Immunisation: a Possible Protection Against Malevolent Flukes

by Dr Paul Hagan

The exact role of one immunoglobulin, IgE, has long intrigued sc-ientists. Now, research by a team from the National Institute for Medical Research, in London, of blood-fluke infestations in a small community in The Gambia, has revealed the protective powers of IgE. The discovery opens the possibility of an effective IgE-based vaccine against schistosomiasis, a disease whi-ch affects millions of people.

IT is not a comforting thought that there are a number of different types of parasitic worms capable of living within the blood or tissues of man. One particular group, the blood-dwelling flukes, or schistosomes, was first described as long ago as 1852, by Theodor Bilharz, who found the adult worms and eggs of the parasites during studies in Cairo, Egypt.

The disease the worms caused was named Bilharzia, although it is now known more commonly as schistosomiasis. The illness described by Bilharz, affecting the urinary bladder and kidneys, is caused by the fluke *Schistosoma haematobium*. Two other schistosome species, *S mansomi* and *S japonicum*, are also important human disease causing organisms, but the pathology they stimulate is associated primarily with the liver and gastro-intestinal tract.

With an estimated 200 million people in tropical countries infected and over 600 million at risk from these parasites, schistosomes present a major public health problem.

People become infected with through contact with fresh water containing fork-tailed cercariae, which are the infective forms of the parasite. Cercariae swim rapidly. They penetrate unbroken human skin, as illustrated, after release into the water by intermediate snail hosts.

Snails are infected by another stage in the schistosome life-cycle, a free-swimming ciliated larva known as a miracidium. Once excreted into fresh water the eggs hatch, releasing miracidia.

Unfortunately, rural communities in which schistosomiasis is rife rarely have ready access to clean piped water supplies. Streams, lakes and ponds provide more convenient water sources than drawing water from deep wells. Even where safe water supplies are available, women do the family wash, farmers water their livestock and, more importantly, children swim and play in contaminated water.

The disease takes time to develop, so the illness is not associated readily with such a harmless activity as swimming in the local pond. But contact with water is important for two reasons. Children are less strict about their toilet behaviour whilst playing. Second, in any schistosome-infected community, children tend to have the heaviest infections. If they urinate into the water they may release thousands or even tens of thousands of eggs. each egg may release a miracidium which can infect a snail.

Hence, tens of thousands of snails may be infected by one child. Within the snails the parasites develop and multiply. For each miracidium which penetrates the snail, thousand of the infective cercariae may spread.

Children at Risk

Heavily infected children are most at risk from the disease, as the more eggs they have, the more severe is the damage to their tissues. When the cercariae penetrates the skin it sheds its tail and after several days in the skin migrates to the lungs and then to the liver.

Male and female sexes are separate but once in the liver they pair and migrate to the site they will occupy for the remainder of their life in the host. For *S haematobium* this is the blood vessels around the bladder. About eight weeks after penetrating the skin, the female worm begins egg production, producing hundreds of eggs a day, every day, for as long as she survives.

Most eggs pass out into the blood, through the walls of the blood vessels, through the wall of the bladder into the urine and hence into the environment. But some eggs become lodged in the tissue and a severe reaction develops about them.

For many years now it has been argued that the children are the most heavily infected section of the community because they have most water contact. This contact often involves total body immersion and so have a high risk of exposure to the infective stages of the parasite.

Adults, is seemed, used streams and pools much less frequently than children and rarely went swimming. Hence 'low risk' water contact activities were thought to explain satisfactorily their lower levels of infection.

Not everyone was happy with this interpretation. Of course, if you keep out of the water their is no possibility of being infected. Alternatively, the low levels of infection in the adults could be due to the development of resistance to infection.

The repots of people remaining uninfected despite high levels of water contact were, at best anecdotal, and the few studies which had looked at water contact in relation to levels of infection had ruled out a role for immunity.

Working with Dr H Andrew Wilkins and Ms Ursula J Blumenthal, then at the Medical Research Council's laboratories in The Gambia, we set out to determine whether or not the pattern of infection with high levels in children and low levels in adults, could be explained solely in terms of their degree of water contact.

If not, we could theorize that immunity might play a part and then go on to examine immune responses, to see whether any responses we measured could be related to resistance to infection. We had to find another way of assessing resistance.

Safe and efficacious

A number of drugs treat schistosomiasis. One of these, praziquantel is both safe and efficacious, practically eliminating infection after a single treatment.

One of the problems doctors face is that after treatment the people become reinfected, often very rapidly, because they continue to use the water bodies which are the source of infection.

We decided that, for once, this could be used to our advantage. If we treated people and followed them after treatment examining their water contact in detail, we would then be able to relate their contact to the levels of new infection which were established. Because the transmission of *S haematobium* in the The Gambia is seasonal, we would only have to examine water contact during a restricted period, not the whole year round. We wanted to assess the risk of infection for all of the people in the study group.

Our trained observers first had to learn the names and to be able to identify, on sight, all of the individuals in the study. Then, working in shifts, and in rotation, to ensure coverage of all the pools which were used by people, the observers recorded the identity of each person who had water contact.

They also recorded when the contact started, when the contact ended and the main activity which was performed by that individual during that contact. They did this on a daily basis for the whole of the time when transmission was possible, some five months.

Striking results

All of this data was then condensed into an "index of exposure" to infection for each individual; who went into the water a lot and who went into the water a little. After a time we went back and measured the levels of new infection which had been acquired by the people during the period in which we made the contact observations.

The results were striking. for children, the higher their 'index of exposure' the higher were their levels of reinfection. But the situation was not the same for the adults.

No matter how high their 'index of exposure' their levels of reinfection remained at practically zero. This was true, even for those adults who had contact levels which were as high as those of the children who had high levels of reinfection. Adults just do not become reinfected.

Our problem then was to examine the immune responses of the people to see if it would be possible to identify any responses which could be related to the apparent resistance to reinfection shown by the adults. The immune system operates through the interaction of various specialised cells with an array of proteins produced within the body.

These are capable of interacting with any materials which are recognised as foreign; ie. those that are unlike the body's own tissue.

The mechanisms of the recognition of foreignness is a complicated story; but the usual outcome is that the foreign material or antigens are destroyed and removed from the body. Thus, the immune system has done its job to safeguard our 'biological integrity': but not on all occasions.

Because of the need for the immune system to be armed with the potential to destroy other biological organisms like viruses, bacteria and fungi, it has at its disposal various vigorous proteins to neutralise intruders.

However, if unleashed in an uncontrolled way, they can also damage the tissue they were designed to protect.

One common manifestation of this is the allergic response. The basis of the allergic response is quite simple.

Normally when the body makes an immune response to foreign material it produces proteins known as immunoglobulins or antibodies. These antibodies come in a variety of forms and usually bind to the foreign material, neutralising it and assisting in its elimination from the body.

For reasons not fully understood, some foreign materials stimulate antibodies of a type known as immunoglobulin E (IgE). These foreign materials are usually termed allergens.

IgE is normally present in minute quantities in the blood but when allergens are introduced the levels may increase by a thousand times or more. IgE has the ability to bind to cells, in particular to crucial mast cells and basophils in the skin and other tissues.

Potent factors

When the allergen against which the IgE was produced is encountered once again, the cells with IgE on the surface release a number of potent factors and enzymes which are responsible for the swelling, redness and itching of the tissue we associated with allergic responses.

Most of us are familiar with skin allergies and the respiratory problems of asthmatics. In extreme cases allergic responses can prove fatal. The allergic response is something of an enigma.

The immune response has evolved as our defence against infection and it seems strange that the harmful allergic response has persisted.

Studies of the immune response to worm infections have thrown some light on this problem. Soon after IgE was first identified, it was noted that the production of high levels of IgE was a common feature of worm infections.

Experimental infections in animals were used to show the IgE which was produced against the worms could interact with a number of cells in the body to kill larval schistosomes. This led to the suggestion that IgE and the various immune (allergic) reactivities in which it participates may have evolved specifically to be the body's defence against worm infection.

In some parts of the world worm infections are no longer common and the allergic response with its unpleasant side-effects is the aspect with which we are most familiar. Evidence that human IgE and allergic reactivities might protect against infection has not been available until now.

Since the adults from our community appeared to resist reinfection we examined their serum for the presence of IgE antibodies against the worms. Only low levels of anti-worm IgE were in the young children, but increased a little at 10-14 and reached high levels over 15 years old.

None of the other antibody types produced during schistosome infection had this pattern. Analysis of the data, with allowances for age and exposure to infection, revealed that those with the lowest levels of anti-worm IgE were 10.2 times more likely to be reinfected than those with the highest IgE levels: convincing evidence, favouring a role for IgE antibodies in protection against schistosome infection and supporting the view that IgE does have a beneficial role. But one puzzle remained.

Normally the body makes a fairly rapid response to infection, typically within a few weeks of exposure. In the case of the people in our study the high levels of anti-worm IgE were found only in adults who had ten years or more of exposure.

Why does resistance take so long to develop? The answer may lie in the production of the other antibodies. One of these in particular, immunoglobulin G4 (IgG4) is known to be inefficient in removing antigens from the body and in participating in immune processes with other cell types. Production of IgG4 may be stimulated by the same antigens which stimulate IgE production.

It is known that IgG4 will interfere with the immune processes in which IgE participates. Those with the highest levels of anti-worm IgG4 were 10.7 times more likely to be reinfected than those who had low levels of this antibody type. IgG4 levels were highest in children and declined in older people. Levels of reinfection were highest in the children and the children had low IgE and high IgG4. Lowest levels of reinfection were fond in those with low IgG4 high IgE, the adults.

Vaccine Possibility

With high IgE levels being associated with resistance to infection and high IgG4 levels with susceptibility, the information we have gained may be of use in attempts to artificially induce a protective immune response, by vaccination.

One approach would be to use a vaccine which would stimulate an IgE response avoiding the production of IgG4, which seems to delay the development of a protective response. But some IgG4 production is desirable.

It is these that are likely to form the basis of the first schistosome vaccine to be tested on man.

Exciting time

The initial stages of such trials will be designed to see that the vaccine does not cause any harmful reactions but they will also tell us whether or not the appropriate antibodies are being produced.

It is an exciting time for those involved in schistosome research but it is also a time to be cautious. It may be a few years yet before clinicians are armed with a vaccine against schistosomes but we have come a long way from Cairo in 1852.

Even though there may be safe water sources available, communities often continue to use traditional sites. These may be streams or ponds and need not necessarily be permanent water bodies. Children tend to make frequent use of pools for swimming and playing and are usually the most heavily infected section of the community. Adult use, as in this case, is often related to domestic activities.

Remedy for Stress Syndrome

by Nicola Cole

A racing heart, sweating palms, churning stomach, knees like jelly. All are symptoms of stress—a syndrome as old as the hills. Yet, reports Gemini News Service, advances in psychological medicine are turning stress into a new and potentially expensive arena of conflict between bosses and workers.

UNTIL five years ago, the King's Cross district of London was most well known for its rail terminus, a gateway to Scotland, and, on a sleazier level for its legion of young prostitutes and pubs where pimps mingled with armbreakers and safe-crackers.

Then, one unforgiving winter evening in 1987, it acquired a new and tragic reputation. Fire broke out on an escalator in the underground station serving the terminus.

Many people died, including a fire brigade officer who was posthumously awarded the George Cross medal for courage in trying to save lives.

Four of his colleagues received £10,000 each for stress disorders incurred fighting the fire. They were the first members of a British emergency service to be compensated for emotional damage inflicted by their work.

The 1990 case was a legal landmark in more sense than one. Insurance lawyers predicted it would unleash a flood of stress compensation suits from employees in both public and private sectors.

"A rapid growth of successful claims within five years" was how the specialist London law firm Davies Arnold Cooper (DAC) put it.

The prophecy is already come in true. In one instance, 17 police officers present at the Hillsborough disaster of 1989 — a football stadium stampede that killed 95 people and injured 400 others — have prepared cases against their own force and its insurers.

They have been hoping for out-of-court settlements similar to those offered to members of the public who suffered are the events or from seeing television coverage of the crush in which their relatives perished.

None of this has gone unnoticed by British industry. Yet companies' awareness of work place stress — "cumulative trauma," as it is known in the United States — is seemingly much lower than their appreciation of the need to protect workers against unsafe machinery and known industrial diseases, according to a DAC report.

The threads of the present scenario trace back to the so-called "shell-shock" of World War One and the "combat fatigue" of World War Two — labels applied to the condition of troops whose ability to function had been impaired by stress.

Sweats, nightmares, bad temper, depression and heavy drinking were common symptoms of this impairment.

So also were a sense of alienation from family and friends, and haunting memories — of gunfire and sudden death, for instance — that became obsessive. Coupled with these were plain, old-fashioned fear.

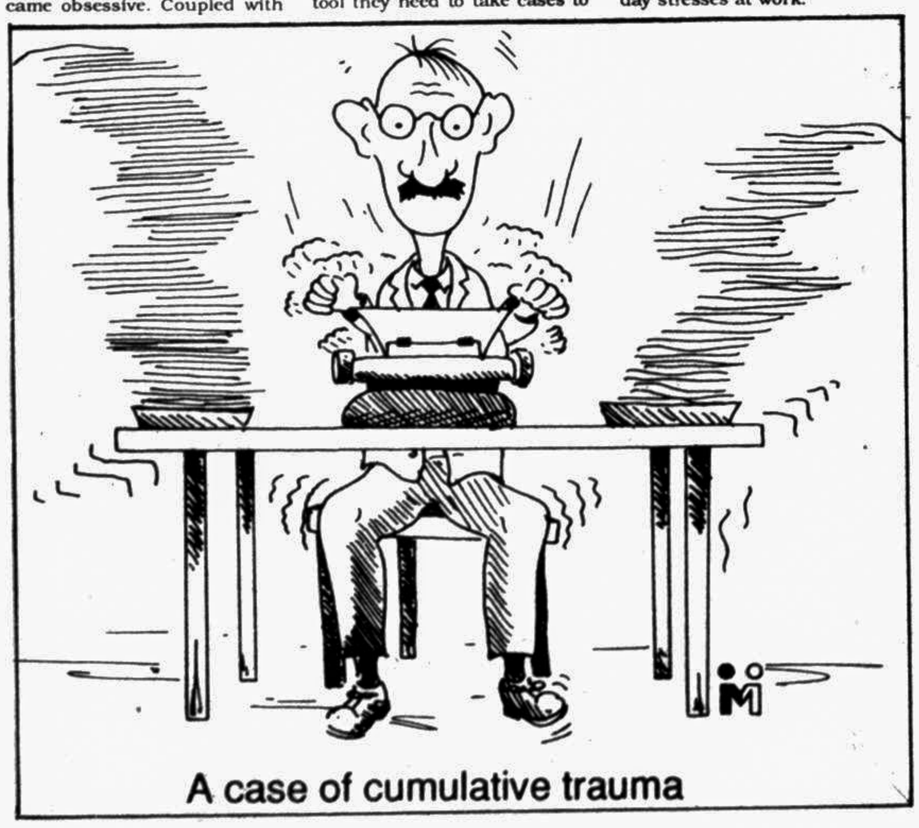
Systematic investigation of stress began in the Thirties. Yet not until the Vietnam War did doctors find it possible to assess and measure is stress damage with any degree of accuracy.

This advance followed extensive research in the US after the widespread collapse of military morale in the field. Psychiatrists now felt a new confidence in diagnosing the point at which stress becomes stress disorder.

Precise medical evidence has in turn given lawyers the tool they need to take cases to court. They have established two key areas in stress compensation cases: "nervous shock," today as quantifiable as a lost limb, and the "trigger event."

To link post-traumatic stress disorder of the kind suffered by front line soldiers or rescuers in a civilian disaster with the sort of stress arising in an office or factory may seem an imaginative leap.

Yet the underlying implication is clear: if degrees of stress can be identified and measured in combat and accident situations, the same process can be extended to everyday stresses at work.



A case of cumulative trauma

Numerous studies have already shown how widespread work place stress is, and how severe the impact on individuals can be. It ranges around the glove and includes:

- German industrial executives, 65 per cent of whom find the "deadlines" for their renowned production efficiency a major stressor;
- Japanese managers who rate "keeping up with new technology" as a main source of mental strain;
- Poorly-prepared Russian students who undergo blood-pressure changes "of near danger levels" during exams;
- Nigerian executives who resent long hours and the adverse effect of work demands on family life;
- Brazilian bosses who have to work with under-trained staff, which creates "pressures on interpersonal relationships";
- American clergymen and women , 75 per cent of whom suffer "periods of major stress" largely through "role overload".

The signs of stress are similar to those of "shell-shock." Notable among them are increased heart beat, breathlessness, upset stomach, sleep difficulties, and increased dependence on alcohol and cigarettes.

Being resilient machines, our bodies can with stand occasional spells of stress. The trouble starts when these become too frequent, too intense and too prolonged.

The result is physical and mental exhaustion plus a build-up of harmful by-products in our bodies. These raise liability to heart attacks.

For this reason, stress has been termed "the biggest killer of modern times." Yet in America and Australia, the rates for heart disease have fallen by up to 30 per cent in the last 10 years.

One main reason is preventive medicine — making people aware of the risks and helping them lead healthier, more relaxed lives.

In America, the preventive approach is integral to occupational health schemes. Much of their cost is borne by private corporations.

— GEMINI NEWS

Spareparts for Humans

by G S Mudur

CENTURIES-OLD prosthetic technology is witnessing a revolution of sorts as biomedical engineering laboratories add vital internal organs to the list of human spare parts available as substitutes for diseased or damaged organs.

Applying skills of engineering design and using new polymers and ceramic materials, scientists now have an impressive inventory of artificial organs, either in routine use — bones, joints, limbs — or under development — artificial ears, hearts and even a biohybrid pancreas.

Prosthetic technology has been around for hundreds of years in the form of dentures that replaced teeth and limbs that substituted for lost legs and hands. Now, backed by the development of bioinertmaterials, that technology is moving inside the human body.

A metal plate can today replace a multiple-fractured jawbone, plastic wrist bones, fingers and artificial tendons can go into repairing a damaged hand, large blood vessels that bifurcate can get grafts of dacron fibre, and severe damaged knees are totally replaced by a hinge-device made of either plastic or metal.

Also on the anvil are ear implants for the deaf. One such device is an implantable prosthesis designed to deliver electrical stimuli to the auditory nerves and is intended to help people whose hearing loss has resulted from damage to the inner ear.

Cobalt-chromium alloys and ultrahigh molecular weight polyethylene have gone into the replacement of hip and knee joints, shoulder joints, dental implants and bone plates and bone screws.

Several hundred thousand people each year receive prostheses for skeltal reconstruction that involves the total replacement of joints rendered nonfunctional either by accidents or crippling arthritis. According to one estimate over 100,000 surgical procedures involving the replacement of hip joints alone are carried out annually around the world, with high rates of success.

Scientists say the recent development of special bioceramic coatings is expected to improve results with orthopaedic implants. Surgeons have found that it is not easy to get bone to fuse tightly with the metal surfaces of the implants intended to replace the joints.

The ceramic coatings, made of calcium phosphate, have a chemical structure resembling that of natural bone. This identical structure it is hoped will make bone cells grow all the way to the surface of the implants, thus making the metallic joint implant as good as a healthy bone joint.

Research efforts have also focussed on implants for the heart and today a range of artificial valves for the heart and electronic pacemakers are keeping thousands of people around the world in fine shape. Several types of whole artificial hearts have also been tested on an experimental basis on patients.

In the United States, the National Heart, Lungs, and Blood Institute has launched a programme aimed at developing an artificial heart that will be entirely enclosed within the body and is capable of functioning continuously for five years.

But the artificial hearts available today are intended to be what doctors call "bridge to transplants," mechanical devices that are only used to keep patients alive until they are able to get natural heart transplants.

Artificial hears that have been used until now have been systems in which the patient remains connected to a power source. In the United States, the National Heart, Lungs, and Blood Institute has launched a programme aimed at developing an artifieial heart that will be entirely enclosed within the body and is capable of functioning continuously for five years.

Scientists have also experimented with a biohybrid artificial pancreas. An artificial pancreas is intended to be an alternative to patients of diabetes which is currently treated with daily injections of insulin and a strict regimen of diet and exercise.

The device will contain pancreatic cells that make insulin and will be placed inside a tube-shaped polymer membrane that will be linked to the recipient's vascular system.

A report in the US journal Science last year said the membrane will permit free flow of glucose, insulin, and blood components needed for maintaining the viability of the pancreatic cells but would keep the transplanted tissue separate from antibodies and killer cells of the recipient's immune system.

A team of American scientists tested the biohybrid pancreas on diabetic dogs. The devices containing canine islets (cells that make the insulin) were implanted in ten dogs requiring 18 to 32 units of injected insulin daily. Reporting their findings in the US journal Science, the scientists said the implants resulted in good control of fasting glucose levels in six of these animals without further exogenous insulin for periods of upto five months.

They said the devices are potentially superior to human pancreas transplants because the implantation of the device is less traumatic than the surgery involved in a pancreatic transplant and immunosuppression is not needed for the survival of the cells implanted through the biohybrid device.

They said this same technology could lead to the development of other biohybrid organs for treatment of other diseases.

Mr G S Mudur is a PTI Science Correspondent based in New Delhi.