers, heart disease and strokes (880).

Genetic cures or treatments are a massively growing area and fall into several groups: (890)

1. Programming bacteria, fungi or mammalian cells to produce missing hormones or other substances including complex chemicals.This has been recognised as an area of major importance for many years (900).

2. Growing white cells (soldier cells used to fight infection) to harvest special "monoclonal antibodies" to attack things like cancers. This is a form of human cloning.

3. Growing skin, bone marrow or other cells as a form of cloning.

4. Producing vaccines.

5. Reprogramming human cells - for example to cure HIV infection and AIDS.

6. Reprogramming genes in an embryo to cure genetic diseases.

The first four will be dealt with here.The last area is so specialised, important and controversial that a separate chapter is devoted to it.

1. Programme Cell Factories

The trouble with so many recent discoveries about how the body works is that we keep discovering more and more complex chemical substances and special structures.Although we understand an enormous amount about what they do and how presence or lack produces disease, they are so complicated that we cannot make them in a chemistry laboratory.

A laboratory the size of a tower block would be needed to make large amounts of some of

these things. It would be very expens -ive, slow and unreliable.

However similar chemical reactions and assembly lines operate in almost every living cell.Could we therefore hijack the factories inside living cells and get them to do the work? (910)The result would be a small production unit maybe in two or three large rooms containing large stainless steel barrels of cells. These would produce enough of - say -a hormone to treat several thousand people.Hundreds of experiments have been going on for some years to refine this technology (920)

The easiest cells to programme are E.coli bacteria from the gut as we saw in a previous chapter.These are now being used quite routinely in medicine to make all kinds of substances in ways that would have looked like science fiction just eight years ago (930).

First 13 genetically engineered drugs to be marketed inter -nationally

Product Originator Year Indication

Insulin (Humulin Eli Lilly 1982 Diabetes

Human Growth Genentech 1985 Growth hormone

hormone (Protropin) deficiency in children

2 a-Interferon Schering- 1985 Hairy cell leukaemia (Intron A) Plough

2 b-Interferon Hoffman-La 1986 Hairy cell leukaemia

(Roferon-A) Roche

Hepatitis B vaccine SK & F 1986 Hepatitis B vaccine

(Engerix B)

Digoxin monoclonal Wellcome 1986 Digoxin antidote

antibody (Digibind)

Orthoclonal OKT3 Cilag 1986 Rejection prophylaxis

in kidney transplants

Somatotropin Eli Lilly 1987 Growth hormone (Humatrope)deficiency in children

tPA (Activase) Genentech 1987 Myocardial infarction

Erythropoetin (Eprex)Amgen/Cilag 1988 Anaemia (RBC)

GM-CSF Amgen 1989 Neutropenia

C-CSF (Neupogen) Amgen/ 1990 Neutropenia

Hoffman-La

Roche

Factor VIII Genentech/ 1991 Haemophilia

Bayer

Some of the vast range of human substances being made genetically

1. Human epidermal growth factor (940)

2. Human granulocyte colony stimulating factor (950)

3. Human growth hormone (960)

4. Human manganese superoxide dismutase (970)

5. Tissue plasminogen activator (980)

6. Human adenosine deaminase (990)

7. Human purine nucleoside phosphorylase (990)

8. Human hypoxanthine granine phosphoribosl transferase (990)

9. Human Insulin (1000)

10. Human Ferritin (1010)

11. Human Fibroblast growth factor (1020)

12. Human calmodulin (1030)

13. Human Factor VIII (1040)

14. Human Factor IX

15. Human Interferon (1050)

16. Human Somatogen (1060)

However although the benefits may be obvious, such work has also caused great controversy with at least one large pharmaceutical company in Germany forced to close a ?20 million plant for genetically engineered Insulin production (1070) following a legal challenge for the Green Party (1080).The response may simply be to move production to another country.

Work is also well developed using reprogrammed fungi cells (1090) and also human cells (1100) as factories for medicine production in the laboratory.Insect larvae have also been used: infected by viruses containing human genetic code, they produce large amount of useful substances: about 8-9 milligrams of pure extract can later be obtained from about 20 larvae (1110).These concentrations are up to 350 times greater than can be obtained from human thymus or leukaemic cells.Complex proteins such as Factor 8 for haemophilia require mammalian cells to be used.Whole mammal bodies such as mice could be used as production units like the insect larvae above (1120) so long as the substance is relatively neutral in effect on the producing animal.

Worldwide, scientists are investigating over 250 possible drugs produced by genetic engineering.Over 100 human drugs and vaccines are currently undergoing trials (1130).Some as we have seen have been remarkably successful.Erythropoetin has helped patients with kidney failure enormously: kidneys not only clean the blood but also produce erythropoetin which stimulates the bone marrow to form red blood cells.Until this revolutionary new treatment existed, those needed dialysis were chronically anaemic, often needing blood transfusions.

Bacteria have been used with great success to produce a substance to stimulate while cell production when it has been damaged as a side effect of cancer chemotherapy.The substance (granulocyte macrophage colony stimulating factor) was discovered and isolated in 1983.A more potent version was isolated a year later and was in full production as a medicine by 1989, manufactured by Amgen (1130).

The search for an artificial source of Factor 8 for those with haemophilia has been enormously accelerated by the tragedy for so many of accidental HIV infection and AIDS deaths.This followed the use of Factor 8 obtained from plasma in blood donations.Special treatments to eliminate viral contamination only began in 1985 by which time over 1000 men and 250 children in the UK with haemophilia were already HIV infected.It was a surprise to many doctors to find that the virus was not only transmitted in the blood, but was also very hardy - surviving freeze drying and storage for several months before injection.The gonorrhoea bacteria would never survive such rough treatment.

Factor 8 constitute 2332 amino acids (building blocks for proteins) in a set order.If only one or two of these are incorrectly placed then the complex shape of the coiled molecule is changed and the structure has little or no biological effect on blood clotting.The molecule is too complex to make in the test-tube.We are also unable to grow human liver cells (which normally make Factor 8) in sufficient amounts.The Factor 8 gene, combined with all the other human genes had first to be "decombined" from the rest of the genetic code in the human cell.Then it was

"recombined" with the genetic code in hamster cells.These grow very well in industrial vats.This new Factor 8 is then called "recombinant".The final stage involves extracting Factor 8 from the brew.It is then mixed with albumin, a protein in human blood which can be subjected to rigorous processes to destroy viruses before it is used

By July 1990 over 150 people with haemophilia had been success -fully treated with genetically engineered Factor 8 in the UK (1140).

Lack of Factor 9 is the cause of another related bleeding disorder.Although a smaller molecule, it is more complicated to produce.Mice cells have been programmed to produce it but it is still experimental.However the biggest aim is a full care for haemophilia by inserting the normal genes for Factor 8 or 9 into the patients own cells to be transplanted back.This is still some way ahead (1140).

Production of antibiotics:

Programming of organisms called streptomyces are one way to produce a new generation of antibiotics (1150), firstly by increasing enormously the variety of new substances to be tested for antibiotic activity but also by allowing us to develop substances that will directly interfere with the genetic code of bacteria (1160).

2. Monoclonal antibodies

Monoclonal antibodies are one of the most important advances in modern medicine.Whereas in the human body cells produce a vast variety of differently shaped antibodies to fit different germs, monoclonal antibodies are antibodies produced with an identical shape, in very large amounts, by cloning the white cells producing the shape you are looking for (1168).

(a) For cancer

Genetics has a huge role to play in the fight against cancer (1170).Primarily this is because so many cancers result from damaged or abnormal genetic code.Genetic engineering is also providing some novel treatments.

A lot has been made in the Press recently about the so-called "magic-bullet" that can be given as a medicine.Genetic engineering is making this a reality by using monoclonal antibodies against tumours although the work is still very experimental (1180).The idea is that the antibody will travel harmlessly in the body until it finds the cancer cells to be destroyed (1182).Once this happens, the antibody sticks to the cancer cells, releases a cell poison of some description, or radioactivity, and the cancer cells die.We desperately need such treatments.Up to one in three of the people you know will die of cancer.Treatments that are currently available to kill cancer cells nearly all kill many normal cells as well which is why side-effects can be so severe.

Up to now the great problem has been to try and find some special feature of the cancer cells which would make them more vulnerable than other cells.Genetic engineering has been used here too to try to understand what turns cells cancerous.We suspect that often the cause is damaged genetic code.Genetic engineers have been experimenting with skin cells from patients prone to get a particular rare kind of cancer called the Basal Cell Nervus Syndrome (BCNS).They found that these skill cells (fibroblasts) differ genetically from normal and are liable to start dividing uncontrollably if exposed to particular chemicals or naturally occurring body substances (1190).Rectifying such differences in genetic code could be a part of cancer cures in the future (1200).

One of the first examples of cancer cured by genetic reprogramming of tumour cells could turn out to be the inherited forms of colon cancer.In these cells, a particular cancer suppressing gene called p53 appears to be missing so these cells tend to grow uncontrollably.The John Hopkins Oncology Centre in Baltimore USA has succeeded in transforming colon cancer cells back to normal by inserting the correct p53 gene into cancer cells grown in the laboratory (1210).The gene acts as a natural brake on cells, causing them to function normally and divide only when necessary to repair or replace bowel lining.The reprogrammed cells then divided at only a tenth of their previous rate.However there are many practical problems to overcome before this could become a viable treatment in humans.For a start we would need to make a specific virus for colon cells and be sure it was completely safe.This is probably around ten years away still.In the meantime we may be able to produce drugs based on the protein that the p53 gene makes.The protein may turn out to control the tumour well.

The same abnormal p53 gene seems to be present in seventy percent of lung cancers which kill 40,000 people a year (1220).

However detecting such genetic difference from the outside is almost impossible because as we all know, cancer cells are basically like any others in the body from which they developed.The only real difference is that cancer cells by definition do not know when to stop growing and dividing, so large balls of cells develop instead of normal tissue.These rapidly growing cells can cause chaos by using up a lot of food and energy, and by blocking normal function of body organs.Some of these cells also release things into the blood - but usually just overproducing normal substances.

For the last thirty years the main weapon we have used has been very clumsy.We have developed chemicals that damage cells as they try to divide.They prevent the genetic code from being duplicated into two so the cell is stuck in the middle of division.Radiotherapy treatment using radioactivity also works the same way by damaging the genetic material - something most likely to happen in cells as they start to divide.

You might think this is an ideal approach to cancer - after all, non-dividing normal cells such as brain and kidney cells should be unaffected.Unfortunately, many cells in the body do divide as rapidly as cancer cells and these too can tend to be severely damaged.Obvious examples are hair producing cells, skin cells, bone marrow cells (producing red and white blood cells), and the cells lining the gut.

One answer being investigated is to programme human cells so they themselves produce the chemotherapy agent being used to fight the cancer cells.Injecting a solution of these factory cells directly into the tumour should then cause the cancer cells to receive a very high dose while tiny amounts of agent leaking out into the rest of the body should be so dilute as to prevent any damage elsewhere.Initial good results have already been seen in mice with transplanted human tumours injected with reprogrammed factory cells.The cells used were fibroblasts reprogrammed by infection with specially prepared retroviruses (1230).

Sometimes we can find types of cancer which need human hormones to carry on growing.This is especially true of some cancers that have grown from the reproductive organs.In these cases we can see excellent results in some by giving medicines to block the normal hormone production.However for the vast majority of cancers we are still unable to destroy them selectively without damage elsewhere.

So how does the "magic bullet" work?Apart from the mysteries of the human brain perhaps the most remarkable part of the body is the Immune System which fights infection.What people do not realise is that destroying germs is often very difficult for the body.You may never know because you continue to feel well while the inner struggle is going on and the germs are defeated.Some cells literally eat germs and rubbish getting into the body, but most germs need to be prepared carefully before eating.In many cases the preparation process kills them directly.They are prepared by anti-bodies.

Every known germ has a different outside appearance and is treated entirely separately by the body.The soldier cells (white cells) have to be extremely careful not to overreact because they can so easily land up fighting and killing normal healthy body cells, thinking they are germs.This can happen very commonly and when it happens we say the person has an auto-immune disease because the body is attacking itself.

Examples of such diseases are rheumatoid arthritis, some forms of diabetes or thyroid problems or kidney failure.

To prevent this from happening to an absolute minimum the soldier cells are programmed before birth with the different shapes and appearances of almost every different cell type in the body.Some cells get missed because soldier cells cannot get to them. The inside of the eye for instance never becomes part of the library of permitted cells.You see the effects if someone has a severe eye injury.If you do not remove the damaged eye fast you find the immune system will start fighting eye cells as foreign.Once this starts it is difficult to stop and even if you now remove the damaged eye the person is likely to find the other eye is attacked and destroyed.

Once the soldier cells are programmed with these thousands of shapes,any germ is measured against the library - this happens also as we have seen with transplants.

If it is not recognised as a body shape it is destroyed.The amazing thing is that the body destroys it by producing a tool like a spanner which exactly fits the outside of this germ.Every germ needs a different set of spanners.That is why having measles does not protect you from chickenpox, or having 'flu does not prevent a cold.If germs change their shapes as cold viruses do then the body has to make a brand new set of spanners to fit each time.

These spanners are called anti-bodies because they fight against foreign cells or other strange things such as splinters or even complex medicines.There are tens of thousands of different shapes available.Surely just one of them could recognise very small differences on the outside of cancer cells so cancers could be destroyed?

We know anti-bodies and white cells destroy cancers very well because cancers are so common in people where the immune system is damaged or put to sleep with drugs such as very high dose steroids.Most of us probably have new cancers developing regularly in our bodies.They are recognised by the body as foreign and destroyed.Sometimes the destruction rate is not fast enough and the cancer keeps growing - even if more slowly than otherwise.

Doctors have been trying to make a magic bullet out of anti-bodi -es by taking white cells from someone and exposing them in a test-tube to cancer cells.Less than one in 10,000 white cells will react: the ones programmed from birth to recognise this particular shape and produce the right fitting anti-bodies.If you then take these reacting cells and clone them you will be able to produce huge amounts of specific anti-body to fit this particular tumour.You can then give it as a medicine by injection knowing that the anti-body molecules will be carried around the body not harming any cells at all except the ones they fit onto.

Cloning of antibodies calls for special techniques (1240): genetic code from the white cells producing the antibody required is transferred into cancerous myeloma cells.These myeloma cells grow well in the laboratory and once reprogrammed will go on multiplying, producing the specific shaped antibody indefinitely.We can even mix up the genetic code inserted into myeloma cells so for example one end of the antibody molecule produced is identical to that in a mouse while the other end is human (1250).Such changes provide a unique set of tools to diagnose and treat illnesses (1260).There have been some concerns expressed at the use of some kinds of cancerous cells in genetic engineering, especially if the reason they are cancerous is because of infection by a tumour producing virus.The risks are generally considered to be minimal (1270).Less than one in a million even if viral genetic code were to find its way into a medical preparation as an impurity (1280).

These cloned anti-bodies are called monoclonal because they are cloned from a single cell to produce a single shape anti-body. They are being used increasingly in medicine both in cancer treatments and in blood testing or other laboratory procedures. They are still experimental in cancer and results have sometimes been disappointing.Latest work is focusing on adding a poison - or even a little radioactivity - to each anti-body molecule so that even if the anti-body and other white cells cannot kill the germ direct, they can at least release high doses of poison or of radioactivity right where it is needed.

This whole area is developing very fast and has a huge potential for new treatments in the future (1290).

2. (b) Monoclonal antibodies as diagnostic or laboratory tools

These antibodies are turning out to be extraordinarily useful in hundreds of applications, ranging from immunoassays in diagnosis by detection of tiny amounts of different proteins, to imaging by attaching dyes, markers or radioactive molecules to antibodies (1295).As genetic engineering techniques improve, new doors are opened.

We already use antibodies against human pregnancy hormones in over the country pregnancy tests.We use them also as part of the test for the AIDS virus (HIV) infection.Whereas we were previously limited to cloning antibody types using strips of previously existing genetic code, we are now able to write the code completely from scratch with infinitely possible variations (1300).Literally any shaped antibody can now be made; and what is more be made to look precisely like human antibody so it survives in the body longer.

List of some monoclonal anti-bodies being used:

3. Growing skin, bone-marrow or other cells as a form of cloning

In a previous chapter we looked at the benefits of cloning skin cells preferably using skin from the person who needs more.This is usually as a result of massive burns.Most people with severe burns die because burnt skin leaks large amounts of fluid.You see this on a small scale if you burn yourself on a saucepan and get a blister.The urgent need is to get a temporary covering of skin.Skin from other humans or even animals may help for the first few days before the immune system attacks and destroys the graft.The only long term replacement is going to be skin from the same person - unless there is a very rare match with someone using all the normal methods of transplantation.

The traditional method is to steal small pieces of skin from elsewhere on the body and cut them up into tiny pieces.These are placed on the healing burn like growing plants which spread until the whole area is covered.

Obviously someone who is severely burned is not going to be able to spread around scarce skin to cover, especially as each donor site also is a painful wound needing to heal and capable easily of becoming infected.

Growing skin for each individual in the laboratory, from their own cells, is the best solution and one which is now working well.Skin cells can be persuaded to grow into large sheets very quickly, certainly a lot faster than when covering a wound during natural healing.

Bone marrow cells are ideal for growing in the test-tube because they tend to operate as individual independent cells rather than as cells permanently fixed together in an organ like the liver. One of the most drastic forms of cancer treatment is that for leukaemia.The stakes are often high because many who have this illness are children or young adults.Despite the huge side effects one method to try and produce a cure is to give the entire body a lethal dose of radiation.All the bone marrow cells die.The person would normally die of radiation sickness in a few weeks.Red blood cells all die in around 100 days so the person becomes very anaemic.Blood transfusions can help on a short term basis.The biggest problem however is that in order to kill off the white cells in the body that were cancerous and dividing too fast, we have also killed off all the others leaving the body completely defenceless against infection.

It is possible to take a small piece of bone marrow from a donor and transplant it.The cells will gradually fill the large bones and make red and white cells as usual.However you can see that if the match is not perfect, the new donated white cells could decide that the entire body of the sick person is foreign and a massive auto-immune reaction could follow, gradually destroying the body from within.

A way round this has been provided by the genetic engineer - a second revolutionary way will be looked at in the next chapter. If we can find some normal white cells from a sample of diseased bone marrow before we give the radiation, we could grow these in the laboratory, giving back the person's own white cells at the end.Growing them in the test-tube also allows us to be absolutely certain that the cells put back are really healthy. This cloning of bone marrow cells is now quite routine in some places.

Another use of cloned cells is to give a biological surface to pieces of medical equipment made of metal or plastics before they are inserted into the body.This is especially important for tubes carrying blood to reduce the risk of blood clotting inside the tube.One medical team has successfully reprogrammed sheep cells from the lining of blood vessels so they produce human anti-clotting substances.They achieved this by inserting the human gene for plasminogen into viruses (retroviruses) which then infected the sheep cells.The cells were then grown in sheets covering the stainless steel tubes before insertion.Results have been excellent (1310).

Progress is also being made in the treatment of blood vessel narrowing caused by arteriosclerosis.Here we find that minor damage to the artery wall causes smooth muscle cells in the wall to start growing and the vessel to close.Genetically altered smooth muscle cells from pig blood vessels have been successfully transplanted and observed to see how they behave.The hope is to develop alternative treatments for vascular disease (1315).

4. Producing vaccines

One of the most complicated of all structures to manufacture artificially is the wall of a bacterium or virus.Creating cell factories to do this enables us to produce very large amounts of germ fragments which are not infectious but which prime the immune system of the body so that when the real germ enters it is rapidly recognised and destroyed (1320).This is the basis of the widely used and highly effective vaccine against Hepatitis B virus (1325), the first genetically engineered vaccine to be licensed for medical use (1330), marketed by Smith Kline and French (1340) and recommended by the Department of Health for health workers (1350).It is also the basis for development of a new vaccine against whooping cough (1360) and AIDS, as we will see in the next chapter.

Another method of vaccination is to use live virus from a different strain that only produces mild symptoms.For such a vaccine to be effective it must have an outer coating which is so similar to the dangerous type that the body will be prepared in future to fight it.It was Edward Jenner in the last century who noticed during a local epidemic of smallpox that women who were milking cows on the farms never seemed to have the disease. He began to realise that there was a very similar virus in cows which produced a mild illness in humans that later protected against smallpox.The cow illness was known as cowpox and vaccination using cowpox quickly became an established medical practice.

Another well known example of a live vaccine is the strain of virus used to fight polio.Polio is an enteric virus, which is to say that it is released into the stools, and is spread by contamination of what goes into the mouth with virus particles. Once inside the lining of the gut the virus quickly multiplies, releasing more viruses into the blood from which they infect and destroy nerve cells producing paralysis or even death.In many countries of the world polio has largely become a thing of the past due to vaccination.

With polio vaccination another very interesting thing often happens: because it is a live vaccine (usually given by placing a drop of virus solution on a sugar lump to eat) it multiplies as you would expect in the gut.Large numbers of infectious virus particles are released in the stools of a vaccinated child. Thus if - say - eight out of ten children in a class at school have been vaccinated, the chances are that the other two will "catch" the same vaccine and the whole class will land up immune. The lesson from this is that viruses can and do travel and we had better be very careful indeed before treating people with live viruses.

Some would say that the polio virus and its milder variant are highly infectious, unlike many of the synthetic viruses now being used in experimental treatments of various kinds.However a recent scientific report should cause us to stop and think.The big question in the minds of some is whether the stability of a synthetic virus can be guaranteed or will it go out of control? Could it change inside the animal or human in some way that we could not have predicted in advance?If it does change, could the change be dangerous for the carrier or to others?

Scientists recently took two different strains of pseudorabies virus one of which had been genetically engineered elsewhere to form the basis of a vaccine.The other strain had been processed in conventional ways (attenuated) to produce milder disease.Both were given to sheep simultaneously.

The result was that sheep cells became muddled as to which virus they were producing.The viral programming and production became jumbled up and hybrids or mutants resulted.A new strain of virus emerged that had never been seen before, and which had the potential for unpredictable and "undesirable" effects.Those who ran the study at the US Department of Agriculture concluded that there was "a need for thorough assessment of micro-organisms in the animal environment" (1363).

Animals and humans may be carrying any number of viruses of various types at any time.Therefore some possibility exists of two strains recombining whenever genetically engineered viruses are used.Having said this, the number of times such recombination seems to happen naturally seems to be quite small, although HIV could be one recent example if we conclude that it arose as a spontaneous mutation of a very similar virus in animals.

Malaria is a disease affecting the health of millions in the two-thirds world.With rapidly spreading resistance to the main anti-malarial drugs, this blood borne parasite is becoming more and more difficult to contain.It is impossible to eradicate the large Anopheles mosquito although numbers can be reduced by eliminating all obvious breeding sites other than marshes or the edge of lakes. Vaccine development is being greatly accelerated by genetic techniques to help us understand the various forms that the parasite takes inside the body and to construct biological weapons against them (1365).

Another group of tropical parasites being investigated geneti -cally are the Kinetoplastids which cause trypanosomiasis and leishmaniasis (1367).Bacteria are also being reprogrammed to produce new vaccines against typhoid and cholera (1368).

5. Reprogramming human cells

In a few years time doctors may be injecting genes into their patients as routinely as they inject antibiotics today - according to Dr. Jon Wolff of the Department of Medical Biochem -istry at the University of Wisconsin (1370).

Once we have learned what genetic code is missing or damaged in people with genetic diseases, it opens up the possibility of "gene replacement therapy" (1380).Three approaches are being considered of which the third is the subject of the next chapter.The first approach is to inject genetic code into the tissue where the deficit is felt in the hope that a certain amount will find its way into human cells.This is likely to be tried in people with muscular dystrophy, a genetic disease resulting in muscle wasting and eventual death.There is some evidence that temporary improvements may be possible following injections of DNA into muscle.

The technique was discovered by accident: in an experiment involving mice, genes contained in artificial cells membranes were being injected into muscle to see what would happen.As a

control, a second group of mice had genetic code injected directly into muscle.Research workers were surprised to find that the control group did best.In five out of a hundred cases, reprogramming resulted.Further experiments have increased this percentage.Such genes appear to go on working in muscle for several months at least.This technique only seems to work in muscle (1370).

There are many other diseases where such an approach is being considered.For example, some children are born with a problem with their metabolism called phenylketonuria (PKU).This can cause brain damage if not picked up at birth.The best treatment of all would be to programme back the defective gene in liver cells after birth (1390).

Another genetic disorder attracting attention is a disorder of red blood cell haemoglobin called Thalaemia.Many attempts are being made with mammal cells to successfully reprogramme cells back so offering a hope of cure.So far progress here is disappointingly slow (1400).With all of these blood disorders you only have to reprogramme a few bone marrow cells to produce a result since these calls have a vast potential to reproduce themselves.Recent progress in mice gave 100% success with every mouse reconstituted with at least one reprogrammed call (1410).

Psychiatrists have been warned to prepare themselves for counselling people with the inherited type of Alzheimer's Disease (pre-senile dementia) and Huntington's Chorea - a progressive fatal inherited brain disorder (1420).Ethical issues are likely to become more complex as our understanding and range of interventions grow.Many other psychiatric illnesses may also have a genetic component (1420).

Another approach might be to reprogramme faulty sperm or eggs (1430).This is likely to be a technical impossibility because the only genetic diseases which could be prevented this way would be recessive ones (see p).In these only one in four eggs or sperm would be suitable for reprogramming.Only a certain proportion of embryos developing would be successfully reprogrammed (quite a low percentage) and we would have enormous difficulty in detecting which were which if the aim of those involved was to abort "non-successes".

However the most effective way of all would be to directly reprogramme human cells using viruses.We can do this routinely in monkeys (1440).Such gene therapy could be used for disorders of bone marrow, liver, central nervous system, some kinds of cancer, deficiencies of circulating enzymes, hormones and coagulation factors.By using viruses which normally cause

disease we are "turning the swords of pathology into the ploughshares of therapy" (1450).However we have to be absolute -ly sure that such viruses when given as medicines infect cells, reprogramme them and are then destroyed.Otherwise a risk exists that the treatment could be infectious: treat one child and the whole schools takes the medicine (1440).

An aerosol spray of live viruses could well be a normal everyday treatment for those with cystic fibrosis, the most common inherited disease affecting one in 2500 babies.Research at the Brompton Hospital in London has shown that new genetic code can be programmed into cells in the lungs of animals by this method (1460).The treatment would be given either by a simple handheld puffer like those used for asthma, or by a nebuliser used with a face mask - a nebuliser turns a liquid into a very fine mist which can be breathed in.Specialists believe such a "gene therapy" could well be available within five to ten years.Cystic fibrosis is caused by a lack of genetic code in lung cells to produce a particular substance to keep secretions runny.As a result those with the condition produce abnormal amounts of thick mucous, especially a problem in the lungs where small airways tend to become blocked and chest infections become a major problem.The defective gene was identified in 1989.Few used to survive beyond their twentieth birthday but better treatments mean a large number are now surviving longer - until middle age.Such a genetic "cure" could revolutionise lives, even if it has to be used daily for life.

The Genetic Revolution - free book by Patrick Dixon - published in 1995