AIDS U•P•D•A•T•E

• By Sean Hosein •

ANTI-HIV DRUGS: AZT and Persantine

Scientists at the National Institutes of Health (Bethesda, Maryland) have discovered that a commonly used drug—Persantine (chemical name: dipyridamole or DPM)—increases the anti-HIV effect of the drugs AZT and DDC. DPM did not worsen the toxic effects which AZT can have on the bone marrow.

DPM has been used in the treatment of heart disease because of its anti-blood clotting effect. Experiments with macrophages (cells of the immune system which are targets for HIV) showed that DPM reduced the amount of AZT necessary to inhibit HIV replication in cells. By itself DPM did not have any significant anti-viral effect.

The side effects of DPM are "minimal and transitory" (according to the Compendium of Pharmaceutical Specialties) at doses commonly used for heart problems. Blood levels of DPM which correspond to those used in the experiments are achieved when 100-400 mg/day are taken orally. What is not known is the safety of DPM in HIV infected people. Test tube experiments indicate no additional toxicity other than that caused by AZT. *Proceedings of the National Academy of Sciences USA* 19889;86:3842-3846. Clinical trials are planned by the National Institutes of Allergy and Infectious Diseases (NIAID) in the USA. DPM is available on prescription in Canada and the USA.

Pasteur Institute studies Chinese herbs

Researchers at the Pasteur Institute, Paris, France, in collaboration with Japanese scientists are studying traditional Chinese medicine to find treatments for HIV infection. Using a precise combination of herbal medicine called SST (Shosaiko-to) and NT (Ninjin-to), Japanese researchers have treated 22 HIV infected subjects. All the people in the pilot study had T4/T8 ratios less than 1.0 (normal value approximately 1.2). Seven out of thirteen SST treated people and nine of ten given NT showed improvement in the T4 cell count and in immune response. Patients also showed weight gain. *V. Intl. Conf. AIDS*, Montreal, 1989, abstract W.B.P. 292.

The Pasteur Institute found that SST was able to cause a 90% inhibition of the viral enzyme RT (which is necessary if new viruses are to be made) at doses that can be achieved with oral use. Even at these high doses SST was found non-toxic to human cells. *V Intl. Conf. AIDS*, Montreal, 1989, abstract, M.C.P. 144.

Meanwhile, Kazuhito Watanabe, a researcher at St. Luke's Roosevelt Hospital in New York, has found that SST was able to reactivate communication pathways between different cells of the immune system (taken from people with ARC and AIDS) leading to an improved immune response. SST may also reduce the activity of the suppressor cells of the immune system, the T8 cells. SST and NT are made from up to eight herbs including liquorice root and ginsent. *V. Intl. Conf. AIDS*, Montreal, 1989, poster M.C.P. 148.

AL-721 Research

HIV consists of two basic parts, an inner region called the "core" surrounded by an outer membrane or envelope. A large proportion of the HIV envelope is composed of cholesterol and other lipids (fats). The drug AL-721 (which is a mixture of lipids) removes cholesterol and this would affect the functioning of the HIV envelope. Test tube studies strongly suggest that AL-721 alters the envelope and this in turn affects the ability of HIV to attack T4 cells. Other research shows that the ingredients of AL-721 inhibit production of HIV inside cells. *V Intl. Conf. AIDS*, Montreal, 1989 abstract M.C.P. 144.

In a multi-centre American study, forty patients with ARC were divided into groups of ten and each group was given either 20, 30, 40, or 50 grams of AL-721 twice per day for eight weeks.

Sixty percent of patients in all dose groups experienced mild diarrhea. This reaction ceased after some time. No preliminary indication of anti-viral or immune restorative effects were seen. This study is continuing to see if viral replication is affected. *V Intl. Conf. AIDS*, Montreal, 1989 abstract W.B.P.312.

Researchers at the University of Munchen, West Germany, have found that AL-721 drastically reduces the level of receptors such as the CD4 receptor on the surface of T-cells. Access via the CD4 (or T4) receptor is thought to be the major means of entry into cells by HIV. By reducing the quantity of CD4 receptors, AL-721 could make cells less susceptible to invasion by the virus. *V Intl. Conf. AIDS*, Montreal, 1989 abstract C.574.

Intravenous Liquorice in Japan

Japanese scientists have extracted the active ingredient, Glycyrrhizin, from the root of the liquorice plant and used it to treat people with severe HIV infection. Researchers at Kumamoto University gave infusions of GL to three people with AIDS intermittently (usually for several months at a time) over a period of approximately one year. The treatment appeared to drastically reduce levels of the HIV protein p24 when GL was given at the high dose of 1600 mg/day. The treatment caused an increase in the T8-cell counts. When given to mice GL has led to the production of interferon. Like AZT, DDC, and DDI, GL treatment did not cause a sustained increase in the T4 counts of the patients. No significant side effects were seen nor was any toxicity detected.

One patient died but he was already suffering from severe brain damage (likely caused by HIV) by the time the treatment was started. GL did not improve his symptoms of brain injury. In fact, it does not appear that GL can penetrate into the brain. The researchers suggest that a future trial of GL might use it in combination with AZT or DDC which are known to penetrate the blood brain barrier. GL in this study was made by the Minophagen pharmaceutical company, Tokyo. *Antiviral Research* 1989;11:255-262.

A small trial of oral GL (sold in Japan under the brand name "Glyceron") appeared to significantly delay progression from ARC to AIDS (see *Treatment Update, #6). GL for oral use is sold in health food stores.*

IMMUNE BOOSTERS: Drug may raise T4 count

One of the hallmarks of HIV infection is the progressive loss of T4 cells. No drug therapy has yet been able to cause sustained increases in the T4-cell count of HIV infected people. Now Dr. Elinor Levy and others (at the Boston University School of Medicine) have conducted test tube experiments with a drug which was able to cause significant increases in the growth of T-cells taken from people with ARC and AIDS. *Clinical and Experimental Immunology* 1989;7:7-10.

The drug used was NAC (chemical name: N-acetylcysteine). Available with a prescription in Canada and sold under the brand names "Airbron," "Mucomyst," and "Parvolex." NAC has been used for over a decade as a treatment for acetaminophen (Tylenol) overdoses. NAC appears to be a drug with little toxicity.

Research by Dr. Levy's team shows that NAC was able to cause substantial increases in the production of T-cells from the cells of people with ARC and AIDS by over 200%. The increase in T-cells was done without stimulating the cells immunologically. This would mean that it would appear highly unlikely that any latent HIV would be activated.

NAC is really an altered form of the natural amino acid cysteine. NAC is thought to work in part by supplying extra cystein to cells (this is important as researchers in West Germany have recently found that HIV infected people have lower than normal blood levels of cysteine, *V Intl. Conf. AIDS*, Montreal, 1989 abstract W.C.P. 93).

The cysteine in turn is used to make an enzyme called GSH (gluthathione) which protects cells from harmful reactions. NAC may thus help cells from the toxic side effects of many drugs used in treating HIV disease. NAC also appears to block and reverse the effect of the suppressor factor which is produced by HIV infected cells. This factor suppresses the immune system.

Long term studies on the oral use of NAC show it to be without serious side effects. *European Journal of Respiratory Disease* 1980;61 Supplement 111, pp. 93-108. For oral use, NAC must be diluted with cola or other soft drinks. A single 200 mg dose of NAC resulted in blood levels which peak in one hour and become undetectable in three hours. The 200 mg dose (which is small in comparison to the doses given for Tylenol poisoning) would result in blood levels which would initially be greater than those used in Dr. Levy's experiments. Repeated oral dosing results in high levels of GSH. *Respiration* 1986;50 supplement 1, pp.31-42. What is not known is the safety of NAC in HIV infected people. Physicians must take this into account when deciding to prescribe this drug.

Antabuse as an immune booster

Doctors with the Community Research Initiative (CRI) in New York have found that the use of the drug antabuse (chemical name: disulfiram) has caused an improvement in the immune systems of some people with ARC and AIDS. Antabuse is available on prescription in North America and has been used for many years in the treatment of alcohol addiction. When people using antabuse drink alcohol they suffer from unpleasant, sometimes fatal, reactions. Antabuse is thought to exert its effects on the immune system because the body changes some of it into DTC (diethyldithiocarbamate). DTC is the chemical name for the French drug "Imuthiol" which appears to significantly delay the progression from ARC to AIDS (see *Treatment Update* #6).

Physician/Investigator Dr. Bernard Bihari presented data on 53 patients with AIDS or ARC treated with antabuse. Results showed that there was a significant increase in the T4 cell count and a reduction in symptoms of HIV infection. About 20% of the patients continued to experience side effects such as abdominal cramps and/or diarrhea. Dr. Bihari and co-workers suggest that large scale trials of antabuse be started because of the promising results they have obtained. In this study antabuse was given orally in a dose of 500 mg twice per week or 750 mg once per week. *V Intl. Conf. AIDS*, Montreal, 1989 abstract C.619.

Research shows that while absorbtion occurs slowly, 80 to 90% of the drug eventually enters the body.

Meanwhile other doctors in Brooklyn, New York, have also used antabuse as the initial therapy for HIV infection. In a pilot study of 10 people with HIV infection but no symptoms and who had less than 500 T4 cells or a T4/T8 ratio of less than 1.2, were given 500 mg of antabuse twice per week. After six months of treatment, eight of ten patients had statistically significant improvements in their T4/T8 ratios. *V Intl. Conf. AIDS*, Montreal, 1989 poster W.B.P. 307.

Naltrexone prolongs survival

People with HIV infection are known to produce unusually high levels of a peculiar form of interferon-alpha. This interferon is thought to decrease the number of receptors used to receive chemical messages sent between the nervous and immune systems. Recent research at the Institute Pasteur, Paris, France, has shown that people with severe HIV infection have significantly reduced levels of these chemical messengers called endorphins. *V Intl. Conf. AIDS*, Montreal, 1989, abstract Th.B.P.241.

The drug naltrexone, used for many years in the USA to treat heroin addiction, is thought to increase levels of certain receptors as well as endorphins. Physician/investigator Dr. Bernard Bihari and others have used low doses of naltrexone (1.75 mg taken every night) in an effort to treat HIV infection. Initially 38 people with AIDS were enrolled in a three month double blind placebo trial of naltrexone. At the end of three months the placebo group was given naltrexone. During the initial three months the naltrexone treated group experienced slightly fewer opportunistic infections as well as a reduction in interferon-alpha levels. Eventually 25/38 patients showed a sustained fall in their interferon levels over a 4-12 month period. The 13 patients who did not experience this decline in their levels of interferon all died within nine months. Four years after having been diagnosed with AIDS, 10/25 patients are still alive with only one patient experiencing an opportunistic infection. The average T4-cell count of this group has not declined during the course of the trial. Naltrexone did not have any effect on levels of HIV protein p24. Certain immune responses remain intact while others have improved while on treatment. Naltrexone appears to promote long term survival in approximately 40% of responding AIDS patients. No adverse effects were reported. *V Intl. Conf. AIDS*, Montreal, 1989, poster M.C.P. 62.

Imreg-1 delays onset of AIDS

Derived from white blood cells, imreg-1 appears to enhance the workings of cells of the immune system. Recently, scientists presented research done under the aegis of UCLA showing that the drug was able to restore some immune system responses after a six month trial of imreg-1. Less people in the imreg-1 treated group suffered from opportunistic infections than in the placebo group. *V Intl. Conf. AIDS*, Montreal, 1989 abstract W.B.P. 279.

In a multi-centre American trial of the drug, only 4/93 people receiving the drug developed AIDS compared to 12/48 who were given the placebo. The people who received imreg-1 also took longer to develop AIDS when compared to the placebo treated group. *V Intl. Conf. AIDS*, Montreal, 1989.

So far the Food and Drug Administration (FDA) in the USA has refused to release the drug on a wider basis, even on compassionate grounds, despite the advice from one of its own advisory groups that the drug was probably of some use.

Steroid and KS alert

KS is a cancer occurring in over 20% of people with AIDS. Why some HIV infected people develop KS and others do not is not clear. There may be co-factors involved in this disease process. One such co-factor appears to be the use of steroids. Researchers in Los Angeles at the LA-USC Medical Centre have found that the use of (cortico-)steroids may lead to the development or worsening of KS lesions. All the patients reported by the researchers were receiving steroids—predinose or dexamethasone—as part of their therapy for PCP, KS, or other cancers. In all cases steroid therapy led to rapid appearance/growth of KS, usually within a matter of weeks.