The Genetic Revolution

We now come to one of the most extraordinary advances ever made by genetic engineers: germ warfare directed against germs.The idea of using one organism to fight another is not new.The naturally occurring rabbit tuberculosis is a disease called myxomatosis.This was introduced deliberately into Australia by releasing a small number of infected animals and was an attempt to reduce the damage to crops.

The one disease that dominates so much research time in the 1990's is AIDS, which stands for Acquired Immune Deficiency Syndrome.It is caused by a virus that some have speculated at times was made in a germ laboratory and released as a result of an accident.We now know that the virus called HIV has been around much longer than the facilities to make it in the laboratory.People went on to suggest that the virus had been forced to alter in the laboratory from an animal strain by using samples to affect a wide variety of animals under strange conditions.

When such infections are forced on creatures usually immune to a virus the result can often be a change in the virus structure. This mutation can make it more infectious and able to affect different species.It is conceivably possible but very unlikely) that such experiments could have accelerated the development of HIV from animal viruses of a very similar nature.

What is certain however is that we now have the tools to take viruses apart and put them back together again.No longer do we need to rely on the random effects of the animal host.These changes can now be programmed in the test-tube with far greater confidence.

Many of the attempts at finding an AIDS cure or a vaccine depend on genetic engineering.The drive to find a cure is vast because the problem is so massive.Almost every country of the world is now reporting cases.While the European situation has turned out to be slightly less severe than feared, the two-thirds world has been severely hit.

In many African towns and cities up to one in three of all the sexually active adults are infected.Across the world as a whole the infection is mainly a heterosexual one with gay men and drug users predominating only in the affluent West.An exception is Thailand where numbers infected have soared from 1000 to 300,000 in just over three years, mainly through blood exchanged by drug users sharing dirty needles.

Already the lives of 11 million people hang on finding a cure. The virus can live in the body for up to 20 years before causing disease so for some there is still time, but all the time the infection spreads.

The World Health Organisation estimated in 1990 that by the turn of the century there would already be some 11 million children orphaned as a result of AIDS with a further 11 million children infected from birth.With such an explosive epidemic of other sexually transmitted diseases HIV is hard to contain.

Traditional values preserved in societies over centuries have often been shattered by modern communications and an a rapidly spreading materialistic Western culture which has put a priority on instant personal satisfaction rather than long term commit -ments.

So far, genetic engineers have concentrated mainly on developing a vaccine.Most of these vaccines are based on using genetic engineering to programme bacteria or other cells to

produce non-infectious fragments of HIV outer coating which can be injected into humans.The body reacts by producing antibodies against these fragments.When HIV particles enter the body later o as a result of sexual intercourse, they are rapidly destroyed and no infection results.That at least is the theory.In practice HIV seems highly immune to attack by human antibody.After all, almost everyone infected produces antibody without being able to get rid of the virus.One reason at least is that these outer fragments are highly variable with up to 30 different shapes emerging in slightly different HIV strains in each person infected.An antibody for one shape is useless against another.

Scientists now think they have found a few parts of the virus structure which change much less often and these are the parts being manufactured (1470).A company called MicroGenesys makes parts called gp160 in insect cells, while Immuno makes gp160 in cells of mammals.Oncogen makes gp160 as part of vaccinia virus while Chiron/Ciba Geigy makes gp120 in yeast cells.Genentech and British Biotechnology are also making fragments containing p24, yet another viral building block (1480).All these vaccines are highly experimental but are much safer than injecting whole HIV particles however damaged we think we have made them before injecting.

Some genetic engineers have also experimented to find an AIDS cure.These treatments are all very experimental and can be hazardous.For example inserting genetic code from HIV into a live vaccinia virus (cowpox) resulted in severe vaccinia disease in two people with AIDS when they were injected with the newly engineered virus.It had been hoped that the new virus would stimulate the immune system vigorously to produce a reaction to HIV.Instead it appears undamaged vaccinia virus produced severe vaccinia disease in patients with AIDS whose immune systems were too weak to fight it (1490).

Another fascinating approach to fighting AIDS is to reprogramme the genetic code of human white cells so that they have a special in-built protection from HIV infection. Antibodies produced by cells only work against whatever appears in the blood or the fluid surrounding cells. Antibodies cannot enter cells through cell walls so what happens inside a cell once the virus enters is beyond antibody interference. However, we could try to generate specific antibody production inside each cell at risk of infection.This approach is known as "pathogen-derived resistance".Such genes could be made and tested quite easily on white cells in the laboratory, before attempting to use them as "gene therapy" in people already HIV infected (1500).

The way this method could work is as follows: first we have to identify how the virus operates inside the cell and decide which part of the machine to jam. This is relatively easy: for some

years we have known about a particular enzyme called reverse transcriptase which is only used by HIV and not by the human cell. This enzyme translates genetic code from the virus (RNA) backwards to make a permanent copy in the DNA of the cell chromosomes. As we have seen the usual pattern is always the reverse, with DNA programming messenger RNA which then gives the instructions direct to the ribosome factories. The main anti-AIDS drug used (Zidovudine) is a drug which is used to try and block the activity of this enzyme.

Here the approach would be to expose human white cells in the testtube to some reverse transcriptase, or some other piece of machinery. Antibodies will then be produced against it. Messenger RNA which is programming the production of this particular antibody would then be extracted and used to make DNA with the same coding. This DNA would then be inserted into bone marrow cells removed from people carrying HIV.

These reprogrammed bone marrow cells should then start to produce antibodies against reverse transcriptase. They should now have some protection against the virus because viruses entering the cell will find antibodies inside the cell are destroying the enzyme needed to reprogramme the nucleus (1505). At the moment such an approach is theoretical only.

In 1987 I wrote a book called The Truth about AIDS which contained all the most up to date information on the epidemic gleaned from hundreds of recently published scientific papers. I speculated then that scientists might by the turn of the century be able to make an anti-virus: a new virus to reverse the effects of the previous one.How realistic is this?

Recent experiments on animals have already shown reprogramming is possible.In 1987 animal cells were grown in a test tube and successfully reprogrammed using special techniques (1510) so that when implanted into mice they produced human growth hormone.The implanted cells tended to be destroyed by the mice and none were still active after three months.However the experiment was a real breakthrough (1520).It is also a relatively predictable technique because reprogrammed cells can be observed carefully to see how they behave before implantation.So what about using viruses to reverse damage done to cells of mammals?Retroviruses have been used to reprogramme liver cells successfully (1530) and bone marrow cells in monkeys (1540).

Building viruses is surprisingly straightforward, given their complexity once assembled.Most viruses are built from basic structures like identical pieces of lego, moulded so they can only be assembled one way.These pieces attract each other and fit together so well that if millions of

them are placed in a liquid, they tend to join up spontaneously, in exactly the right shape, built around a core of genetic code.We can even build virus outer shells with an empty core.As you might have guessed by reading this far, we can also programme cells to make them.Such experiments have been carried out using human cells to make empty shells of a virus which causes bone marrow failure in children (1550).

Sickle cell disease is yet another disease affecting red blood cell haemoglobin.Genetically caused, it is extremely common in countries where malaria is present because these unusually shaped red cells provide some resistance to malaria, so people with sickle cell genes tend to survive longer and have more children.Unfortunately when oxygen levels in the body fall for any reason, these abnormal red cells alter shape (into a sickle shape seen under the microscope) and clump together blocking blood vessels and causing serious problems.Researchers are trying to infect bone marrow cells with viruses to programme back the faulty genes (1560).So far animal experiments are not far enough advanced to try it out on humans.The approach would to be (1560):

1. construct viruses containing both the human beta-globulin gene and a suitable market gene (see p);

2. remove bone marrow cells from a patient with sickle cell disease;

3. infect the cells in the laboratory and select out the reprogrammed ones using the marker;

4. destroy all remaining bone marrow cells in the patient by radiother -apy;

5. transplant back the patients own reprogrammed cells.

The virus contains a small section of genetic writing - usually just enough instructions to tell the

infected cell to stop all normal factory production and instead to produce millions more viruses.The virus does this by several methods.The virus causing AIDS does it by reversing the normal chain of command in the cell.

Usually the genetic code in the nucleus gives messages which are carried out of the cell to tell the cell factories what to do. In this case, a form of genetic code injected into the cell is used as a messenger in reverse.This reverse messenger gets into the nucleus and makes a permanent change to the messages recorded there.The book of life has been permanently altered and every cell formed as a result of growth and division will be similarly affected.Using a computer analogy, the virus is a computer disc and the nucleus is the memory of the computer.The computer disk is corrupt and fills the computer with incorrect programs.

Using the computer analogy it seems obvious that the answer to treating such cells is to program them back to normal using a second virus as you would a new manufacturers computer disc.

We have been playing around with pieces of viruses for years.One way of vaccinating people is to take normal virus particles and damage them so they are incapable of causing infection.

If they are injected, the white cells will see them as foreign and destroy them.The Immune System will be prepared for the real thing in the future with no risk of disease.Such vaccines do not work with HIV for several reasons.The first is that damaged viruses do no bother the Immune System very much and the body tends to ignore them.Because of this the value of the learning experience for the body is much less.The second reason is that the virus is very variable.While the 'flu virus undergoes a change in shape every few months or years somewhere in the world, HIV is so variable that even in the same person you will find up to 30 different shaped variations, each of which may require a slightly different shaped anti-body to fight it. Experience has shown that HIV is effectively immune from all known human anti-bodies.

You can try to get a better response to a vaccine by creating a new virus which is capable of causing infection but not disease. Sometimes you find these occurring naturally.

The cowpox virus produces very mild illness compared to smallpox, but because their outside

coatings are so similar infection with cowpox in the past produces protection against smallpox in the future.Attempts have been made to do this with HIV.

Billions of dollars every year are being poured into this process - trying to find a way of producing anti-bodies in people that will protect against HIV.However even if an effective vaccine is found it will be some years before tests will show it to be fully safe.Even when a good vaccine comes (ignore sensational reports) it will do nothing to save the lives of the millions who are already infected. We also need to find a vaccine that will work against a second major type of HIV called HIV-2. This is gradually spreading from countries in West Africa where it was first identified in the mid 1980s. Almost certainly the develop -ment of this too will be a direct result of genetic engineering (1565).

To do this we need to make a new virus with an identical outside coating so it sticks onto and affects the identical cells in the body, but with the correct genetic message inside.Huge progress has been made: in 1987 scientists took bone marrow cells and successfully infected them with a virus containing genetic code for resistance to an antibiotic called neomycin.they did it by mixing bone marrow cells in a liquid containing a high concentra -tion of viruses and virus producing cells.They managed to reprogramme up to 16% of the bone marrow cells by this method (1570).The virus type used was very similar in action to the virus causing AIDS and is of a family called retroviruses because they programme back (retro) into the nucleus of the cell instructions which normally come from the nucleus.In a normally operating cell, the genetic code of the cell rules over what happens.Here the virus genetic code takes charge and copies itself into the nucleus genetic code (see fig).

In February 1991 it was announced that such an extraordinary achievement had now been made.

The disease was not AIDS but a very similar deficiency of the Immune System present at birth as an inherited illness rather than one happening as a result of virus infection.The disease is called ADA for short.Remember that even though children are born who will develop AIDS, they do so as a result of being HIV infected through their mothers' blood in the womb, not because of a genetic mutation.

Bone marrow cells (T type white cells) were taken from a four year old girl with the illness and infected with viruses containing a normal copy of the ADA gene.The reprogrammed cells were then grown in the laboratory and then transfused back into the person again.Cells transfused

back were correctly producing the missing ADA for up to 40 days after reintroduction.The experiment was carried out in September 1990 by the US National Institute of Health (1580).

Such a therapy could be available quite soon on an experimental basis to those with HIV.However one further technical problem will need to be overcome.

Viruses are very sophisticated structures.There is a second message in almost all viruses which is designed to stop another virus from being able to enter the same cell.Viruses like to have sole occupation it seems. It could get very confusing if two types of virus were budding out of the same cells at once.The risk would be chaos on the production lines.

The chemical made by human cells as a response to viral infection is called Interferon.Unless we can find a way of neutralising its effects we could find it almost impossible to get a second virus into a cell already infected.You can program bacteria to produce huge amounts of Interferon as a medicine of course.This has been tried for cancers and for AIDS with results which have been very disappointing as a whole.

Once we begin to build viruses accurately and with confidence we will find almost overnight a revolution has taken place in medicine.Not only will we have the ultimate cure for HIV infection, but also for 'flu and a host of other viral infections including sore throats and pneumonias.We may well find in the future that diseases like Multiple Sclerosis also have a viral origin and can be similarly cured.

Much attention is being focused on the common cold, produced by around 120 different types of virus called rhinoviruses (1590).These viruses are highly variable so you can catch the same strain of cold virus several times in a lifetime - by the time it hits you a second or third time, its outer coating is so altered as to be unrecognisable by the body's immune system.

All cold viruses have one thing in common: they all have a surface feature which can latch on to cells lining the inside of the nose.these nose cells are unique in the body which is why cold viruses do not give you spots on your skin or - say - cause diarrhoea.Over 80% of the viruses attach to exactly the same component of the walls of cells in the nose.The whole component (surface receptor molecule) has been genetically engineered (1590).Perhaps one day we will have a nasal spray of surface receptor molecules which - if used twice a day - will mean cold

viruses entering the nose latch onto false receptors and are immobilised.

A similar approach is already being tried in humans with HIV: here the receptors on T4 white cells are called CD4 and are the ones the virus causing AIDS is shaped to lock onto.Genetically engineered CD4 has been produced in vast quantities in the laboratory and injected as an experimen -tal treatment.Results so far have been poor, partly because the body destroys these particles very fast and they have to be injected regularly to keep the blood concentration high.Such a treatment would need to be taken for life.

The massive drive forward because of AIDS will undoubtedly bring many of the things we have looked at here to a practical reality within ten to fifteen years.

Once in a lifetime medicines

Many of these medicines would only need to be given once in a lifetime.For example, if these synthetic viruses were used to alter genetic code other than because of previous infections, then the results should be permanent.We have many curious possibilities.In 1987 I first raised the possible of permanent hair colourant.We are a hundred steps nearer.If you want blond hair instead of brown then you buy a bottle of hair follicle virus.The viruses in the mixture have an outside coating that fits only to cells which make hair.They contain the instructions for fair hair instead of dark.If by some accident a few other different cells in the body are also infected the results will be unnoticeable.After all, stomach cells do not use that part of the book of life anyway, so however much it is altered the stomach cells will continue as normal.

Unless the virus medicine also infects the cells producing eggs or sperm then the changes will die with the person and will not be passed on to the next generation.

The implications of all this are mind-stretching.Perhaps an adult could buy a change of skin colour.We should be able to turn on or off all kinds of instructions that certain cells use every day.We should certainly be able to cure a great many cancers.A tumour sample would be analyzed and the code checked for the fault.This is then corrected with a virus injection. For mainly cancers we will find that there are a number of faults which are very common so one medicine will cure a great number of people rather than different viruses needing to be designed for each person.

Medicines to cure your grandchildren

The outlook should improve dramatically for those who discover that they have an inherited disease.In addition to major obvious diseases such as haemophilia we should also be able to deal with bad genes that occur in most of the population.Have you ever wondered why doctors in hospital routinely ask what your parents died from and at what age.Family history is possibly one of the greatest clues to what problems you or I may face in the future.

Some genetic code is more likely to produce strokes, while other genetic code is more likely to produce breast cancer.Some code makes eczema or asthma likely while other code produces a tendency to certain mental problems.None of these things are certain unless you have a disease like haemophilia with a fixed inheritance pattern.Many of these other genetically based problems are influenced enormously by the environment: foods, behaviour, stress, and other diseases picked up along the way.

There is therefore a huge market for genetic cleaning techniques: viruses to infect eggs or sperm to make sure that you own children are less likely than your parents were to drop down dead of heart attacks before they were 60 years old.Doubtless such techniques will be refined extensively in animals before trying on humans.However, so long as society is so willing to abort what is inconvenient or unwanted, such experiments will continue more rapidly.For someone with severe inheritance problems it may be the only chance the person is willing to take to have a child.Removing a cell from within the womb could allow genetic analysis to make sure the viral reprogramming had happened correctly.The other alternative would be instead to make a full analysis of the eggs or sperm to check the code is now permanent -ly satisfactory before allowing conception to occur.

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