Search for a chemical agent against AIDS

A group of CSIRO scientists with expertise in designing biologically active chemicals has turned its attention to anti-AIDS agents. The Division of Applied Organic Chemistry group, led by Mr George Holan, is attempting to produce drugs that at least temporarily halt the progress of the disease.

Mr Holan has had many years' experience in creating chemicals for particular biological tasks. His group developed the first commercial 'designer' insecticide — cycloprothrin — which is due for release soon.

This chemical is more potent than DDT, but is biodegradable and has a low toxicity towards fish and mammals. The insecticide was designed by stipulating that its molecular shape should be such as to lock into an insect's nerve-cell receptor (but not a mammal's), forcing the nerve to keep firing uncontrollably.

Other agricultural chemicals designed by the group are currently passing through the development process and more are on the way. Now Mr Holan and his team hope their sophisticated chemical-design techniques will enable them to come up with compounds active against the AIDS virus.

First diagnosed in 1981, AIDS (Acquired Immune Deficiency Syndrome) is a frightening disease that has now become a world epidemic. There is no prospect in sight of a cure or a preventive vaccine.

Its spread in North America, Europe, and Australia has been thoroughly reported in the media. Less well known is its progress in Africa; in Zaire, an estimated 27% of the population is already affected.

By late 1986, AIDS had claimed some 300 victims in Australia, and the number is doubling approximately every 10 months. Some tens of thousands of Australians are carrying the AIDS virus; only time will tell what proportion of them will go on to develop the disease. What causes the change from dormancy to an active phase remains unknown.

Most of the research effort to date has been undertaken by immunologists, virologists, and molecular biologists. They are finding great difficulty in producing an AIDS vaccine, mainly because the virus continually changes its outer coat.

Mr Holan believes there is scope for organic chemists to contribute by producing compounds that may trip up the multiplication of the virus, providing a useful respite in the advance of the disease or preventing the disease developing in carriers of the dormant virus.

One such chemical is azidothymidine (AZT), which last year was widely publicised after American clinical trials indicated that it prolonged the lives of many AIDS sufferers. In a human cell, AZT is converted into a molecule that resembles the sugar molecule used by the AIDS virus in its reproduction. Acting as a decoy in this way, it interrupts DNA synthesis by the virus.

Other experimental drugs now being tried in AIDS therapy are compounds already known to have some antiviral activity.

The AIDS virus is one of a rare class among those affecting humans called retroviruses. As these carry their genes in the form of RNA rather than DNA, drug trials have focused on inhibitors of reverse transcriptase, the enzyme by which the virus can produce DNA copies of itself. The DNA copy inserts itself into the infected cell's genes, through which hundreds of new RNA virus cores can be made.

Inhibitors used in overseas clinical trials have included HPA-23 (apparently effective, but toxic to nerve cells); suramin (developed in 1917 against trypanosomiasis, a parasitic disease endemic in much of Africa); foscarnet (used in the treatment of herpes); and the ansomycins (used against leukaemia and some other cancers). Of these, suramin failed to have useful effects, and HPA-23 gave uncertain results after initially promising results reported from France.

Mr Holan is eager to try out a number of novel chemicals that may work as antiviral agents in another way. Over the past two decades he has synthesised hundreds of new compounds in a quest to produce novel insecticides, fungicides, and antiviral agents for sheep and cattle.

Many of these interfere with a cell's synthesis of that ubiquitous DNA base adenine. Because of the important role of adenine in the make-up of the AIDS virus, it is possible that those same compounds would also interfere with replication of the AIDS virus in humans. They may therefore protect the virus's target — the immune system's T-4 helper cells (which assist B-cells to produce antibodies) — from attack.

A first step is to try these compounds in cell-culture tests with the AIDS virus and — with the co-operation of Fairfield Hospital in Melbourne, the national reference laboratory for AIDS in Australia — this work has begun.

The first compound to be tested is not a novel one, but a known analogue of adenine — dideoxyadenosine — which Dr Brian Elmes, a member of the CSIRO group, has synthesised. The compound has been used in biological research as a so-called DNA chain-stopper; however, recent American research has shown that compounds of this

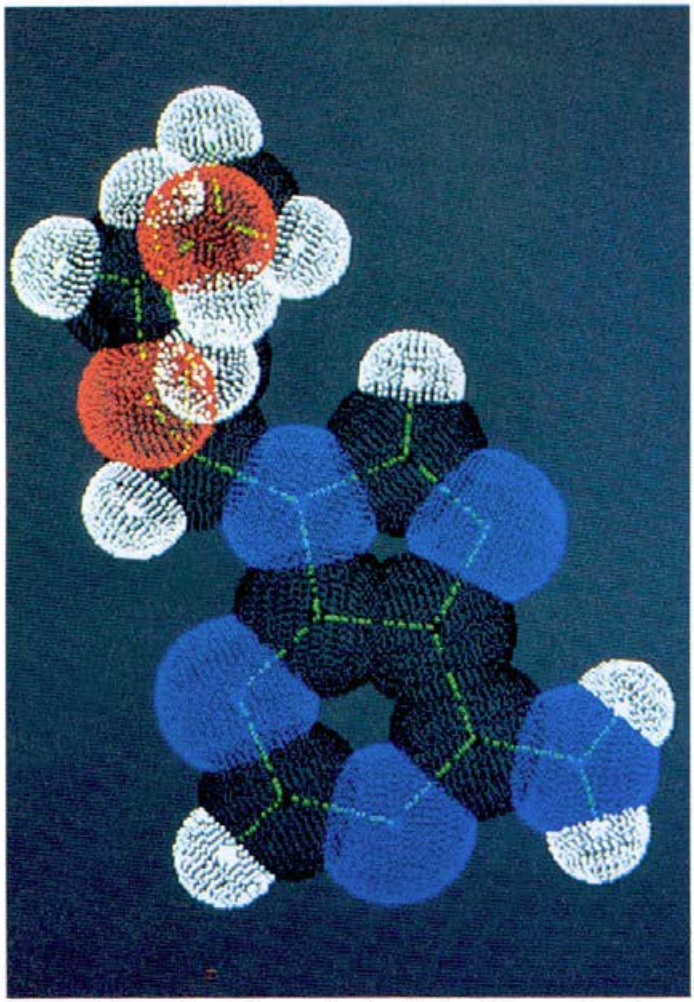
type are converted into agents with the capacity to inhibit the AIDS virus's reverse transcriptase.

If the cell-culture tests give promising results, the next step for the group will be to supply the compound to the AIDS Task Force for possible use in clinical trials.

There is no shortage of novel compounds potentially worth screening for antiviral activity. Mr Holan originally prepared one group of compounds (2-halogenomethyl benzimidazoles, adamantane analogues, and related structures) as possible antiviral agents for the treatment of bovine tracheitis virus, which is also a retrovirus. Samples of these potentially active compounds still remain on the Division's laboratory shelves.

On another tack, another member of the group, Dr Helmut Weigold, has plans to modify HPA-23, hoping to decrease its toxicity while retaining its antiviral properties. It is an inorganic compound of tungsten and antimony (ammonium 5-tungsto-2-antimoniate).

A tool that may help progress towards this end is a set of computer programs that can be used to predict the biological activity of molecules from their shape. The programs can show how closely the molecules match the protein receptors of known viruses. Dr David Winkler of the group will try to model the protein receptors of the AIDS virus as described by scientists overseas. The programs are backed up by a data base of the comparative activity of some 1500 molecules synthesised by the CSIRO group, and tens of thousands available from other biological data bases.



A computer-produced image of a chemical — dideoxyadenosine — that is being tested for its antiviral properties.

In collaboration with the Victorian School of Pharmacy, the Division has become a foremost centre for the computer design of synthetic biological agents.

The team plans to use the computer to design further antimetabolites to the genetic material of the AIDS virus. Another possibility is to design 'suicide agents' for infected T-4 helper cells. Mr Holan thinks it may be possible to incorporate a metabolic poison into cells infected with the virus, which would effectively stop the cell's energy cycle and thus kill the cell and its parasitic virus.

To effectively engage this most powerful and mysterious virus the international scientific community will need to call on all the diversity of research approaches available and every resource it can muster.