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## Historical perspectives

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One of the more satisfying sequelae arising on being asked to address this distinguished group on “Historical perspectives” is the realization that you are finally dead, passé, even extinct, fit only to be placed in a display cabinet in the museum where the curious scientist can stare and wonder why and how did such a person become involved with all that dated stuff on transmission of schistosomiasis, its chemotherapy, snail control, health education, installation of safe water supplies and sanitation and all the public health trappings of parasitic disease control. This realization is doubly satisfying since the removal to museum status allows one time to go ahead and control schistosomiasis, untrammelled by the enormous mass of accumulating data, often on a weekly basis, on the immunological brave new world of this parasitic socio-economic cultural syndrome.

There has never been any doubt that immunity exists in schistosomiasis. Fujinami, in the *Kyoto Medical Journal* in 1916 noted that uninfected persons entering an endemic *S. japonicum* district became very ill, while the local inhabitants, at any rate the older ones, were less ill. He found the same thing happened among calves, which became resistant in their second year. Mohammed Bey Khalil's Bibliography of schistosomiasis, published in 1931, contains 2649 references of which 5 or 0.19% were on immunological topics containing such evocative titles as R. G. Archibald, 1914, *British Medical Journal*, “Intestinal schistosomiasis in the Sudan, with notes on the treatment of two cases by means of autogenous vaccines of coli-like organisms”; or Neil Hamilton Fairley, 1919, *Journal of the Royal Army Medical Corps*, “The discovery of a specific complement-fixation test for bilharziasis and its practical application to clinical medicine.”

As an aside, I still visit the Sudan at least once a year and have done so for the last quarter of a century, where we are currently struggling to control *S. mansoni* in the Gezira/Managil area of 2 million feddans where preintervention

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tion prevalence is 70% and advanced morbidity so common that one third of local hospital beds are occupied with complications of schistosomiasis.

In one of the best books ever written on schistosomiasis, in 1934, that by Rameses Girges, who spent his clinical life at Tanta, in the centre of the Egyptian delta, he noted that the Editor of the *Lancet*, who was commenting on the work of Fairley and his co-workers on infections of goats with *S. spindale* said: "Every animal has a restricted range in the world, and every parasite is equally restricted within its small world – its host. The restriction of free-living animals is in no way due to the presence of chemical anticonditions in other parts of the world, but to the absence of specific proconditions in those in which they prosper. There is nothing to suggest that this general principle does not hold for animal parasites, including schistosomes, or that the antibodies which appear in the host are in any way inimical to the parasites, and do not merely serve to neutralize their toxins, for, as has been noted, these antibodies remain in high titre at a time when further decrease of the fluke population is held to have ceased."

Girges also asked: "Is there an immunity in schistosomiasis?" and commented: "The presence of a partial immunity or a state of allergy in schistosomal patients cannot be denied. The reasons for believing its presence are manifold. First by the complement-fixation test the presence of immune bodies was proved beyond doubt; secondly the leucocytosis, fever and wheals (urticaria) prove a reaction against foreign proteins, and thirdly the disease is more prevalent amongst young people, 85 per cent of my patients being between the ages of 15 and 30. This, together with the low mortality amongst schistosomal cases in spite of the gravity of the malady and the subsidence of the symptoms of the disease as the case becomes more chronic, shows that the fellaheen acquire an obvious immunity through their infection in the early part of their field life. Though individuals can be infected during the first weeks after infestation, it is probable that the patient in the first or toxæmic stage, a few weeks later, when the worms become mature, can more or less resist infection. The cercariae, though succeeding in piercing the skin, find the blood medium unsuitable for the continuation of their growth. If there were no immunity frequent exposure to infection would result in the presence of a massive number of worms, and this, combined with the longevity of the worms (15 to 25 years) would have made the life of the victim an impossibility. For suppose the fella was exposed to infection on an average twice a week during the infection season, beginning in April and ending in October, that is more than six months, he would then be exposed about fifty times a year, and each time receiving fifty cercariae; in fact, I counted as many as 130 to 150 papules on the skin of some of them, each representing the entrance gate for one larva; then he would receive at least 2,500 worms a year, and not less than 100,000 during the forty years of field work, which is incompatible with life and has never been recorded; the greatest number ever observed did not exceed 400, although in my opinion it reaches one

to four thousand. This massive infection is particularly present in Egyptian splenomegaly.”

In 1934, Fisher’s work in the Congo demonstrated, by means of induced human infections that, in *S. intercalatum* infections, a high degree of resistance to infection is present in adults over 35 years of age.

Moving over the years, Newsome, one of the most original thinkers on the problems of schistosomiasis said in 1956, in a discussion on fluke immunity: “Nearly all the lines of work suggested have of necessity been in animals. It cannot be too strongly emphasized that the results may be no more than pointers to what may happen in man. Working with animals has well-known drawbacks, the chief of which is that a parasite of man is being studied in an unnatural host. Although this is perhaps not the case in *S. japonicum* work, investigations on small animals infected with *S. haematobium* and *S. mansoni* should not be expected to give final answers to problems of schistosomiasis in man.”

One of the more recent workers who has not yet quite passed into historical perspective, Smithers, said in 1962: “It is generally agreed that a number of years must elapse before a protection develops in man which is effective in limiting symptoms. There is, however, little conclusive evidence as to the degree of resistance which can be attained, and there is only speculation on the conditions which favour the build up of resistance. There is need, and ample opportunity in endemic areas, for further observations and experiments on this aspect.”

I shall skip the next 25 years which saw, indeed, further work, the introduction of sociological and behavioural studies and the arguments on the relative importance of acquired immunity and diminished water contact in the genesis of the epidemiological age, prevalence and intensity picture.

We now arrive in the mid 1980s – some 70 years after the first description of “immunity” – and in reading one of the latest schistosomiasis updates, I notice 148 articles on immunology in a total of 517 reviewed, i.e. 28.2% – a quantum proportionate leap from the 0.19% of Khalil.

Further, within the last year, I have read:

1. A conference report on the molecular biology of schistosomes, with heavy emphasis on the objectives of recombinant DNA technology.
2. A symposium in Parasitology, 1986, on the application of molecular biology in parasitic diseases with stress on the cloning of schistosome genes and the use of recombinant DNA technology to helminth identification, and
3. the May 1986 issue of the Journal of the Royal Society of Medicine containing the report of the Section of Clinical Immunology and Allergy on Immunology and Molecular Biology of Schistosomiasis in which epidemiological data were reviewed with their evidence thought to be suggestive of a protective immunity together with detailed studies of the micro-phenomena of the varieties of immune response and the progress made towards the production of vaccines.

To the clinical scientist, the phenomenon of protective immunity has never been in doubt, from 1916 onwards. What has been, and is, in doubt is its

specificity, its duration, its capacity against high cercarial exposure and the stages against which it is effective.

I look forward in this meeting to hearing of the further recent advances but leave you with the words of one pre-museum piece, George Nelson, who, in opening the British Parasitology Symposium uttered these wise words:

“Molecular biologists and immunologists working with parasites may have the satisfaction of winning a scientific race but, unless they are in close contact with the problems in the field, they will become frustrated and disillusioned if their elegant diagnostic tools and synthesized vaccines remain on the shelf whilst the parasites continue to take their toll in the countries which cannot afford or are not prepared to use the new tools. We must not be deceived into believing that what is of value in diagnosing or preventing parasitic diseases in London or Liverpool is necessarily what is required in Lucknow or Lahore.”

“There are more serious problems relating to the use of antiparasitic vaccines. Some progress has been made in developing partially effective anti-parasitic live vaccines in veterinary medicine but always at some cost in terms of morbidity and some degree of breakthrough. Vaccines against human parasites will have to be much more effective and long acting if they are to replace or even supplement chemotherapy, vector control and environmental sanitation in campaigns aimed at reducing the public health importance of malaria, schistosomiasis, filariasis and other parasitic diseases of man. So far the only vaccine which has proved highly effective in control campaigns against tropical diseases has been the yellow fever vaccine and it is not generally realized that smallpox eradication was not achieved by vaccination alone but mainly by the old-fashioned methods of surveillance and isolation. Even where vaccines have been developed, for example, against typhoid, cholera, plague, measles and tuberculosis, they have had very little impact on the prevalence of these diseases in the tropics. Other measures have proved to be far more effective. The same is true of some of the parasitic diseases. In some areas vaccines could be superfluous.”

“I believe that with few exceptions, for example, the protection of special groups like tourists or troops operating in endemic areas that vaccines against parasitic infection are unlikely to be anything other than adjuncts to other control measures. They may be important adjuncts for the prevention of reinfection in areas where other control measures have reduced transmission but in the longer term the control of parasitic and vector-borne diseases will depend on modifying the environment and human behaviour or by interfering with the vectors.”

These remarks, far from being meant to discourage basic scientists, are, as I interpret them, a stimulus to marry the highest technology of molecular biology with the operational constraints of an economically depressed world. I wish you luck.

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