The Persistent Challenge of Tropical Parasitic Infections

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Like Dr Leonard Rogers, Milroy Lecturer for 1907, I consider my appointment as being 'due to a desire on the part of this College to recognise the work now being done in the investigation of tropical diseases'[1]. In choosing my subject I have been guided by Milroy's suggestions for the lectureship in which he wrote, 'There is a vast amount of protracted malaise and suffering, disablement, or lessened capacity for industrial work, and often, too, of slow but eventually fatal sickness, in almost every region of the world. . .'.

In many parts of the tropics, malaria and other parasitic infections remain major causes of disease, death and disability, killing some, maiming others and, in a variety of ways, limiting the scale and scope of human endeavours and often denying man the full enjoyment of the fruits of his labour and enterprise. Even where the diseases have been eliminated or controlled, they continue to exact a toll by requiring that vigilance be maintained indefinitely to offset the ever-present risk of resurgence or re-invasion. These diseases present problems that confront individuals, communities and governments in the developing countries of the tropics.

In the efforts to control these infections, the successes in some places have been as dramatic as were the failures in others. The overall picture is of the persistence of the challenge—with the parasites displaying an arrogant defiance to attempts to bring them under control and confounding optimistic forecasts that they would fade away. The challenge posed by these infections can be examined at three levels: the community, the clinical state and the cells and tissues.

Community

In extreme cases, the impact of tropical parasitic diseases can be devastatingly obvious, even determining the course of history. There is the familiar example of the role of these diseases in deterring, in fact preventing, European settlement in West Africa[2]. River blindness resulting from infection with *Onchocerca volvulus* caused the depopulation of large tracts of arable land in Africa[3]. The waxing and waning of epidemics of African sleeping sickness in endemic foci have had a similar devastating effect on many communities in Africa[4]. Epidemics of kala-azar in India caused '. . .a decrease in population of the affected tracts and the falling out of cultivation of much land. . .'[1].

It is more difficult to assess the specific contributions of individual parasitic infections in the typical situation, where the community is afflicted by a variety of parasitic and other infectious diseases, often compounded by malnutrition[5].

The specific contributions of individual infections can be teased out by using case-control studies and multiple regression analyses. The situation is further complicated by the interactions that occur in cases of concurrent infections as, for example, the peculiar syndrome of chronic typhoid infection in association with *Schistosoma mansoni* infection[6].

Dr Morrow and his colleagues have devised and tested a quantitative method for assessing the health impact of different diseases in less developed countries, based on the concept of the number of useful days of life lost[7]. This single index adds the deleterious effects of different degrees of disability to the losses due to premature death. Morrow's approach and similar ones require a conceptual leap to set up a table of equivalence between deaths and morbidity in clinical cases. One must take this leap in order to be able to compare the impact of diseases like malaria, which is a major cause of death in children in the highly endemic areas, with that of leprosy, which is a chronic disabling disease.

In order to determine the full impact of these parasitic infections, it is important to recognise and assess their indirect effects on the community. Dr Molineaux of WHO[8] recently reviewed three methods of estimating the number of deaths caused by malaria in highly endemic areas:

(a) Deaths attributed to malaria.

(b) Reduction in death rates on specific anti-malarial control.

(c) The distribution of the sickle cell gene.

These approaches have yielded estimates that are conflicting and internally inconsistent. The number of persons recognised as dying from the classical manifestations of malaria grossly under-estimates the total mortality due to this infection. Some of the difference is accounted for by the indirect mortality caused by the infection. For
example, Gigioli[9] noted that, following the eradication of malaria in Guyana (a) the decline in the general mortality greatly exceeded the fall in mortality specifically related to malaria; (b) in infants, there was a marked fall in prematurity, and (c) in adults there was a marked fall in deaths due to chronic nephritis and chronic respiratory disease; the decline continued for some 10 years after the registration of the last death from malaria.

Since Gigioli’s observations, the syndrome of nephrosis in association with Plasmodium falciparum infection has been more clearly defined by studies in Nigeria[10]. Malarial infection is also associated with immunosuppression, but it is not clear to what extent this phenomenon aggravates the morbidity and enhances the mortality of other concurrent infections.

Analysis of the distribution of the sickle cell gene gives the highest estimates of the mortality due to falciparum malaria. If it is assumed that malaria is the only selective factor conferring the advantage to AS heterozygotes, then the high sickling rates of 10-20 per cent in some African populations suggest that as many as 20 per cent of the subjects with normal haemoglobin, AA, die of malaria in childhood.

Onchocerciasis provides another example of the need to include indirect effects in estimating the impact of tropical parasitic infections. In a prospective study of adults (30 or more years old) living in an endemic area of onchocerciasis, Prost and Vaugelade[11] found that the mortality rate among the blind was four times greater than among non-blind; such excess mortality would not normally be attributed to onchocerciasis but it clearly represents a significant element of the burden of disease. In addition, there is clinico-pathological evidence of renal pathology in association with onchocercal infection but there has been no proper appraisal of the contribution of this renal complication to morbidity and mortality on a community basis.

If epidemiologists are having difficulties in assessing the health impact of these diseases, the methodological difficulties in assessing the economic impact are even greater, but social scientists have made brave efforts to tackle this difficult area[12].

It is well recognised that these diseases have their maximum impact in the developing countries of the tropics. This association has misled some to assume that the more significant association is with development rather than with the ecological effects of climate. Some have promulgated the doctrine of spontaneous regression, suggesting that these diseases would fade away, as they did in Europe, under the pressure of social and economic development or in response to broad non-categorical measures such as personal hygiene and environmental sanitation. To overlook or underplay the role of climate is a dangerous over-simplification. After all, there was no onchocerciasis in Oslo, no sleeping sickness in Siberia, and no schistosomiasis in Stockholm.

Even though malaria did occur in colder climes, its incidence was miniscule and its impact trivial compared with the intensive transmission in the tropical belt, especially in tropical Africa where it is deeply entrenched. In England, at its worst malaria was estimated to kill 8 persons per million population per annum; compare this with the estimated 10-20 per cent of children in Africa dying of falciparum malaria[13]. Not to recognise this enormous difference in scale would be tantamount to equating a raging tornado with a storm in a teacup. Added to the development equation is the fact that man-made lakes, irrigation schemes and similar agro-engineering projects tend to extend and intensify the transmission of malaria and schistosomiasis.

Clinical State

The clinical features of malaria and other parasitic infections have been so well described that this mass of information tends to obscure our deep ignorance of the subtle features of the host/parasite relationship. For some of these infections there is a wide spectrum of clinical manifestations ranging from asymptomatic or mild cases at one end to acute life-threatening illness or chronic crippling disease at the other extreme.

What factors determine the position of the individual patient in the clinical gradient? For some helminthic infections the severity of the disease can be correlated with the number of worms in the particular patient. Thus, in hookworm infection, there is a correlation between the load of infection, the intake of dietary iron and the occurrence of anaemia. In a series of elegant studies on schistosomiasis, Cheever and his colleagues[14] have shown the correlation between the egg count in the tissues, the number of worms recovered at autopsy and the severity of the pathological lesions; but there was still a considerable amount of variation in the severity of the pathological lesions at each level of intensity. In Schistosoma haematobium infections, there is a correlation between the load of infection, as measured by the egg count in the urine, and the lesions shown on radiological examination. In Ibadan, Nigeria, our findings suggest that in the natural history of this infection there is a crucial stage of reversible obstructive uropathy; but as yet there is no clue to the factors that determine the outcome either in the direction of relief of the obstruction or of irreversible damage[15].

Similar problems are encountered in the filarial infections. In lymphatic filariasis, only a proportion of those infected show lymphoedema. Although some of the immunological differences between these types of patients are being described, we do not know why some patients develop swollen limbs but others do not. Similarly, in onchocerciasis there is some correlation between the severity of the anterior lesions of the eyes and the intensity of infection as measured by the microfilarial count, but the risk factors associated with the posterior lesions have still to be identified.

In 1908, Carlos Chagas made the important discovery of the parasitic infection that bears his name. He found the parasite Trypanosoma cruzi in the blood of a two-year-old girl Berenice[16]. In 1961, at the age of 53, Berenice still showed immunological and parasitological evidence of the infection but there was no evidence that she had developed any of the cardiac or gastrointestinal lesions normally associated with this infection. She died in June
1981 at the age of 73 with a form of heart disease but probably not Chagas’ disease. Whereas Berenice lived in peaceful co-existence with Trypanosoma cruzi for over 70 years, there are countless others infected with the same organism whose damaged hearts and other organs show the battle scars of the confrontation between host and parasite and in whom the infection traces a relentless downward course of chronic disease and disability, leading inexorably to premature death. Why the difference? There are many theories and suppositions as to factors in the parasite, in the host or in some incompatibility in their relationship which determine the nature and the intensity of the struggle as well as its outcome; in most cases we are still groping in the dark.

Therefore, it is not surprising that the management of patients tends to be based largely on the stereotyped approach of killing the parasites with drugs. The current crude chemotherapeutic approach, with the single-minded aim of killing the parasites, is associated with the twin hazards of the toxic effects of the drugs and the reactions of the host to the decaying mass of the dead parasites. It is conceivable that if and when we know more about these subtle relationships, we could devise treatments which could be more suitably tailored to the needs of individual patients; we could decide whom to treat, when to treat, what drug to use, not merely to kill the parasites, but, more specifically, to modulate the host/parasite relationship in favour of the host.

New techniques bring the hope that light can soon be shed on these dark areas. For example, with the use of monoclonal antibodies and gene probes, it is now possible to define more precisely the strains and species of the parasites of man. In the case of Chagas’ disease, studies are under way to correlate the genetic variations of the parasite with the clinical epidemiological features of the disease. Immunological and genetic studies of the host may also provide useful clues. New imaging techniques and other non-invasive diagnostic methods should make it feasible to study the evolution of the pathological lesions and their response to various types of treatment. With this new information, we would gain a better understanding of the clinical challenge and this should lead to a more rational management of infected persons.

**Cells and Tissues**

New powerful research tools of various basic biomedical disciplines have led to a major explosion of knowledge of living cells, their membranes and their constituent organelles. Parasitology has benefited from these advances. Immunologists, molecular biologists, biochemists and geneticists are expanding our knowledge of the parasites and their relationships to their hosts at the level of cells and tissues. I wish to highlight three important aspects: host/parasite relationships; vaccine development, and new drugs.

**Host/Parasite Relationships**

Except for Entamoeba histolytica which is truly carnivorous, most parasites do not display specific aggression towards the host. Their activities seem to be directed towards the achievement of the four cardinal requirements of parasitism: to multiply, to emerge from the host, to find a new host and to infect it.

In the course of these events, damage to the host is usually incidental, and is, as often as not, due to the misguided attempts of the host to evict or destroy an inoffensive but persistent guest, or else to inappropriate reactions of the host to the dead or dying parasites, their eggs or other products.

It is fascinating to discover the intimate details of the mechanisms by which these organisms adapt to parasitic existence, how they exploit the available resources within the host and how they protect themselves in what is clearly a hostile environment. Take, for example, Plasmodium falciparum, whose biology has been intensively studied since its continuous in vitro culture was achieved [17]. It has devised mechanisms for dealing with the aggressive immune responses of the host. With regard to humoral immunity, the parasite protects itself by several mechanisms, some of which are not fully understood. These include antigenic variation and the occurrence of changes in the antigenic structure of the parasite as it switches from one stage to the other. The overall effect is to present the host with an antigenic ‘smokescreen’ obscuring the most significant antigens that could provoke protective immunity. Its sequestration in liver and red cells at crucial stages of its development provides additional routes of escape from the host’s immune system.

With regard to cellular immunity, the phenomenon described by Udeinya et al. [18] suggests a mechanism by which falciparum avoids destruction by the reticuloendothelial cells in the spleen and elsewhere. At the stage when the infected red cells are most clearly recognisable as foreign elements and the mature schizont is therefore most susceptible to the scavenging action of the spleen, the parasite extrudes knobs, covered with a histidine-rich protein, that specifically adhere to the endothelial cells of bloodvessels. This sequestration of the mature schizont is one of the mechanisms by which falciparum malaria builds up a level of parasitaemia far higher than that achieved by the freely circulating malarial parasites of other species.

**Drug Resistance**

The apparently unlimited capability of falciparum malaria to deal with the challenge of anti-malarial drugs is remarkable. The parasite has had thousands or even millions of years to adapt to the immune responses of the host; in fact, this is a prerequisite of successful parasitism. But in the short space of a few years, falciparum malaria has devised metabolic answers to the challenge posed by practically every anti-malarial drug that has been extensively used. The parasite has developed resistance to pyrimethamine, proguanil, chloroquine and other 4-aminoquinolines, to combinations of pyrimethamine and long-acting sulphonamides, and even to quinine, which is regarded as a general protoplasmic poison. The success of falciparum malaria may eventually be traced to mecha-
Vaccine Development

Attempts to develop vaccines against malaria and parasitic diseases have encountered four major problems.

1. Natural infections do not confer a lasting immunity.
2. Parasites possess a wide variety of mechanisms to evade and/or compromise the host's immune responses.
3. Parasites are large complex organisms as compared with the viruses and bacteria against which successful vaccines have been developed.
4. Problems with in vitro culture and the lack of appropriate animal models have made it difficult to manipulate parasites in the laboratory.

Natural Infections. With most of these parasites, natural infection confers no immunity or at best an incomplete protection. Even though most parasitic infections do not confer sterilising immunity, subsequent attacks may be clinically less severe; for example, patients recovering from amoebic liver abscess are unlikely to develop this complication when reinfected[19]. Falciparum malaria provides an even more striking example of the way in which repeated attacks of infection modify the severity of the clinical manifestations and the outcome of the illness. In areas of intensive transmission of falciparum malaria (the so-called holo-endemic areas) adult males and non-pregnant women become immune to the severe complications of the infection; in particular they have absolute immunity to cerebral malaria, even though some complications tend to occur during pregnancy. Pre-school children, pregnant women and foreigners are highly susceptible and tend to develop fulminating, rapidly progressive disease[20].

This immunity from cerebral malaria is lifelong, persistent after long absences from the endemic area, and passively transmitted to the fetus, providing protection against cerebral malaria during the first few months of life. The host achieves an accommodation with the parasite—not total victory but a sort of armed truce.

The knowledge that the adult male inhabitants of holo-endemic areas can stand up to falciparum malaria was exploited in the deployment of West African soldiers to fight in Burma during the Second World War. Falciparum malaria provides a convincing case that man is able to mount some degree of protective immunity to parasitic infections. The immunity develops slowly and the protection is not absolute but it is nevertheless clinically and epidemiologically significant. The response to malaria is not typical of all parasitic infections; it is but one example of the many variations of the complex relationships between man and his endo-parasites.

Evasion of Host Immunity. Parasites evade host immunity by hiding in safely secluded places in the body of the host, sometimes finding refuge in the most unexpected places, e.g. Leishmania organisms in macrophages; hypnozoites (the dormant phase of P. vivax) in hepatocytes.

Some parasites are able to escape from the host defences by manipulating their antigens. Each developmental stage of the parasite in man is usually associated with different sets of antigens. This stage specificity keeps the parasite one step ahead of the specific immune response of the host. Antigenic variation is another phenomenon by which some parasites, notably the blood stages of African trypanosomiasis and falciparum malaria, escape the host defences. Schistosome worms adopt antigenic disguise by acquiring a surface coat of host antigens.

Host Responsiveness. Parasites undermine or compromise the host’s defence mechanisms by various mechanisms. These include immunosuppression, antibody cleavage, complement consumption, the formation of circulating immune complexes, and polyclonal lymphocyte activation. Some of the parasitic infections provoke clinically significant immunopathological effects including anaphylactic, cytotoxic and delayed hypersensitivity reactions, as well as lesions associated with immune complexes. It is important to identify the antigenic components of the parasites provoking these undesirable effects so that they are excluded from the candidate vaccines.

Size and Complexity of Parasites. Parasites are large and complex organisms. Modern immunological techniques for purifying and characterising antigens, in particular monoclonal antibodies, have provided immunologists with precision tools for dissecting parasite antigens, a means of separating the wheat from the antigenic chaff.

In Vivo/In Vitro Culture. For many of these parasites there are no satisfactory animal models. It is also difficult to extrapolate to man the results obtained from model parasites in surrogate hosts. In vitro culture techniques have improved, particularly for the blood stage of falciparum malaria, Trypanosoma brucei, and some filarial worms[21].

Methods are being devised for the production of the specific antigens in quantities sufficient for laboratory tests, clinical trials, field trials and eventually for operational use. Three main approaches are currently being explored: (a) splicing the parasite gene material into Escherichia coli; (b) determining the sequence of amino acids in the reactive sites of the polypeptide chains and synthesising them, and (c) the use of live carriers, e.g. the vaccinia virus.

There is now an atmosphere of cautious optimism about recent steady progress leading to the development of vaccines against some of the major parasitic diseases of man. The most exciting progress has been made in the search for malaria vaccines. Candidate antigens have been identified for three developmental stages of the parasite—sporozoite, merozoite and gamete stages. If the present progress is maintained, clinical trials of a malaria vaccine may start within the next few years, and others are likely to follow[22].
Drug Development

Until recently, the strategy for the development of anti-parasitic drugs was based on screening natural and synthetic products; more often than not they were discovered through fortunate accidents. In the case of herbal remedies, from quinine to Qing-hao-su, we were literally borrowing a leaf from nature, or perhaps a root or a bark. We are now moving into the era of the rational development of anti-parasitic drugs based on the identification of leads from comparative biochemistry. The study of the metabolic pathways of the parasites is revealing likely targets for therapeutic attack.

(a) Trypanosoma brucei, like other haemoflagellates, is highly vulnerable to agents that interfere with polypeptide synthesis. This clue led to the screening of specific inhibitors of ornithine decarboxylase and the identification of di-fluoro-methyl ornithine (DFMO) as a likely drug for the treatment of African trypanosomiasis.[23]

(b) The scavenger pathway utilised by Leishmania organisms instead of de novo purine synthesis led to the testing of allopurinol and its riboside for the treatment of Leishmaniasis.[24]

(c) Peculiarities of the folate metabolism of the filarial worms may provide a suitable target for chemotherapeutic attack in filariasis.[25]

These new approaches promise the development of anti-parasitic drugs that are more potent, more selective and specifically targeted by using lysosomotrophic agents or suicide substrates, or that can achieve special effects, e.g. blocking the receptors on host cells, reducing egg production in worms, or disrupting the trigger mechanism for antigenic variation. It should then be possible to banish such notorious poisons as arsenic and antimony from the pharmacopoeia of tropical medicine.

Conclusions

We have three ways of responding to the challenge of persistent parasitic disease.

Biological. The biological responses of the host include a variety of immunological defence mechanisms, both humoral and cellular. Genetic factors are also important, as in the case of the high prevalence of the sickle cell gene in areas of endemic falciparum malaria; there are other genetic markers, such as glucose-6-phosphate dehydrogenase deficiency, whose relationships to parasitic infections are less well defined.

Behavioural. Changes occur as part of the adaptation in endemic areas, an extreme reaction being the total abandonment of areas that are heavily infested with infections such as onchocerciasis or sleeping sickness.

Biomedical, or the deliberate fashioning of weapons of offence and defence against the parasite invaders and their vectors. In recent years there has been an intensification of biomedical research on parasitic diseases and it is hoped that the discoveries will widen the range and effectiveness of our armamentarium of anti-parasitic weapons to include vaccines, drugs with novel properties, powerful diagnostic methods, and innovative vector control measures, including biological control.

If these expectations are realised in the coming decades, if the public health services in the endemic countries can be equipped with these new weapons, and if their strategic plans for controlling these diseases can be based on sound epidemiological analyses with inputs from the appropriate social sciences, we can confront the persistent challenge of malaria and other parasitic infections with a reasonable hope of attaining greater success than in the past.

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