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Introduction

Many viral and bacterial diseases are now controlled, at least in developed countries, by vaccination; indeed, smallpox has been eradicated from the earth by this strategy. Despite the fact that three-quarters of the global population currently harbour single or multiple parasitic infections, we have at present no effective vaccines against these ancient scourges of mankind. For many such diseases, chemotherapy is presently under evaluation, and some of the problems posed by parasites which have thus far frustrated our efforts at immunological control.

Existing vaccines

Almost all current anti-parasite vaccines relate to diseases of domestic animals. This undoubtedly reflects the notion that one can be more adventurous when dealing with immunological intervention in animals other than man, perhaps accepting a greater degree of vaccine-induced pathology. Cynics may suspect this may also have to do with commercial interests!

Live vaccines. The one ‘vaccine’ that has been exploited in man concerns Leishmania major. Inoculation of small numbers of live parasites (leishmanization) has proved useful where the incidence of infection is high and other attempts at disease control are not feasible (MODABBER, 1989). A small skin lesion is produced, usually in a site hidden from view; this lesion heals more rapidly than that induced by natural infection and induces good immunity. A somewhat similar procedure is used to vaccinate Australian cattle against the piroplasm Babesia bovis. This vaccine comprises parasites whose virulence has been reduced by passage in splenectomized calves (MORRISON, 1989); it does not induce sterile immunity and has only a short shelf life, but demand ensures continuous production. Live parasites are also used to vaccinate against east coast fever in Africa. Cattle are inoculated with a potentially lethal dose of Theileria parva sporozoites and, after a few days, treated with tetracyclines. The animals suffer mild infections from which they recover, but acquire a useful degree of immunity to challenge with the same, but not different, strains of the parasite. ‘Cocktail vaccines’ comprising 2 or 3 different strains are being explored (MORRISON, 1989). The first anti-parasite vaccine to be produced commercially consisted of radiation-attenuated infective larvae of Dictyocaulus viviparus, the nematode parasite causing pulmonary bronchitis in cattle (JARRETT et al., 1960). This vaccine was first marketed in 1959 and is still in use; it is claimed to induce better than 95% protection. A similar vaccine against dog hookworm (Ancylostoma caninum) was developed by MILLER (1978) but, whilst preventing disease, this preparation did not entirely eliminate infection. This feature detracted from public appreciation of its value and the vaccine is no longer in use (HUTZE et al., 1987). Another irradiated larval vaccine was tested against bovine schistosomiasis. Administration of radiation-attenuated Schistosoma bovis cercariae to cattle in the Sudan substantially protected against the disease, but again did not totally prevent infection (BUSHARA et al., 1978).

Non-living parasite vaccines. Killed whole Leishmania parasites, used in human trials in Brazil, gave a promising degree of protection and, most importantly, did not exacerbate disease. Localized cutaneous leishmaniasis may also be susceptible to immunotherapy; 3 treatments with killed L. mexicana plus BCG (bacillus Calmette-Guérin), over a period of 32 weeks, achieved similar cure rates to chemotherapy and induced fewer side effects (MODABBER, 1989).

Novel vaccines under investigation

Antigens of killed parasites generally stimulate low levels of protective immunity, despite provoking a variety of antibody- and cell-mediated responses. In particular, many of the antibody responses are similar to those produced in resistant hosts following natural infection, but are evidently without protective power. The most popular explanation for this is that the key ‘protective’ antigens are present in only small amounts, and are perhaps masked or competed with by ‘non-protective’ antigens present in larger quantities (TERRY, 1968). Accordingly, many workers have attempted to identify antigens which induce protective immunity and, using the new tools provided by molecular biology, to produce them in quantities suitable for vaccination. Early findings on the efficacy of such vaccines will now be reviewed.

Malaria vaccines in man

Amongst eukaryote parasites, malaria has attracted the most vigorous effort in respect of vaccination (G. H. MITCHELL, 1989). Immunity does develop in man following natural infection, but takes some time to become manifest; a number of small animal models of disease also demonstrate good resistance. Three life cycle stages have attracted attention as potential...
targets: the infective sporozoite, the blood stage merozoite and the gametocytes. Interestingly, all 3 stages possess surface molecules characterized by repetitive epitopes, which a priori might be expected to be highly immunogenic. However, the results of human trials so far, although not without promise, indicate that much still remains to be done.

Circumsporozoite protein (CS) vaccines. CS-derived subunit vaccines against *P. falciparum* protected only 2 of 9 volunteers in each of 2 separate trials, although patency was delayed in all volunteers compared to controls. Disappointingly, further doses of vaccine failed to boost antibody titres, and lymphocytes from vaccine recipients failed to proliferate in response to CS antigens. Perhaps importantly, it was subsequently demonstrated that CS failed to stimulate T cell proliferation in up to 40% of adults from regions of Africa where malaria is endemic (Good et al., 1988).

Merozoite vaccines. Sequences based upon fragments of PMMMA (precursor of merozoite major surface antigen) and RESA (ring-infected erythrocyte surface antigen), combined into a hybrid vaccine, achieved a similar level of success to that recorded in the CS vaccine trial: 3 recipients were totally protected, although most volunteers showed modification of disease. Neither pre-challenge antibody levels, nor lymphocyte proliferation assays, correlated well with the outcome of this trial.

Gametocyte vaccines. Antigens which induce transmission blocking immunity would be a very useful and perhaps essential feature of anti-malarial vaccines. Some promising results have been obtained in experimental rodent infections but, again, unresponsiveness has been demonstrated in both mice and men to defined gamete surface antigens (Good et al., 1988).

Experiments with rodent malaria have highlighted the importance of cell-mediated immunity in these infections. Thus, in *P. chabaudi* adami infections, B cell deficient mice resolve the infection, and ‘immune’ B cells fail to transfer protection to naive recipients. Conversely, a transfer of immunity is achieved with T cells of the helper phenotype and with an antigen-specific IL-2 expanded T cell line (Good et al., 1988). It now seems clear that successful anti-malarial vaccines can be designed only through detailed insight into the nature of protective immune responses. Such vaccines will need to stimulate cell-mediated immunity to cope with initial attacks, and perhaps memory cells to fend off subsequent infections. They will also need to be effective against the various life stages of the parasite and be made up either of mixtures of antigens or perhaps hybrid antigens.

Other novel anti-parasite vaccines

Progress in the development of ‘designer vaccines’ against parasites other than malaria lags behind and will be reviewed only briefly.

Schistosomiasis. A variety of animal hosts has been successfully immunized against schistosomes, using either radiation-attenuated larvae or defined antigens, but the levels of protection achieved are so far insufficient to warrant human trials (McLaren & Smithers, 1987; Sher et al., 1989). Of the many candidate immunogens tested, the most promising have been glutathione-S-transferase (P28), GP38, a membrane glycoprotein sharing homology with nema-tode myosin, paramyosin (Sm 97), and GP18, a stably expressed surface antigen. These defined antigens stimulate less resistance than radiation-attenuated parasites, however, even when presented as ‘cocktails’. Again, much remains to be learned about the nature of protective immunity to schistosomiasis, in particular the role of T cells. However, some schistosome enzymes, such as glutathione-S-transferase, may serve as targets for biochemical as well as immunological intervention (Mckernow & Doenhoff, 1988).

Firoplasms (Babesia and Theileria). For these parasites what is needed is improvement of the vaccines already available. Protective antigens are being identified through the use of monoclonal antibodies and recombinant deoxyribonucleic acid technology is being explored. The antigenic and genetic polymorphism shown by both groups may, nevertheless, hamper progress (Morrison, 1989).

Coccidia. These important parasites of poultry have hitherto been controlled by chemotherapy, but increasing drug resistance has led to serious consideration of immunological intervention (Long & Jeffers, 1986). Attenuated lines of parasites have been developed and a genetically engineered *Eimeria tenella* antigen has given some degree of protection. A particular problem in this industry is that a vaccine must be capable of mass rather than individual administration and should cost no more than a few pence.

Leishmaniasis. Animal models of leishmaniasis are now under intensive study (Mobarre, 1989). Antigens of particular interest are based on a promastigote surface protease (gp63) which is considered to promote binding of the parasite to host macrophages (Greenblatt, 1988). Resolution of these infections requires stimulation of effective cell-mediated immunity, but not such as to produce unacceptable inflammation. Cutaneous leishmaniasis may be more susceptible to immune control than the mucocutaneous and visceral forms.

Hookworms. Proteases released from *Ancylostoma caninum* have now been characterized and put forward as candidate vaccines (these probably represent the ‘secretory nematode antigens’ which so concerned workers in the 1950s and early 1960s). ‘Concealed’ antigens have also been suggested as conceptual targets for vaccines (Fritchard et al., 1988). This strategy envisages a primary attack against cuticular surface epitopes and a ‘follow-up’ attack directed against deeper and normally concealed collagens that are crucial for maintenance of cuticle structure.

Ticks. Besides being responsible for transmission of *Babesia* and *Theileria*, ticks are themselves major parasites of livestock. Calves inoculated with ‘concealed’ antigens prepared from the dissected midgut of *Boophilus microplus* showed more than 80% reduction in tick burden at challenge and the ticks themselves exhibited gut damage (Willadsen & Kemp, 1988).

Trypanosomiasis. Molecular biologists have made impressive progress in unravelling the complexities of antigenic variation in African trypanosomes, but the enormous antigenic repertoire coupled with the parasite’s ability to switch antigen synthesis surely rule out conventional vaccines. Efforts in this field may yet, however, yield profit. If, for example, a drug could be devised to interfere with antigen switching, trypano-