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The Role of the Spleen in Protozoal Infections with Special Reference to Splenectomy

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One of the first things that a student of tropical medicine has to learn is the list of conditions which may cause splenomegaly. A gigantic differential diagnosis is thereby revealed of which the most important item is malaria though most of the other parasitic protozoa with the exception of the intestinal commensals are capable of producing enlargement of the organ. Attention is focussed on the spleen today for various reasons, including the still doubtful aetiology of the "big spleen syndrome" (usually thought to be the effect of chronic malaria), the occurrence of fatal cases of piroplasmosis in people without a spleen and the increasing frequency of splenectomy as a therapeutic measure.

In this paper, I intend to review in particular the effect of splenectomy on two protozoal infections, piroplasmosis and malaria, including certain experimental data which have been obtained in the course of my own work.

Structure and Functions of Spleen

It is desirable at first to describe very briefly the structure and functions of the spleen, a subject which has advanced very little in the last quarter of a century. The monograph edited by BLAUSTEIN (1963) contains little more fundamental knowledge than was current at that time, and the relation of the spleen to other organs of the body is still shrouded in mystery.

The surface of the spleen is composed of a unicellular layer of peritoneum. Beneath this is a fibro-muscular coat which is projected into the interior as trabeculae. The amount of muscle in this layer varies in different animals and is small in man; it was thought at one time that the parenteral injection of adrenalin or the effect of other stimuli (e.g. cold) caused the muscle to contract and drove blood and parasites from hidden corners of the sinuses into the peripheral circulation, provoking a relapse – as of malaria; but deliberate and carefully controlled experiments by BRUCE-CHWATT (1963) in Nigeria failed to confirm this idea.

The role of sphincters in controlling the circulation in the spleen is still doubtful and it is unknown how much stagnation or how many closed pockets exist, which could serve as reservoirs of parasites, perhaps for years and where the parasites may live, in hibernation, protected from drugs and even perhaps from immunity. At least this was the theory of the old Italian malariologists, like BIGNAMI (1913), and some of the modern school also.

The blood vessels travel in the trabecular framework. The arterioles (branches of the splenic artery) acquire a covering of lymphatic tissue. At intervals this tissue becomes agglomerated into large, asymmetrical nodes – the Malpighian bodies or white pulp, for on cross sections they stand up as greyish-white specks. The arterioles break up into capillaries which open directly into the sinuses, or perhaps into the spaces enclosing the red pulp. The blood is taken back by a venous system into the splenic vein. The sinuses are lined by phagocytic endothelium. The red pulp consists of a varying mixture of erythrocytes in various stages of destruction, monocytes, lymphoid-macrophage cells and plasma cells. The white pulp consists of lymphocytes, with germinal nodes and the central arteriole.

The reticulo-endothelial cells of the spleen, constitute in man about $^1/_7$ of the total reticulo-endothelial tissue of the body. They have an important function in immunity and this paper is largely devoted to a consideration of what happens when this source of lymphoid macrophage activity is removed by splenectomy. The system is responsible for the destruction of the effete erythrocyte, and for the phagocytosis of débris and of certain parasites. In foetal life, erythropoiesis occurs in the spleen and in adult life the organ has other functions, such as the storage of iron, the production of bilirubin and the metabolism of lipids.

The function of the liver is better known than that of the spleen, and liver function tests are numerous and effective. There appear to be no standardised procedures for the determination of splenic function; it is true that radio-active erythrocytes can be introduced into the circulation and radiation over the spleen can be measured to ascertain hyperactivity of the organ in their removal, but this is not a practical technique for determining deficiency of function. The speed of removal of particles of colloidal carbon offers a possible method of observing reticulo-endothelial activity, but it would not relate solely to the spleen. In other words, there appears to be no good test for determining defects in function of the spleen, and this is a handicap, both for clinical practice and experimental work on animals.

Effect of Splenectomy

Let us now see what happens when the spleen is removed in relation to protozoal infections.

Splenectomy is now a fairly common surgical procedure, mainly for injuries to the organ after accidents and in the course of major abdominal operations. In the tropics, splenectomy is often performed for chronic schistosomiasis and for the tropical splenomegalic syndrome.

An interesting follow-up of the remote results of splenectomy was made in England and Wales in 1966 by the late Professor LOWDON of Newcastle and his collaborators (1968). Details were obtained from 1118 cases; fatal bacterial infections were not uncommon, especially in children. 417 deaths were found to have occurred in the 5 years following the operation, all but six of which were ascribed to a clear cut cause. None of the fatalities appeared to be due to piroplasmosis, but this condition could easily have been overlooked or mis-diagnosed.

Removal of the spleen has a profound effect on *some* protozoal diseases while on others, it influences, *not at all,* the course of the infection. Let us dispose of the ones unaffected by splenectomy first.

Toxoplasmosis either in man or animals is usually a latent, practically asymptomatic infection, but various adverse circumstances can convert it into a malignant, fulminating disease. Thus deep X-ray therapy or treatment of, say Hodgkin's disease with cyto-toxic drugs may light up occult toxoplasmosis and cause a fatal meningo-encephalitis. The loss of the immune defences of the spleen after removal of this organ might also be thought to result in a similar rampaging of the parasite, but splenectomy in chronically infected animals is totally without effect and the infection remains latent. However, the first human case of this disease was characterised by gross splenomegaly and Castellani made the diagnosis by finding *Toxoplasma gondii* in the spleen smears.

Kala-azar is characterised by great enlargement of the spleen, though it is sometimes not realised that the organ may only be affected comparatively late in the disease; the usual cases that one sees in the indigenous inhabitants of the tropics have had kala-azar for several months and of course splenomegaly is present, but immigrants may easily present for fever early in the disease, before the organ is enlarged and diagnosis may then be difficult (STAM, 1968). I mention this condition, because splenectomy may sometimes be performed in long standing cases as a therapeutic measure, and instead of causing the leishmanial infection to flare up, the removal of the organ (together with millions of the organism) may result in a permanent cure.

The course of infections with intestinal protozoa such a *Entamoeba histolytica, Balantidium coli* and coccidians appears to be unaffected

by splenectomy. Likewise, removal of the spleen is without effect on trypanosomes of most types, though results are variable. Some studies on *T. cruzi* (e.g. the ipsilon strain) have a marked tropism for the spleen; in fact, I have found this tissue admirable for studying mitotic changes in the nucleus of the amastigote or leishmanial forms. In the late stages of Gambian sleeping sickness, the organ may be enlarged and trypanosomes may be found in spleen smears when absent elsewhere. Splenectomised rats or mice do not seem to be much more susceptible to the salivarian trypanosomes. If they had been, they would surely have been used for isolating strains of *T. gambiense,* which is difficult to establish in laboratory animals. Occult trypanosomes, like *T. rangeli,* do not increase in numbers after splenectomy and the diminution of *T. lewisi* in the post critical phase of this infection in rats is also unaffected by this operation.

Although *Haemobartonella, Eperythrozoon* and *Borrelia* are not now regarded as protozoa, it might be noted that these infections, which are usually latent in rodents and monkeys are easily activated by splenectomy, and may then kill the animals. In fact, splenectomy seems to be particularly relevant to organisms which grow and multiply in erythrocytes. This is the generalisation which emerges from the present study.

The spleen is the all powerful organ which protects the host from the danger of multiplication of the parasite. In many parasitic infections, the splenic barrier proves too great a problem for the organism to surmount; but occasionally the parasite is in luck, if by chance the spleen is non-functioning or actually absent. The immunogenic cells may have been blocked, in nature perhaps by a virus, or experimentally by repeated inoculations of carbon particles; then, if the animal is inoculated with a parasite which is normally non-lethal, the parasite is able to multiply without hindrance and kills the host. Thus, SALAMAN et al. (1969) inoculated a certain strain of mice with *P. berghei yoelii* and simultaneously with a leukaemogenic virus; all the mice died of fulminating malaria. Without the virus practically all of this strain of mice survive the infection, as their reticulo-endothelial system is fully functional.

Splenectomy and Piroplasmosis

An even more striking effect is produced when a normally harmless organism gets into a host *without* a spleen. There have been three dramatic occurrences in the last few years, where men who had lost their spleens by operation became exposed to piroplasms – protozoal parasites of cattle and other animals which normally do not affect man. Transmission takes place by tick bite, and in these three cases, very

severe infections occurred, two of which were fatal. The cases were first diagnosed as malaria and the parasites were only later correctly identified. The first was from Zagreb in Jugoslavia (SKRABALO & DEANOVIC, 1957) and was due to *Babesia bovis;* the man was a farmer who eleven years previously had had a car accident and his spleen had to be removed. He was admitted to hospital with fever, jaundice and haemoglobinuria; "rings" were found in his blood and these were identified as *Plasmodium falciparum.* The patient died eight days later and the case was diagnosed as blackwater fever. Blackwater fever had not been seen in Jugoslavia for many years and the films were therefore sent to various protozoologists (Geigy, Swellengrebel and myself), and we were all convinced that the organisms were a species of *Babesia.* An investigation of the farm showed that the pastures were heavily infested with ticks and the cattle had red water fever.

The second case occurred in California and has been described by SCHOLTENS et al. (1968). The patient was a keen photographer and spent most of his spare time in isolated coastal areas near San Francisco. Early in June 1966 he became seriously ill with fever and chills and was admitted to hospital. Parasites resembling malaria "rings" were seen in the blood films; malaria was diagnosed and he was treated with chloroquine. The history, however, revealed no recent exposure to malaria and the blood films were sent to the National Communicable Diseases Center at Atlanta for confirmation. The parasites were found to contain no pigment and were sometimes in the Maltese Cross form, typical of certain piroplasms. It was then discovered that a splenectomy had been performed on the man two years previously, on account of congenital sphaerocytosis. Serological tests were positive for piroplasmosis but negative for malaria. It seems probable that the infection had originated in wild rodents and was due to some species of *Nuttallia* transmitted by tick bite.

The third case was contracted in Ireland (FITZPATRICK et al., 1968) and was due to *B. divergens.* A man went on holiday in August, 1967 to Lough Corrib in Galway, and camped with his family on its western shore. The fields around the camp are alive with ticks dropping off the cattle; and the cattle here suffer from red water fever. The man spent his time, resting in the fields, for he was still not fully recovered from a severe operation for a duodenal ulcer, which he had undergone four months earlier. Owing to adhesions, the spleen had had to be removed in the course of the operation. The patient was completely unaware of his peril, but the splenectomy had rendered him vulnerable to the cattle infection, and he must have been constantly exposed to the bites of ticks during the five days he was there. On return home, he became severely ill with fever, jaundice and anaemia, and malaria-like rings were found in his blood. He had received a blood transfusion after

the operation earlier in the year and transfusion malaria was suspected. He died the next day and before the parasite had been correctly identified. The blood film was sent to the Malaria Reference Centre, at Horton Hospital, where we diagnosed the parasite as a piroplasm and not malaria.

I was interested in pursuing the matter further, as I had come to the conclusion that people with intact spleens and bitten by infected ticks should harbour, at some time or other, occult parasites in their circulation, as happens so frequently in other parasitic conditions – the so-called inapparent infections of Nicolle. Such parasites should be most easily demonstrable by inoculation of heparinised blood into splenectomised calves.

The Irish case seemed to present an excellent opportunity to put the theory to test and I went to the site exactly a year later, where I was met by Dr. Cotton Kennedy, the pathologist who had investigated the case, and by Harry Hoogstraal and Gerald Walton, the tick experts. The regional medical officer (Dr. MacCon) and the veterinary officer (Patrick Fagan) helped us with our work and took us to the place where the patient had camped. Just before reaching the camp, we saw a large gethering in a field: it was the Irish Army participating in the new MGM film on Alfred the Great. The men had been there for about a fortnight, spending most of their time, in between the mock battles, in sun-bathing on the grass and were inevitably much bitten by ticks. Our experiment had been done for us. Instead of trying to find some Irish peasants working in these fields and to persuade them to let us take their blood, we seized the opportunity that lay before us and asked the commanding officer to provide volunteers for blood samples. He at once agreed, gave 10 mls. of his own blood and produced 35 soldiers also. The samples were mixed in suitable containers in the travelling laboratory of Dr. Kennedy, which was parked on the site, and were then transferred to a large thermos flask containing ice. The chilled blood was flown from Shannon to London Airport where Mr. Donnelly of the Central Veterinary Laboratory, Weybridge met the plane, and within 24 hours of taking, the material had been inoculated into two splenectomised calves. We also collected ticks, nymphs and larvae *(Ixodes ricinus)* from the vicinity and these were later taken to Weybridge by Dr. Hoogstraal and fed on other splenectomised calves.

The end of this long story unfortunately had a negative result; at least no babesial infections arose in the calves. However, one calf which had been bitten by the *Ixodes* developed "bovine tick-borne fever", a rickettsial disease confined to the British Isles and Scandinavia (TUOMI, 1966). When this animal, and the other calves were later challenged with *B. divergens* (to confirm that a subpatent infection of the piroplasm had not occurred), the others all developed severe red water fever,

but the rickettsial calf exhibited only a mild infection (GARNHAM et al., 1970).

I still feel that subpatent infections of babesiosis are likely to occur in agricultural workers throughout the world, although the Irish experiment and other attempts that I have made, have failed to establish this theory. Dr. Hoogstraal and other workers in NAMRU 3 in Cairo intend to investigate the subject intensively in the inhabitants of the Delta, where the disease is common in the local cattle and where many people have been splenectomised for chronic bilharziasis.

The latest development in our knowledge of human piroplasmosis has been reported from the U.S.A. by BENSON et al. (1969), who describe a case which occurred in a woman with an intact spleen. She was found to have spent some time on Nantucket Island, where her dog caught wild rodents and was much bitten by ticks; one of these ticks became deeply embedded in her own skin and about 6 weeks later she developed a febrile illness. Parasites (thought at first to be *P. falciparum*) were found in her blood and on inoculation into a hamster gave rise to a typical babesial infection. The patient was treated with chloroquine and gradually recovered. It is possible that this case arose because of some deficiency in splenic function, but it might be noted also that the two, non-fatal, American infections were thought to be of rodent origin; perhaps the species of piroplasm in the rodent is less lethal than those of cattle.

Further investigations on this interesting subject are not dependent upon waiting for the occurrence of new human infections, because excellent animal models exist. We used this system first in Liberia (GARNHAM & BRAY, 1959) with chimpanzees and *Babesia divergens:* intact animals were totally resistant but when splenectomised, proved to be highly susceptible, though the infections were not fatal. Later, we showed (GARNHAM & VOLLER, 1965) that a similar effect occurred in rhesus monkeys and *B. divergens*. On the contrary, splenectomised primates could not be infected by the bites of ticks infected with *Theileria parva*. One unexpected result of these experiment was the demonstration that the interval between splenectomy and infection had no influence on the severity of the disease; it might have been thought that after months or years other organs or accessory spleens would have taken over the specific functions. There must exist a special protective device in the spleen which is absent elsewhere in the body; as yet, this remains unidentified.

Splenectomy and Malaria

Singularly little is known about the influence of splenectomy on human malaria, and even today when this operation is often performed

in holoendemic malarious regions for tropical splenomegalic syndrome (T.S.S. or big spleen disease), severe manifestations of malaria have rarely been reported. Perhaps this is because the patients have been kept under the cover of chloroquine.

HAMILTON (1967) observed a series of patients who had been splenectomised for T.S.S. in Uganda. They were given chloroquine for 6 months after the operation and were closely watched. Naturally no resurgence of malaria occurred during this time, but their ultimate fate is unknown, because a longer follow-up was impossible. It is desirable that any such work in future should have suitable financial provision for protracted longitudinal study.

Quartan malaria is usually thought to be associated with T.S.S., but the evidence is limited and indirect, e.g. practically none of the huge spleens on removal exhibit any malaria pigment. HAMILTON's work was carried out in highly malarious territory in East Africa, where immunity is at a high level.

Examples in the literature of recrudescence of malaria after removal of the spleen are very few. A case was reported by WALTON (1931) of a man who developed so-called *P. vivax* malaria 15 days after splenectomy (for what was then termed Banti's disease). He had lived in England for the previous 33 years, and before that in Demerara as a boy when he had suffered from malaria. Two paroxysms of fever occurred at a 72 hours' interval, and it is much more probable that the true diagnosis of this infection was quartan rather than benign tertian malaria which is not known to persist for more than 7 years. This patient was quickly treated with quinine and the parasitaemia soon disappeared. In splenectomised chimpanzees inoculated with *P. vivax,* the infection builds up to a very high level (50,000 parasites per cu.mm.), but does not kill the animal.

COVELL (1955) reviewed the subject of spontaneous rupture of the spleen, for which splenectomy is the usual therapy, but although the rupture occurred most often in the course of acute malaria, practically no information is available on the course of the subsequent infection; presumably because drug treatment inevitably followed; and the malaria was cured. COVELL, however, stresses the danger of further malarial attacks and the undesirability of exposure to infection.

A splenectomised non-immune subject might be expected to develop a fulminating infection of *P. falciparum,* and perhaps the severe case described by Watson-Williams in Ibadan was in a man who had lost his immunity through living under antimalarial cover; this was the only example of cerebral malaria in a West African adult ever seen by the author, and the man was found to have been splenectomised.

ADAMS (1960) described a rather similar instance in a West African seaman, who had undergone splenectomy in Rotterdam in 1956 and

four years later walked into the Tropical Diseases Department, Liverpool. He complained of fever and malaise and had suffered from similar mild attacks in 1958 and 1959. His temperature was 41°C, but he did not seem very ill and he had no cerebral symptoms. The blood film showed *all* stages of *P. falciparum* with a 25% invasion rate. The smear looked like a Bass Johns Culture; there were many rings (chiefly double-dotted) but also large numbers of uninucleate solid forms with a prominent mass of pigment and numerous schizonts (12 merozoites) and immature crescents – cigar forms and smaller – but no mature gametocytes. Chloroquine was given and within 48 hours the parasitaemia had disappeared. It would be interesting to know the subsequent history of this man and to speculate on what would have happened if chloroquine had not been given. My opinion is that his combined natural and acquired immunity would have tided him over this and any subsequent attacks.

This case is also interesting in the demonstration of how *P. falciparum* develops to maturity in the peripheral blood, in the absence of the spleen. It is well known that *P. falciparum* retreats from the peripheral blood to the internal organs, after about 24 hours' growth or less, so that the peripheral parasitaemia is normally confined to ring forms. Actually if spleen punctures are made in ordinary cases of falciparum malaria, schizogonic stages are only found with difficulty in the spleen smears and I think that this organ is perhaps *not* the chief seat for the development of *P. falciparum.*

If the spleen is removed in chimpanzees and the animal is then inoculated with *P. falciparum,* numerous schizonts appear in the peripheral blood, just as in the human case; the same picture is seen in the natural infection *(P. reichenowi)* of chimpanzees which shows few schizonts in the blood, unless the animals are splenectomised first. A similar effect is produced with *P. coatneyi* in rhesus monkeys, with and without spleens: schizogony in the peripheral circulation is practically absent in the former and prolific in the latter.

Intact chimpanzees are on the verge of susceptibility to the human parasites; their livers can completely support the growth of the sporozoite into normal exoerythrocytic schizonts, maturing on the correct day (*P. malariae* in 15 days, *P. ovale* in 9 days, *P. vivax* in 8 days and *P. falciparum* in 6 days). But the merozoites cannot develop properly in the erythrocytes – *unless* the spleen is removed, and then normal schizogony and probably gametogony occurs. The reverse experiment – putting *chimpanzee parasites into man* – has only been partially done, as we cannot of course use splenectomised volunteers; nevertheless it seems likely that the same effect would occur.

To everybody's surprise, it has recently been found that some lower monkeys are susceptible to *P. falciparum* and *P. vivax* by various

American monkeys particularly the owl monkey *Aotus trivirgatus* from South and Central America. If its spleen is removed, an immunosuppresant drug like Imergan is given, and a large dose of *P. falciparum* is inoculated, the Aotus easily takes the infection and after several passages, the intact animal will also show a high parasitaemia, including the production of gametocytes, capable of infecting mosquitoes. The drain on these animals for research purposes is becoming enormous, and although the supply in the Latin American forests seems inexhaustible, it would be as well if we started trying to breed them. They are nocturnal, rather delicate creatures, which do not respond too well to life in a laboratory. But they cost only £15 each, as compared with the £200 plus for a chimpanzee. Anyhow, the use of these small animals has changed the outlook for malaria research and we can use the true human parasites now instead of trying to draw deductions from experiments on chicken, lizard or rodent malaria.

For the last 25 years I have been working on malaria in monkeys and must have performed several hundred splenectomies on chronically infected animals. Almost the most delicate test for the presence of a latent infection of malaria is to remove the spleen and see if parasites appear. Acquired immunity is thus abolished and the animal suffers from a relapse. Very often large numbers of viable gametocytes (i.e. capable of infecting mosquitoes) accompany the relapse – many more than in primary attacks.

I will refer to a series of malaria infections in monkeys which are briefly summarised as follows:

P. cynomolgi cynomolgi. 27 monkeys were splenectomised after an average period of infection of 27 months; one as long as 44 months, and parasites usually appeared in the blood 9 days after the operation. Five cases failed to recrudesce, presumably because a sterile immunity had developed.

P. c. ceylonensis. Five monkeys were splenectomised, including one that was splenectomised 43 months after the primary infection, when parasites took over a month to reappear. This was the only instance when it was necessary to wait longer than a month for the recrudescence. In the other four, parasites appeared in 4 days on an average and the infection became so virulent that it often killed the host.

P. cynomolgi (langur strain). Five monkeys were splenectomised, after about 6 months' course of infection and the parasites reappeared in about 15 days.

P. c. bastianellii. Twenty monkeys were splenectomised after an average of 4 months' infection and all recrudesced in about 4 days.

P. inui (17 cases) and *P. gonderi* (4 cases) behave differently from the *cynomolgi* group because a strong premunition persists in these infections and the parasite never disappears, even in the intact animal;

so the only result of splenectomy is to cause a great flare-up in parasitaemia which may be fatal.

In the cynomolgi infections, the longer the interval between primary infection and splenectomy, the longer the parasite takes to reappear. In all mammalian malaria infections, splenectomy usually destroys acquired immunity and very heavy parasitaemias arise. There is a curious exception, which I have called the "Schmidt effect": Leon Schmidt of Cincinnatti noticed that if rhesus monkeys infected with *P. cynomolgi* are splenectomised, and the infection is then allowed to run its course for some months, a strain of the parasite arises which is unusually non-virulent on inoculation into clean monkeys.

The above examples demonstrate the great effect of removing the spleen in primate malaria. Its lymphoid macrophage cells have the greatest capacity for becoming sensitised and hyperplasic, while the plasma cells are responsible for producing powerful antibodies of different sorts. The liver and bone marrow can also perform these functions but much more slowly, and often too late.

A similar picture is demonstrated in *P. berghei* in rats, mice and other rodents, but strangely enough in avian malaria, splenectomy hardly affects the course of the disease, perhaps because the spleen in birds is differently geared to deal with nucleated erythrocytes.

In the so-called malaria infections of monkeys *(Hepatocystis kochi)* and of birds *(Leucocytozoon* and *Haemoproteus)* where there is no multiplication of the parasites in the blood stream, splenectomy is entirely without effect on the course of the infection. Reports to the contrary in the early literature are erroneous, probably because of misidentification of the parasites, or because of the periodic rise and fall in numbers of the parasites in the course of the prolonged infections. The latter may be the explanation of the recent report by VAN PEENEN et al. (1968) that splenectomy exacerbates infections of *Hepatocystis vassali* in squirrels.

The effect of splenectomy in rodent malaria and its relationship to immunity have been studied in great depth by Corradetti and his colleagues, and a good review of the subject is provided by TODOROVITCH et al. (1967).

Avian malaria has been largely omitted from this discussion, because the role of the spleen seems to be less important in birds. The recent experiments of TODOROVITCH et al. (1967) may, however, be noted in that they rendered rats and mice susceptible to *P. gallinaceum* by extirpation of the spleen – another remarkable extension of host parasite range.

Conclusion

A brief review of the functions of the spleen denotes that the relations of this organ to the other tissues of the body are still "shrouded in mystery".

The insignificance of the spleen in certain infections is pointed out. These include toxoplasmosis, kala-azar, coccidiosis and other intestinal infections, and probably trypanosomiasis (including "occult" forms).

On the other hand, the spleen is of paramount importance in controlling other blood infections, including *Haemobartonella, Eperythrozoon* and *Borrelia* spp. and in particular piroplasms and mammalian malaria parasites.

The multiplication of intraerythrocytic parasites in protozoal infections of mammals is largely governed by the existence of a fully functional spleen. Parasites (such as haemoproteids) which do not multiply in the blood are unaffected, and probably avian and saurian infections are also not much influenced by splenectomy.

The spleen has its own peculiar and powerful properties of combatting these infections by cellular and humoral activity; this is a function possessed by no other organ, and cannot be taken over by any other tissue of the body even up to 11 years after removal of the spleen.

Acquired immunity is easily destroyed by removal of the spleen and the infection flares.

Similarly, natural immunity may be broken in some instances by splenectomy; parasites which are unable to develop in a host with the intact organ may fulminate in one without. Splenectomy can result in a rupture of the most unnatural and unexpected boundaries.

The action of the spleen in inhibiting the schizogonic development in the peripheral blood of certain malaria parasites (*P. falciparum, P. coatneyi* etc.) is still unexplained.

The susceptibility of a host to certain parasites may possible be enhanced in nature by the presence of other parasites (e.g. viruses) which block the defence mechanism of the spleen.

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Zusammenfassung

Ein kurzer Überblick über die Funktionen der Milz weist darauf hin, daß die Beziehungen dieses Organs zu den übrigen Geweben des Organismus noch höchst spekulativ erklärt werden.

Die unbedeutende Rolle der Milz bei bestimmten Infektionen wird unterstrichen. Ein solches ist der Fall vor allem bei der Toxoplasmose, bei Kala-Azar, der Coccidiose und andern Darminfekten, möglicherweise auch bei der Trypanosomiase (welche «versteckte» Formen einschließt).

Andrerseits spielt die Milz eine Rolle von hervorragender Wichtigkeit bei der Kontrolle von andern Blutinfektionen, die durch *Haemobartonella, Eperythrozoon* und *Borrelia* spp. sowie ganz besonders durch Piroplasmen und durch Parasiten der Säugetiermalaria verursacht werden.

Die Vermehrung der intraerythrozytären Parasiten bei Protozoen-Infektionen der Säugetiere wird weitgehend von einer gänzlich funktionellen Milz überwacht. Parasiten (wie zum Beispiel die Haemoproteiden), welche sich nicht im Blut vermehren, fallen nicht unter diese Kontrolle, und wahrscheinlich werden die Infektionen der Vögel und Lurche auch nur sehr wenig durch eine Milzextraktion beeinflußt.

Die Milz besitzt in der Tat die ihr eigene, stark wirkende Eigenschaft, solche Infektionen durch zellulare und humorale Aktivität zu bekämpfen. Dies ist eine Funktion, die kein anderes Organ besitzt, und die auch von keinem andern Gewebe des Körpers übernommen werden kann, selbst nicht bis zu 11 Jahren nach der Entfernung der Milz.

Eine erworbene Immunität kann ohne weiteres durch Herausoperieren der Milz aufgehoben werden, so daß eine starke Infektion ausbrechen kann.

Ähnlich kann auch eine natürliche Immunität in gewissen Fällen durch eine Milzextraktion gebrochen werden, so daß Parasiten, die sich nicht in einem Wirt entwickeln konnten, solange er das intakte Organ besaß, sich massig vermehren, sobald die Milz fehlt. Eine Milzextraktion vermag so zu einer Ruptur harmonischer Beziehungen führen, die äußerst unnatürliche und unerwartete Auswirkungen haben kann.

Die inhibierende Wirkung der Milz auf die schizogone Entwicklung gewisser Malaria-Parasiten (*P. falciparum, P. coatneyi* usw.) im peripheren Blut bleibt unerklärt.

Die Empfänglichkeit eines Wirts für gewisse Parasiten kann möglicherweise in der Natur erhöht werden durch die Gegenwart anderer Parasiten (Viren zum Beispiel), welche die Verteidigungsmechanismen der Milz blockieren.

Résumé

Un bref aperçu des fonctions de la rate montre que les relations de cet organe avec les autres tissus de l'organisme sont encore « enveloppées de mystère ».

L'insignifiance du rôle de la rate lors de certaines infections est soulignée. C'est le cas pour la toxoplasmose, le kala-azar, la coccidiose et pour d'autres infections, probablement aussi pour la trypanosomiase (refermant des formes « occultes »).

D'autre part la rate joue un rôle éminent dans le contrôle des infections du sang dues à *Haemobartonella, Eperythrozoon* et *Borrelia* spp. et plus particulièrement à des piroplasmes et à des parasites causant la malaria des mammifères.

La multiplication des parasites intra-érythrocytaires lors des infections des mammifères par des protozoaires est largement surveillée par une rate en pleine fonction. Des parasites (comme les hématoprotéides) qui ne se multiplient pas dans le sang ne sont guère affectés, et il est probable que les infections des oiseaux et des batraciens ne sont pas non plus influençées par une extraction de la rate.

La rate a des propriétés curieuses et importantes qu'elle possède à elle seule, à savoir la faculté de combattre certaines infections par une activité cellulaire et humorale intense. C'est là une fonction dont elle a le privilège et qui ne peut être transmise à aucun autre tissu corporel, même pas après l'extraction de la rate, ce qui a été vérifié jusqu'à la onzième année après l'extraction.

Une immunité acquise peut être détruite sans autre par l'extraction de la rate, et l'infection peut alors se manifester avec violence.

D'une façon similaire une immunité naturelle peut être levée dans certains cas par l'extraction de la rate. Des parasites qui sont incapables de se développer dans un hôte possédant une rate intacte peuvent faire une apparition massive dans un autre qui en est dépourvu. L'extraction de la rate peut tirer à conséquence et causer un dés équilibre aux effets les plus contre nature et les plus inattendus.

L'action de la rate dans l'inhibition du développement schizogonique de certains parasites causant la malaria (*P. falciparum, P. coatneyi* etc.) n'a pas encore trouvé d'explication.

La réceptivité d'un hôte pour certains parasites est probablement accrue dans un milieu naturel par la présence d'autres parasites (p. ex. des virus) qui arrêtent les méchanismes de défense exercés par la rate.