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THE HOST-PARASITE RELATIONSHIP IN AMOEBIASIS*

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An understanding of the relationship between *Entamoeba histolytica* and man implies an appreciation of many factors in host-parasite relationship, and some understanding of the whole question of association between members of different species.

Since the beginning of time living things have been constantly in contact with other living things, either of their own or some other species, and it is not surprising that over the course of aeons some of the associations have become permanent and obligatory. In some cases they have become so close that it is almost impossible to distinguish one partner from the other. The progress has been taken by steps so infinitesmal that it appears to have been continuous, but it has been evolutionary and associated with modifications of habit and of structure just as in evolution generally.

Some species associate regularly with their own kind—man for example is a gregarious animal—others associate with species other than their own. A well-known example is the herding together of zebra and wildebeest, that one may see in the game reserve, but there are many others. It may be that zebra and wildebeest merely like the same food and country, but there might be a more romantic reason—such as mutual protection. A wander along our coasts will reveal many examples of association between different species. Sometimes, this is mere inquilinism—a sharing of the same home—and such close association may give rise to malpraxis and dichotomy. The hermit crab uses a mollusc shell as a home—a home which may be disguised by sea anemones. The crab has no objection and the anemones gain by the additional mobility. Some crabs have taken advantage of the poisonous nature of the anemone and use them to stun fish, making them easier to capture. It is not all one way, for the crab may find that he has a lodger in the shell in the form of a nereid worm which, while it does not attack the crab, steals the food from between its very jaws.

Invasion of the bowel

It is no great step from such association to invasion of the intestine; a pioneering adventure which undoubtedly first took place by chance, but one of which the newcomer was quick to take advantage. He soon realized the delights of a plentiful supply of food and a controlled environment. Adaptation soon followed, even though it imposed the difficulty of getting from one host to the next. Such parasites, many of whom are only parasitic in that they live inside another species do but little or no harm to the host—and as you well know—the host may take advantage of their presence and make use of their metabolism. From such mutual advantage arose the phenomenon known as symbiosis, which in some pairs of species has developed to the extent that neither can do without the other. An interesting example, of local importance, is the association between *Cryptotermes brevis* and its intestinal protozoa. *Cryptotermes*, though it eats the woodwork of our homes, cannot digest cellulose and for this process is dependent upon the micro-organisms in its bowel. If these are somehow destroyed the termite will starve. Larval termites are fed with faeces by the adults in order to set this process in action. Man and other animals too are very dependent on their intestinal inhabitants for such processes as the bile cycle and vitamin-B synthesis. Despite our aesthetic objection to such invaders we cannot do without them.

Some invaders, however, make no evident contribution to the general good and, though most are merely robbers of food, some have so transgressed the rules of hospitality as to invade their hosts further. This invasion may be minimal, as exemplified by the tapeworm, whose attack is confined to its anchor in the turbulent environment in which it lives.

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That invasion may go a trace further without much damage to the host is exemplified by *Trichocephalus*, which usually does not make itself felt until there are thousands of worms. The next phase may be illustrated by the hookworms, whose habit of nibbling the mucosa may lead to a loss of blood which, taken the world over, has been estimated at some 500 tons a day, but with which the average individual can cope by adequate nutrition.

Invasion of the blood stream

Parasites can and do go further. The bilharzial worms have found that the portal vein—that *cloaca maxima*—provides even better accommodation. The adults, while alive, do not appear to do much damage, and the haemorrhage caused by the passage of the eggs is but slight. The main damage done by such a parasite follows sensitization and over-response of the host and, though cases may appear numerous, this occurs in but a small proportion of cases of a widespread condition.

Parasites by their mode of life have been able to dispense with organs and processes which would be necessary for an independent existence. Perhaps the most extreme example is illustrated by *Sacculina* in the crab. This copepod, in its adult stage, has discarded all its organs except those of sex and depends on its host for everything, including its hormones.

On the other hand, adoption of a parasitic existence has not been without its complications. Passage from one host to the next may require most involved processes and may necessitate the use of one or more intermediate hosts. For example, *Diphyllobothrium latum*, the broad tapeworm, passes first through Cyclops and then through fish after fish until it reaches its final host. The development of so complex a cycle illustrates not only the devious routes by which some parasites attain their ultimate host, but also two other points: Such a process must have taken a very long time to evolve and, equally, it must be very easily deranged.

Malaria, that parasite most destructive of man, probably started out as a parasite of the insect gut. Other sporozoa, such as the *Isospora*, which also affect man, have remained as gut inhabitants. When, however, the mosquito took to blood-sucking, the malaria parasite was quick to adopt this as a means of transmission from one mosquito to the next. The adoption of an asexual phase in the new host greatly increased the chances of transmission to the definitive host. If we argue by analogy from other haematozoa, and take into consideration our new knowledge of the liver cycles, it seems possible that the phase of schizogony in the red cells is a new development, an experiment in evolution by the parasite for which the intermediate host is the primary sufferer, and for which the parasite itself would suffer in due course by the destruction of its intermediate host.

Host-parasite equilibrium

As a general rule, it does the parasite no good to destroy a host. A plentiful supply of hosts is to the advantage of the parasite and, in fact, he cannot survive without them. The only exception to the general rule is where the second host is a predator of the first. *Multiceps multiceps*, which causes giddiness in sheep, presumably makes its victim more easily caught and eaten by the next host—the dog. *Trichinella spiralis* is a parasite which may make its host ill, but this is usually during the phase of invasion, during which the parasite is non-infective. It must be remembered that man is not the usual host of *T. spiralis*, which is, fundamentally, a parasite of rats. The little spiral we see encysted in the muscle is a parasite prepared to wait for its present host to die and be eaten by the next host, which is usually another rat. Thus it is a disease of cannibals. If, perchance, the dead rat is eaten by an unusual host, such as a pig, the parasite will repeat its life-cycle, in host after host, presumably hoping some time to meet its true host once again. Other parasites are prepared to repeat a larval phase in host after host on the off-chance of some day meeting a host suitable for the adult phase.

Thus the process of parasitism has been a long one, with a series of adaptations by both parasite and host. Each evolutionary essay by the parasite has been countered by a corresponding change in the host. Where the experiment in evolution has been too drastic, the host has died out together with its venturesome parasite. Where the change has been acceptable to the host, the process and the parasite have continued. Thus there has been a process of 'give and take' which over the millenia has for the most part reached a state of equilibrium.

Therefore we must look at parasites in a slightly different light. They are so dependent on their host that they must be gentle in their attack—where they are not, there is some aberration or variation from normality, the cause of which we must find.

Habits and Hygiene

Normality in the relationship between host and parasite should really be considered as the primitive state. Man has changed his own habits considerably, and this change of habit has affected also his parasites. The change from a nomadic to an agricultural life must have affected their chances of survival. The cultivation of the land, especially where there is fertilization by faeces, gave some parasites an easier passage from host to host. Where previously the parasite had to produce enormous numbers of offspring to have any hope of finding another host, now those enormous numbers readily find hosts, and in numbers to which those hosts had not been accustomed. The advent of hygiene must have been a considerable blow to the parasite world, and one which if fully adopted would mean the end of many species parasitic in man. It might well also eliminate those helpful parasites on which we depend and which we all gain originally by some more or less remote degree of coprophagy. Ultimately we too, like the termites, may have to feed our young with faeces to initiate such processes as the bile cycle and the like.

Where, in cave-man days, the probability of acquiring a parasite from outside one's home circle was small, with modern crowding it is not surprising that parasites pass more easily from one human to another. Parasitism has even developed within the human species. Where there is crowding without hygiene, the parasite population will build up to a degree never attained in the primitive state—a degree upsetting the host-parasite balance. Man's closer association with his animals has meant, too, that interchange of parasites is taking place—often involving new manifestations.

The picture is, therefore, by no means simple and, when we come to a parasite such as *E. histolytica*, it becomes more and more complex, a muddle further complicated by our lack of knowledge. It is a horrible reflection that there has been so little advance since the original paper by Lösch[1]—a paper which all students of the subject should read, not only as an example of meticulous study, but also to impress on us just how little has been done since 1875.

Our first failure with *E. histolytica* has been in its recognition. When one is dealing with an object as flexible as an amoeba it is not surprising that taxonomy is difficult. Add to this the fact that it does not grow readily in culture—alone, practically never—and we are denied the biochemical approach made by the bacteriologist. We have failed, too, in our appreciation of the pathology—and pathogenicity of the parasite—a failure accentuated by our failure to treat and to prevent the disease process.

Let us examine the evidence available on the parasite. Amoebae called *E. histolytica* have been found in practically all parts of the world and, though the disease is generally considered 'tropical', the first adequately described case occurred in St. Petersburg—60°N. The variation in incidence of the parasite in different parts of the world is enormous, but the variation in incidence of disease associated with the parasite is even greater and the two do not by any means run parallel.

The apparent variation in incidence in different parts of the world can be attributed in part to the varying ability of the observers. There is no parasite more often misdiagnosed than is *E. histolytica*. It is neither easy to find nor easy to identify, and it has been said[2] that 'in the diagnosis of *E. histolytica* the enthusiasm of the uninitiated is only to be matched by the scepticism and caution of the expert'. One has seen so many things labelled as *E. histolytica* which have but slight resemblance to the parasite, that one finds there are but few acceptable observations of incidence on record.

The variation in incidence of disease due to the parasite comes under criticism. So many conditions have been attributed to infection with the parasite that the picture is completely confused. It has been said that pregnancy is the only condition for which the amoeba has not been blamed. When, however, one takes such acceptable manifestations as true dysentery and liver abscess the variation in disease incidence takes on a better perspective. Except under unusual circumstances the disease could be labelled 'tropical', for in truly temperate zones frank manifestation is uncommon. When, however, we relate the distribution of the parasite to the distribution of the disease it becomes evident that there are additional factors involved.

For Great Britain, Hoare[3] states that of the resident population about 10% are carriers of *E. histolytica*. This seems an enormous figure but, were the figure only 1%, there should be manifest disease in the population *if* the parasite is always pathogenic. Such cases could not escape recognition in a country so well served medically as Great Britain. However, when such cases do occur they merit report in the medical press. By contrast take our city of Durban, where various populations show an incidence varying from 5% to 20%, the disease is common and, in the African, appears in a florid form in which there can be no doubt of the association between the parasite and the disease.

Our assessment of the disease must take all the factors into consideration. Is there more than one strain of *E. histolytica* involved? Is there perhaps an organism we are labelling as *E. histolytica* which is not pathogenic? Are these strains of *E. histolytica* interchangeable? Is the incidence of disease a question of massive infection? What is the effect of climate, of diet, and possibly of other organisms in the bowel such as bacteria and other parasites.

Two forms of Entamoeba histolytica

The identity of *E. histolytica* is still by no means clear. Despite study by numerous observers over the course of some 60 years, there is still considerable doubt about the exact characteristics of this parasite. A current opinion suggests that *E. histolytica* may exist in two forms: a large pathogenic and a smaller commensal, the latter being the 'minuta' form of Hoare[4] and possibly the *E. dispar* of Brumpt.[5] Another species of amoeba, *E. hartmanni*, is morphologically indistinguishable from the commensal form of *E. histolytica*. All these three parasites are currently reported as *E. histolytica*, for there is no practicable way of telling one from another.

As the large race of *E. histolytica* seldom produces cysts, it is difficult to conceive how infection with this particular form can be passed from one man to another and, therefore, the next point of confusion arises. Is there any switch from the so-called small form to the large form or *vice versa* under some change of environment? It must be remembered that *E. histolytica* is absolutely dependent for its supplies of some enzyme system on the presence of other organisms. It has so far proved impracticable to grow *E. histolytica* in the test tube without some other concomitant organisms. In the bowel there are plenty of bacteria available, in the liver presumably man supplies the missing enzyme system.

This means of course that *E. histolytica* is singularly susceptible to its environment, and one will need to examine *E. histolytica* under many varying conditions. In the culture of *E. histolytica* from the stool one is always confronted by the fact that there is a mixed bacterial flora present. However, by various manoeuvres it is possible to reduce the number of organisms in our mixed cultures and even, on occasion, to re-establish the amoeba with but a single concomitant organism. We have achieved this in the past by micromanipulation, that is to say, by picking up the amoeba and washing it free of bacteria which, as you can imagine, is a pretty tedious procedure. Lately we have been isolating the amoebae directly from liver abscesses where there are no extraneous organisms. We have been able to grow such amoebae alone with *Clostridium welchii*, and also with an organism known as the Streptobacillus of Frye. We have also been able to pass the amoebae through several passages in minced chicken embryo which of course contains living cells. By this means we are able to vary the flora to a certain extent. The whole process is fraught with frustration but, so far, one or two interesting observations have been made.

We do know that *E. histolytica* does not encyst in the tissues. It was at one time postulated that *E. histolytica* might, by embarking on an invasive stage, be giving up all chance of posterity. One of our early experiments was to see whether such large amoebae could be made to encyst in culture.

Operating from stool material was always difficult because one could never be sure that there was but a single strain of amoebae in the culture. However, by utilizing material from liver abscesses, we were able to start monoxenic strains and we find that by changing the flora of the cultures we have been able to induce the invasive amoeba to form cysts. So it would appear that the change is not irreversible. Further, when these amoebae from the liver were initially isolated they were large and fat, and remained so as long as they stayed with *Clostridium welchii* but when they were switched to a stool flora previously associated with an encysting amoeba they then not only formed cysts but became considerably smaller. It would seem, therefore, that it is not unlikely that the invasive commensal forms of histolytica are variations brought about by some environmental factor. Just what that environmental factor is we do not know.

Commensal or invasive

What is the application of this concept to the epidemiology of the disease? It would appear that *E. histolytica* can live in the human bowel without causing any disturbance. Here it lives as a pure commensal, feeding on bacteria and debris and not in any way harming the host. It is this phase which

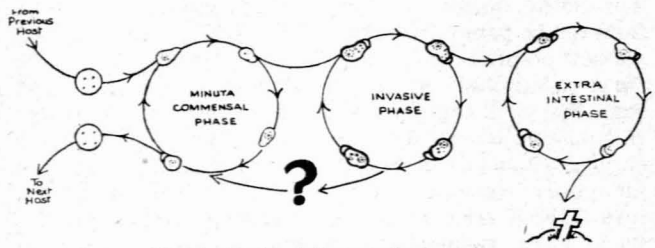

Fig. 1. Cycle of *Entamoeba hystolica.*

produces the cysts that carry the parasite from one host to the next. Under some unknown stimulus the amoeba invades the tissues, becoming larger and haematophagous and at this stage causing disease. It would seem that the differences between the manifestations in the tropics and sub-tropics on the one hand and in the truly temperate zones on the other are due to this environmental factor. What do we know of this environmental factor?

Durban itself forms a microcosm, in that in this one city we have the various manifestations of this parasite. The Whites commonly show the picture of *E. histolytica* found outside of the tropics; the Africans, on the contrary, show a fulminant dangerous disease. The obvious solution to the problem lay in the question of diet, but even this was confused because we have shown that where experimental animals are fed on diets in which the carbohydrate is supplied by wheat, rice and maize, the animals most affected were those on a wheaten diet. However, study of the epidemiology of the cases in Durban indicates that it is the African eating a purified wheaten diet and largely confining himself to such a diet who provides the large majority of cases. It was in this connection that we coined the phrase, 'the bun and lemonade diet'. It would seem that the confining of a diet to purified carbohydrate is dangerous in this respect, for it must be obvious that there are protective elements in the remainder of the White diet.

A further clue has been provided by our remarkable success in the treatment of the acute disease by the use of a wide anti-bacterial attack. By changing the flora of the bowel we are able to profoundly modify the condition and in a high proportion of cases to eliminate the parasite as well as to cure the disease. It would appear, therefore, that such change as is originated by incorrect diet is mediated by the bacteria of the bowel.

This is the position as we see it at the moment; there are many questions yet to be answered and much work yet to be done. In conclusion, we can only hope that our probings will lead to a better appreciation of the relationship between amoeba and man—and a recognition of ways to re-establish the conditions under which they may live in complete harmony.

SUMMARY

Parasitism is but an extreme development of the association between two animals, and all shades of such association are to be found, ranging from casual acquaintance to an intimacy so close as to be all but identity.

Though this association may be close, it does not imply that one member is harming the other, and indeed there may be mutual benefit. There are once again all grades ranging from indifference to vicious attack.

Theoretically there are few cases where it is to a parasite's advantage to destroy its host. It is true that some parasites —usually vegetable in character—seem to have no thought for posterity, but the higher up the development scale the greater is the respect of the parasite for his source of food and warmth.

Most parasites reach an equilibrium with their hosts, the parasites renouncing further territorial claims in exchange for the tolerance of the host, and the host accepting the demands of the parasite up to a limit. Such an equilibrium may be upset in many ways—for example, by an overload of parasites, or by some deviation from the fundamental cycle of the parasite.

The relationship between man and *E. histolytica* is by no means simple. There are many confusing factors, and opinions reach to extremes. Proofs remain to be found and many questions remain to be answered. Is *E. histolytica* always pathogenic? Is there more than one organism currently called *E. histolytica* in the human bowel? If *E. histolytica* is not always pathogenic, what determines its invasiveness?

These are but a few of the fundamental questions and there are others. Durban affords a suitable place for investigation of this problem, for the three races respond to infection in differing ways. The work done is discussed and future programmes outlined.

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