Cure for AIDS in the offing?

by Veronica Rose

SCIENTISTS are excited but cautious after the announcement that two drugs mixed together may help to delay the infections that can kill people with AIDS.

Research seems to show that the drug Zoftrax (also called Acyclovir) combined with Retrovir (the conventional AZT treatment) may slow the onset of infections in patients with Acquired Immune Deficiency Syndrome.

The announcement follows newly completed studies undertaken over a two-year period in Britain, Germany and Australia, co-ordinated at London's Royal Free Hospital. Full analysts of the studies has yet to be finalised.

"We have a series of snapshots," says a spokesperson. "The full picture has yet to be completed before we know for sure that our optimism is justified."

Initially, the research was intended to learn if Zofirax has any effect on the sufferers of another kind of infection caused by cytomegalovirus, a virus with a similar form and structure to the herpes virus but characterised by an "owl-eyed" appearance. It is as life threatening as herpes, especially to a foetus.

During the studies, 300 patients suffering from either AIDS or cytomegalovirus were treated with Zofirax for 48 weeks. At the conclusion, it was seen that Zofirax had no effect on the cytomegalovirus, but delayed the onset of infections in the people with AIDS.

Zofirax was discovered in the laboratories of the Welcome Foundation and made available in the summer of 1984, following more than a decade of research work and investment of £81 million. It was intended as a new therapeutic agent to control an increase in herpes infeotions without producing the damage to healthy cells that was caused by existing agents.

The research was prompted by increases in herpes genitals, herpes labialis (the cold sore, affecting the lips), and herpes ophthalmic, which can lead to blindness. Herpes zoster (shingles) can even be life threatening, and causes almost intractable pain by damaging nerve roots.

Pharmacological researchers were finding the virus to be one of the most impudent and mischevious of all the microbes affecting human beings. It is difficult to see under normal laboratory conditions and enjoyed almost total anonymity before the introduction of the electron microscope exposed its highly complex behaviour: the herpes virus can enter a cell and live very comfortably by controlling cellular activity, including reproducing itself.

By manipulating genetic material, the virus can also persuade the cell to produce toxins.

Basically, scientists wanted something to prevent the virus dividing and replicating, and Zofirax achieved this. It is known to be 3,000 times more active against the virally affected cell in herpes infections than an uninfected cell.

It is also known that the herpes-type virus never leaves the body following initial infection, but travels to the sensory nervous system, where it can lie dormant for as long as the host's lifetime.

If, however, the host's immune defence system is lowered or impaired in any way, the virus reactivates itself and can travel anywhere in the body — including to the exceptionally sensitive neurological system.

Zofirax is effective in herpes viral infections only when given at the onset of the disease. Nevertheless, those treating and caring for people with AIDS have used the drug effectively to help their patients, whose immune defence system has been compromised or weakened by HIV infections.

Inevitably, there will be moral arguments based primarily on the cost of the drug (which is not exorbitant), and whether we are encouraging those who can infect the innocents to resume a pattern of life that has given the AIDS virus to more than a million people.

Since this has not been the attitude usually perpetuated by carriers, it is doubtful they will assume this mantle now.

In prolonging life, providing we ensure its quality is not diminished, we enable scientific research of any parasitic action that invades humans and animals to continue.

Inevitably, the message of Zofirax in 1992 is that science will accept this new opportunity and in some way we or our successors will be the beneficiaries. Whatever happens, the battle between the scientist and the virus will continue to excite interest.

The facts

Aids cases

- Countries reporting AIDS cases :163
- Reported AIDS cases worldwide : 371,802
- Estimated AIDS cases worldwide : 1.5 million
- Of 1.5 million estimated AIDS cases, one third in children

HIV-infected people

- Estimated no. of people infected worldwide: 9-11 million
- Of estimated HIV-positive people: more than 3 million women and 1 million children
- Average time from diagnosis to death in developed countries: 1-2 years
- Average time from diagnosis to death in developing countries: 6-12 months
- Median incubation time from probable time of infection to AIDS: 10 years

Projections

- By 1995: 10-20 million new infections
- By 2000: 30-40 million people will have been infected with HIV
  - -90% in developing countries
  - -25% will be children
  - -up to 10 million people will have been diagnosed with AIDS
  - -80% of HIV infections will result from heterosexual transmission

2560

Source: World Health Organisation

Euthanasia

Looking Death in the Eyes

by ASM Nurunnabi

EUTHANASIA means "mercy killing" — an act or practice of painlessly putting to death persons suffering from painful and incurable disease or incapacitating physical disorder. Because their is no specific provision for it in most legal systems, it is considered as suicide performed by the patient himself or murder if performed by another.

The opinion that euthanasia is morally permissible goes back to Socrates, Plato and the Stoics. The organised movement for legalization commenced in England in 1935. In the United States, the Euthanasia Society of America was founded in 1938. The growth of this concept has since been ominously steady.

Lately more and more people — whether they are terminally ill, knows someone who is they are simply confronting their won mortality — have been led into a new line of thinking about death. Now-a-days, with the rapid progress of medical science, an increasing number of patients, particularly in developed countries spend their last days in a hospital or nursing home. They often attached to sophisticated machinery that can extend even the most fragile life.

But this has been causing a purturbing issue — to avoid the crushing burden of extended illness, many people now consider the possibility of taking life and death into their own hands. They are asking what they can and should do and to ensure a dignified humane death.

The option that more and more patients and their families demand is to leapfrog dying if death is all that awaits. While many people choose death, no one chooses dying. Although there are no national statistics in the western countries, anecdotal evidence suggests that more than half of hospital deaths in those countries follow a decision to limit or withhold life sustaining treatment. This is not suicide or euthanasia. It is rather a desire to stop dying — to pass gently into the night without tubes running down the nose and ventilator insensately inflating lungs that have grown weary. Yet so often the life leaves few clues to how the dying should come.

In a Gall-up poll conducted in the US in 1975, only 41 per cent of the respondents said that they believed that some one in great pain, with no hope of improvement, has the moral right to take his own life. By 1990, the figure had risen to 84 per cent. Against this backdrop, Derek Humphry, President of the Hemlock Society, a euthanasia organisation founded in the US in 1980, thought that the present time was right for a "responsible" suicide manual. The result was his widely circulated book "Final Exit". The book fires debates over when it is right to let life go — and who should make that choice when the patient no longer can.

On this issue, there have been certain problems. On the one hand, passively doing nothing to prolong life or life-support measures has resulted in criminal charges being brought against physicians; on the other hand, the families of comatose and apparently hopeless patients have instituted legal action against the medical establishment to make them stop the use of extraordinary life support.

As society in Europe and America becomes less stable, more people are taking their own lives. Suicide experts see the transformation of their society as the key to the steadily increasing trend of suicide in their societies. The modernisation of the work force, the increasing social and geographical mobility, and the consequent breakdown of old family structures and support networks all play a role. All these factors are contributory factors for the growth of the concept of euthanasia in their societies.

Under the full glare of the media, courts and medical journals are debating right-to-die decisions. Most of us have some choice in how to live, certainly in how we conduct our lives. How we die is an equally personal choice — and, in the exhilarating and terrifying new world of medical technology — perhaps almost as important. .

Baby-friendly Hospitals

FIVE years from now, thousands of hospitals throughout the world could have a plaque by the front entrance designating them as 'baby-friendly'. To qualify for baby-friendly status hospital will have to comply with a new code of practice drawn up by UNICEF and the World Health Organization. The code is designed to ensure that all maternity units give babies the best possible start in life by encouraging their mothers to breastfeed.

Decline in breastfeeding

The 'baby-friendly' idea is the latest advance in a ten year campaign to reverse the trend towards the bottle-feeding of infants.

The reason for the decline in breastfeeding, says UNICEF's 1992 State of the World's Children report, is that more families are living in cities, more women are going out to work, and more advertisements are persuading mothers that bottle-feeding is more modern and sophisticated.

In fact, breastmilk is the world's most sophisticated food, says UNICEF. It is so nutritionally complete that an infant normally needs no other food or drink for the first four to six months of life.

It is hygienic and inexpensive. It immunizes infants against common infections. It can protect mothers against pregnancy. And it reduces the risk of breast and ovarian cancer.

Apart from being inferior in quality, powdered milk mixed badly with poverty. Without enough money to buy adequate quantities of powder, and without enough education to read the instructions on the tin, many families overdilute commercial milk powders. And without clean water or sterilizing equipment, fridges or fuel, the milk powder is often mixed with contaminated water and fed to babies from unsterile bottles.

As a result, bottle-fed babies in poor communities have been found to be approximately 15 times more likely to die from diarrhoeal disease and 4 times more likely to die from pneumonia than babies who are exclusively brestfed.

Overall, the World Health Organisation estimates that more than a million children's lives could be saved every year if all mothers gave their babies nothing but breastmilk for the first four to six months of life.

Advertising ban

Ten years ago, WHO and UNICEF published a 'code of practice' to try to stop infant formula companies from advertising their products to the public. The new 'baby-friendly' code for hospitals seeks to reinforce this by making sure that maternity units are on the side of breastfeeding rather than bottle-feeding. "Unwittingly, maternity services have often contributed to the decline of breastfeeding", says UNICEF.s Executive Director James Grant. "The vast majority of hospitals and maternity services have tragically depended on free supplies of infant formula. Too often babies are separated from their mothers at birth and fed sugar and water or infant formula from a bottle before the mother's milk has 'come in'. Even one or two bottle feeds increases the risk that a mother will have difficulty in breastfeeding."

The new code, which sets out Ten Steps to Successful Breastfeeding, is now being communicated by WHO and UNICEF to virtually every hospital in the world. All hospitals that cosnistently follow the code will be awarded 'baby-friendly' status.

Men can help

UNICEF has now called on all manufacturers to end free and low-cost supplies of infant formula to maternity units and hospitals by December 1992. The International Association of Infant Food Manufacturers has agreed to the request in principle and promised its co-operation.

So the worldwide campaign to make hospitals more baby-friendly, says UNICEF, is only one step among the many needed in the journey back towards breastfeeding. "Mothers need the support of hospitals," says the reports, "but if they are to continue breastfeeding they will also need the support of their employers, their families, their communities, and their husbands."

Making a Heartbeat Stronger

by Professor Reg Chapman, University of Bristol.

A new way of preventing heart attacks has been suggested by research at Bristol University. The idea comes from the discovery of the effect on heart cells of a deficiency of an amino acid called taurine. The possibility of using taurine supplements to fortify a healthy heart is being explored by a research team supported by the British Heart Foundation.

Amino acids are the building blocks of life. There are twenty which react in countless combinations; producing the huge variety of protein molecules that form bone tissue, cartilage, skin, different blood cells, insulin and thousands of other hormones, enzymes and essential biological agents.

Some amino acids are dispersed freely in the body and not incorporated into proteins. In general, they have a clearly identified function in the body's metabolism or as neurotransmitters — the chemical messengers involved in the transmission of nerve impulses.

One of the exceptions is taurine. Although it occurs at relatively high concentrations in a wide variety of cells, its only previously established function was in breaking down cholesterol, the fatty substance that can block arteries and heart cells. However, the levels of taurine in some types of cell very with age and clinical disorders. The result of a deficiency can be wide ranging; affecting the eye of the cat, the ear of the ferret, and development of heart disease in the hamster. So the investigation of taurine extends naturally the research into the electrical and mechanical properties of the heart, especially its relationship to cellular level of calcium.

Calcium is essential to trigger muscular contraction to make the heart pump blood, and it regulates the production of the energy used. Conversely, too much calcium can damage the muscle cells of the heart and, therefore, the heart itself.

Analyses at Bristol of calcium levels showed that heart cells did not collapse like a row of dominoes when there was an excess of calcium, but, rather, staged a series of defensive actions before being overwhelmed. That perception led to the idea of a new mechanism in which taurine helped protect heart cells against failure.

Of course, while taurine concentrations are now known to change with age and some illnesses, the amino acid has first to get into a cell. The molecule seems to cross the cell wall membrane with sodium ions, which, in turn, are vital in regulating normal activity of heart cells by regulating critical levels of calcium and hydrogen ions. In animal heart cells, the amount of taurine ranges between four and 50 millimolars (concentrations of about four to 50 parts per million). In people the levels exceed 20 millimolar in heart cells. And its concentration in the serum, the clear fluid residue of the blood, is a thousand times lower.

Over the past decade research on the heart has benefited from a method pioneered by Dr Trevor Powell, now at the University Laboratory of Physiology, at Oxford, to extract functioning single muscle cells from an isolated heart.

The Paradox

The technique is to bathe the heart tissue in a physiological fluid, similar to normal serum but containing special enzymes that will digest heart tissue — providing there is no calcium in the fluid. The procedure exploits the so-called calcium paradox discovered in earlier research. The earlier work showed that reducing calcium in the fluid bathing a mammalian heart predisposes heart cells to dramatic and damaging changes when the calcium level is restored.

Furthermore, the changes when calcium levels are restored resemble closely those that occur during and after a restriction in blood flow, ischemia, and shortage of oxygen, hypoxia, in heart conditions.

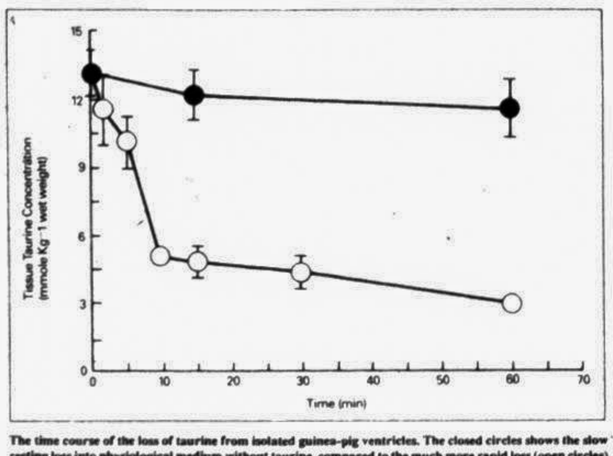
One of the frustrations of the technique to isolate cardiac myocytes, heart muscle cells, is the variability of the yield of viable cells. The search for improvements led to storage of myocytes in a cocktail of chemicals called Krafebruhe or other special culture media. Others, including our group at Bristol, obtained good yields of viable myocytes without resort to "special brews" simply by carefully controlling the level to which the calcium is reduced during the enzymatic digestion.

This difference in the way in which the cardiac myocytes are isolated we believe to be responsible for conflicting experimental results that have led to a dispute as to whether or not isolated cardiac myresistance to the calcium paradox, hypoxia and exposure to high doses of cardiac glycosides are produced by the introduction of additional amino acids into the cells (amino acids are a major component of "Krafebruhe" and culture media). This is achieved either by performing the isolation in the presence of taurine or by the introduction of taurine directly into a heart cell by diffusion from a penetrating micropipette, as shown in the illustration. The introduction of other amino acids like glutamate, and aspartate is much less effective than taurine in increasing the resistance of the isolated myocytes.

What leads to cardiac muscle cell damage or death? One outcome of the functional organisation of the heart is that every cell is activated at every heartbeat. Consequently, individual muscle cells of the heart cannot rest and the performance of the heart as a pump is regulated at the cellular level. This has profound implications, for the effects of the electrical and mechanical changes associated with each heartbeat must be corrected before the next beat if the heart is to remain in a steady state.

To achieve this the heart possesses a range of powerful ionic pumps and exchangers in the cell membrane which act to expel the sodium and calcium gained and to retrieve the potassium lost by the generation of the cardiac action potential and to expel the H ions generated by the expenditure of energy.

These regulatory systems are effectively coupled together with the sodium-potassium pump, which uses achieved by the "downhill" movement of sodium ions driving either calcium or hydrogen ions across the cell membrane and out of the cell.



The time course of the loss of taurine from isolated guinea-pig ventricles. The closed circles shows the slow resting loss into physiological medium without taurine, compared to the much more rapid loss (open circles) that occurs when intracellular sodium levels are elevated by exposure of the hearts the hearts are exposed to media free of calcium and magnesium.

Fuel Levels

The regulation of the intracellular levels of both calcium and hydrogen ions within narrow limits is essential for the normal functioning of cells. The first sign of failure to control hydrogen and calcium ions within the heart is the appearance of electrical and mechanical abnormalities. In the three conditions that lead to cellular damage or death and which have been well studied in the heart (ischemia, metabolic inhibition and the calcium paradox), the conditions prevailing within the cell just before the irreversible damage can be detected are remarkably similar. The intracellular levels of sodium, calcium and hydrogen ions are raised and the levels of cellular fuel (the energy-rich phosphates adenosine triphosphate and creatine phosphate) are markedly depleted. Although these changes act in consort, it would seem that it is the rise in intracellular levels of calcium ions that is the more important. Because we found that isolated cardiac myocytes survived and maintained their electrical properties when subjected to otherwise damaging conditions if a chemical that mopped up calcium ions was previously injected into the cells.

How does taurine have its protective effect? It is obvious that the sodium-potassium pump is central to the regulation of calcium and hydrogen ions within the cell so that a reduction in the cell's ability to regulate its level of intracellular ionic sodium will affect the regulation of both intracellular calcium and hydrogen ions. Our research found that in myocytes into which additional taurine has been introduced, the measured level of resting intracellular ionic sodium is significantly reduced. Taurine-containing myocytes are also better able to control the rise in intracellular sodium that occurs when the regulation of intracellular sodium is challenged, either by the poisoning of the sodium-potassium pump with a cardiac glycoside or by inducing a marked increase in the influx of sodium ions into the cell by the removal of calcium and magnesium from the bathing medium. This means that elevated intracellular taurine aids the regulation of intracellular ionic sodium. But this added ability to regulate intracellular ionic sodium levels is "antagonised" by the presence of taurine in the bathing medium and by the presence of chemicals known to inhibit amino acid transport in other tissues.

These results suggested that the outwardly directed gradient for taurine can be used by the cell to expel sodium ions, by means of a coupled sodium-taurine transport, when other systems are compromised.

Exploiting a Discovery

To make these measurements we returned to a well established procedure, using a Langendorff perfused isolated heart, so that sufficient material would be available for the determination of tissue levels of amino acids using High Pressure Liquid Chromatography. To raise intracellular levels of ionic sodium significantly we have exploited a discovery we made some years ago in relation to the development of the calcium paradox, namely that on the removal of bathing calcium indices and influx of sodium ions and a marked rise in the measured levels of intracellular sodium. The rise in intracellular sodium ion activity is further augmented by the additional removal of magnesium from the bathing fluid and inhibition of the sodium-potassium pump with cardiac glycosides. This rise is antagonised by elevation of the bathing magnesium, the application of calcium channel blockers and antiarrhythmic drugs. On exposure to media free of both calcium and magnesium, when intracellular sodium levels will rise, the taurine level with guinea-pig hearts falls dramatically with time.

This loss of cellular taurine (and incidentally that of other free amino acids) is reduced by procedures that would be expected to inhibit the rise in the intracellular sodium (increase bathing magnesium calcium channel blockers etc) and by exposure to inhibitors of amino acid transport. The fall in tissue taurine is augmented by procedures that would enhance the rise in intracellular sodium (such as exposure to cardiac glycosides).

The reciprocal relationship between the levels of intracellular sodium and taurine would seem to be established so that a coupled movement of taurine and sodium would seem to exist.

By this mechanism an elevated intracellular taurine would enhance resistance to hypoxia and the calcium paradox by aiding the regulation of intracellular sodium and maintaining the regulation of intracellular calcium and pH.

What about ischemia? Ischemia is difficult to induce in isolated preparations of cardiac tissue, but occurs under controlled conditions during by-pass surgery. The levels of free amino acids in biopsies of human ventricular muscle taken before and after the ischemic period associated with by-pass surgery have begun in collaboration with the surgical team led by Jonathan Hutter at the Bristol Royal Infirmary. In the first few patients, we find that the levels of all free amino acids including taurine have fallen dramatically after a period of by-pass. This suggests that the heart is using the amino acid-sodium transporter to counteract the rise in intracellular sodium caused by the either ischemia, hypothermia or cardioplegia. The question remains as to whether or not, elevation of taurine levels within the heart cells of humans will enhance their ability to withstand an ischemic insult during surgery and possibly beyond. (Spectrum)