Current Practice

MEDICINE IN THE TROPICS

Splenomegaly in the Tropics

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A palpable spleen, which may even be visible, is a common physical finding in the tropics and sub-tropics (Fig. 1). For example, in a cross-sectional survey half the medical inpatients at Mulago Hospital, Kampala, Uganda, had clinical splenomegaly, and Pryor¹ has recorded 62% of a village population in New Guinea with splenomegaly to the level of the umbilicus. Many specific causes of splenomegaly are now known, but there

FIG. 1.—Visible splenomegaly associated with scars of therapeutic lacerations by local practitioners.

still remains a large group of patients in the tropics with gross splenomegaly of unknown aetiology. This condition has recently² been termed "Tropical Splenomegaly Syndrome." In order to discuss this group in the true context of splenomegaly it is important to consider first the known aetiological agents, and to remember that all causes of splenomegaly in Europe and North America can also occur in the tropics.

The spleen is an important site for the production of lymphocytes and plasma cells. It is also rich in phagocytic cells. It removes defective red cells from the circulation, and the so-called pitting function of the spleen relates to its capacity to remove intracellular granules, leaving the cells intact. In health

the bloodflow through the spleen is mainly rapid and intra-sinusoidal. In splenomegaly there is usually a second slower circulation through the pulp cords.³ The spleen becomes congested following any rise in pressure within the splenic vein. Occasional intrasplenic erythropoiesis as in myelofibrosis suggests that the spleen retains its capacity to produce red cells. Hypersplenism is a term applied to a depression of one or more blood elements (red cells, white cells, platelets) associated with splenomegaly.

Detailed lists of the causes of splenomegaly can be found in standard texts.⁴ Only certain groups of conditions associated with splenomegaly which are important and prevalent in the tropics will be discussed here (see Table I).

TABLE I.—A Guide to Common Causes of Splenomegaly in the Tropics

- (1) Parasitic infections
  - Malaria
  - Leishmaniasis
  - Schistosomiasis
- (2) Other infections
  - Viral
  - Rickettsial
  - Bacterial
  - Fungal
- (3) Blood disorders
- (4) Infiltrative conditions of the spleen
- (5) Congestive splenomegaly
- (6) Tropical splenomegaly syndrome
  - (a) With hepatic sinusoidal lymphocytosis
  - (b) Without hepatic sinusoidal lymphocytosis

Parasitic Infections

Malaria.—The incidence of splenomegaly in the population where malaria is endemic is related to the intensity of malaria transmission in that area. In adults "spleen rates" tend to be lower in areas of stable malaria than in areas where unstable seasonal malaria occurs. In a variety of experimental animals the remarkable splenic activation following plasmodial infection can be easily demonstrated, although the degree of response varies among individuals within a population. In children in malarious areas spleen rates are higher than in adults, and the parasites are easier to find in the peripheral blood. As immunity develops parasitaemia decreases, but a high level of immunity to malaria is associated with the persistence of small numbers of parasites in the circulation. Dramatic reactivation of such latent infection may be seen after splenectomy. In acute malaria, however, a palpable spleen may not be present. The careful and repeated examinations of thick and thin films for malaria parasites stained with Giemsa or Leishman stain remains one of the most important laboratory procedures in tropical practice.

The spleen enlarges in malaria as the result of several pathological processes—namely, reticulo-endothelial and lymphoid hyperplasia probably reflecting the immune response, pigment deposition, and varying degrees of sinusoidal dilatation.

All degrees of splenomegaly, often associated with hepatomegaly, are encountered in malaria.

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Leishmaniasis.—*Leishmania donovani* infections are associated with notable hepatosplenomegaly, both organs progressively enlarging as the load of parasites increases. The enlargement is due to intense multiplication of leishmania in the reticuloendothelial cells of the liver and spleen, and resolves with successful therapy. There is surprisingly little fibrosis or sign of inflammation in these organs as a result of this parasitic invasion. The presence of very high serum globulins and the marked leucopenia, should suggest this diagnosis in patients from endemic areas. *Leishmania* are best demonstrated in Giemsa-stained smears of the bone marrow or splenic aspirate. Splenic aspiration carries more risk than that of the bone marrow, but with practice using an intramuscular needle attached to a syringe adequate specimens can be obtained with little discomfort or danger to the patient. Culture of such material on blood-enriched agar at 24° C. produces *L. donovani* leptomonads in one to four weeks. The behaviour of different strains of *L. donovani* in man from different parts of the world (China, India, East Africa, the Mediterranean, Brazil) varies as to the frequency of certain physical signs, the prevalence of circulating leishmania, and the response to drug therapy. Visceral leishmaniasis usually responds dramatically to one or more courses of a pentavalent antimonial.

Schistosomiasis.—A soft tender hepatosplenomegaly may occur during the acute invasive phase of schistosomiasis. A high eosinophilia may be present at this stage. The commoner type of splenomegaly associated with schistosomiasis, however, follows egg deposition in the portal tracts of the liver with consequent portal fibrosis, presinusoidal portal hypertension, and resultant congestive splenomegaly. Lymphocytic hyperplasia within the spleen may also contribute to splenomegaly. The liver is usually firm and palpable. Marked portal fibrosis may be associated with a liver palpable only within the costal angle. A disproportionate enlargement of the left lobe of the liver has been noted.

The development of schistosomal portal fibrosis is related to the species of schistosome and the load of adult flukes. Since *S. japonicum* and *S. mansoni* adults both live in the veins of the portal system, these species are more frequently responsible for this type of liver disease in contrast to *S. haematobium*. *S. japonicum* produces ten times as many eggs as *S. mansoni* per gravid female, and in areas of the Far East where transmission is intense schistosomal portal fibrosis is often well established in childhood.

The diagnosis is established by finding the characteristic fluke eggs in stool concentrates or in rectal snips. Liver biopsy may show egg deposition, schistosomal granulomata or pigment, portal fibrosis, or eosinophilic trails. Cheever⁵ has shown that established portal fibrosis may be present when eggs and adults are difficult to find, and that this relates to the age of the infection and the site of the flukes in the portal tree. The antischistosomal drug niridazole tends to give rise to central nervous system side-effects in patients with portal hypertension.

These parasitic infections cannot be overstressed as important causes of splenomegaly in tropical practice. Every practitioner working in the tropics should establish at the outset whether these infections are prevalent in his area. Double infection with malaria and schistosomiasis may be common in endemic areas.

Other Infections

Many infections cause minor degrees of splenomegaly. Some examples of the types of infectious agent producing acute or chronic splenomegaly are listed in Table II. Diagnostic criteria are outside the scope of this article.

Acute splenic enlargement, even in areas where the prevalence of palpable spleens is high, can be suspected clinically if the spleen is soft and tender. Infarcts of the spleen can be

TABLE II.—Infectious Agents Producing Splenomegaly

Acute Infections		Chronic Infections
Virus	e.g. Infectious mononucleosis Infectious hepatitis Measles (in children)	Tuberculosis Brucellosis Deep systemic mycoses
Rickettsia	e.g. Typhus	
Bacteria	e.g. Typhoid, relapsing fever, Brucellosis Bartonellosis Subacute bacterial endocarditis	

either spontaneous or associated with emboli; they produce sudden pain and perisplenitis, and a rub may be audible. Brucellosis produces acute splenomegaly, and may be associated with giant splenomegaly in the chronic phase. *Bartonella bacilliformis* infections illustrate the value of knowledge of the geographical distribution of a disease—with the possible exception of Thailand,⁶ this infection is restricted to the Andean Cordillera.

Blood Disorders

Splenomegaly often presents in adult life in African homozygous sickle-cell disease if the patient survives. This probably represents the effect of more than one condition, as similar Negro subjects in the United States very seldom have an enlarged spleen. The importance of malaria in this respect has been shown by the findings that long-term antimalarial drug therapy dramatically reduced the incidence of splenomegaly in Nigerian children with sickle-cell anaemia.⁷

Haemoglobin C disease in West Africa and haemoglobin E in the Far East are associated with splenomegaly. Thalassaemia syndromes are widely distributed in the tropics and subtropics. The interaction of these genetically determined haemolytic anaemias in a variety of combinations (for example, SC, sickle-cell thalassaemia, Hb E thalassaemia) makes haemoglobin electrophoresis an essential investigation in many areas, but unfortunately it is still not widely available.

The white blood count and cell morphology will often confirm the provisional diagnosis of leukaemia in a patient who has lymphadenopathy and splenomegaly. Lymphomas require histological confirmation. Polycythaemia and myelofibrosis may be associated with marked hepatosplenomegaly.

Whether the acute idiopathic thrombocytopenic purpura of African males associated with blood-filled bullae of the buccal mucosa justifies the specific term "onyalai" remains undecided, but splenomegaly is a clinical feature.⁸

Infiltrative Conditions of the Spleen

In a sense leukaemias and lymphomas are infiltrative, since the increase in splenic mass is the result of growth of these tissue elements. Carcinoma of the lung, stomach, and pancreas can metastasize to the spleen. Primary tumours are rare.⁴ Non-malignant infiltrations include amyloidosis and the lipoidoses, which may rarely be responsible for gross splenomegaly in childhood. Iron deposition in the liver and spleen may be associated with liver fibrosis and congestive splenomegaly. Apart from the orthodox causes of splenic abscesses two require special mention in relation to tropical practice. Melioidosis may present as a deep-seated abscess of the spleen, especially in Asiatic practice. In some patients with sickle-cell anaemia gaseous abscess of the spleen is an unusual complication, and x-ray may reveal a fluid level.⁹

Congestive Splenomegaly

Cirrhosis implies hepatic fibrosis with disruption of the normal hepatic architecture. This causes obstruction to portal flow with consequent portal hypertension. The splenic congestion which results is the commonest cause of splenomegaly

in some parts of the tropics—for example, Algeria, Hong Kong, and Calcutta. In a book¹⁰ with the misleading title of "Tropical Splenomegaly," Basu and Aikat discuss this syndrome in Calcutta and resurrect the old concept of Banti that splenomegaly may precede liver fibrosis and influence the development of cirrhosis. The evidence brought forward to support this hypothesis is weak, and we prefer the concept of primary liver disease.

Boyer *et al.*¹¹ from Calcutta suggest that congestive splenomegaly may arise in some patients as the result of portal hypertension due to non-cirrhotic portal fibrosis associated with intrahepatic portal vein sclerosis—a process which can be demonstrated histologically in wedge liver biopsies. Since such portal fibrosis is common in many parts of the tropics this mechanism may operate in many cases of the tropical splenomegaly syndrome. Sherlock¹² has recently reviewed the literature relating to hepatolienal fibrosis without cirrhosis.

Extrahepatic portal obstruction due to portal vein thrombosis and cavernous malformation of the portal vein is another important cause of portal hypertension and congestive splenomegaly. Umbilical sepsis in childhood is common in the tropics, and may result in more frequent extrahepatic portal obstructions in later life.

Clinical stigmata of hepatic insufficiency or hepatic failure suggest cirrhosis. Liver biopsy may settle the question of whether or not cirrhotic or non-cirrhotic portal fibrosis is present. A bruit may be present in the splenic and hepatic areas in patients with portal hypertension. A barium swallow may show oesophageal varices. Direct measurement of portal pressure and splenovenography are required to establish the degree of portal hypertension and whether an extrahepatic block is present. Techniques for measuring liver and splenic flow are seldom available in tropical practice.

Tropical Splenomegaly Syndrome

This is really a diagnosis by exclusion, and has been variously termed idiopathic splenomegaly, tropical splenomegaly, "Big Spleen Disease," cryptogenetic splenomegaly, Bengal splenomegaly, splenomegalie algérienne, and African macroglobulinaemia. Clinically patients complain of a dragging pain in the abdomen, intermittent fevers, and debility with marked splenomegaly present for many years, and hepatomegaly particularly of the left lobe. There is seldom any peripheral lymphadenopathy.

Present evidence suggests it is helpful to classify these cases as follows:

(a) Association with Hepatic Sinusoidal Lymphocytosis

A curious liver biopsy change, hepatic sinusoidal lymphocytosis (H.S.L.) (see Fig. 2) has been observed in many such patients in Algeria, India, Aden, New Guinea, and many parts of equatorial Africa. The hepatic sinusoidal infiltrate is mainly lymphocytic, though other chronic inflammatory cells are seen. In both liver and spleen there are varying degrees of sinusoidal and reticuloendothelial hyperplasia, but no malaria pigment. Marked erythrophagocytosis has been described in the spleen.¹³ The association of marked splenomegaly with this liver change has been called "Big Spleen Disease,"¹⁴ although lesser degrees of H.S.L. do occur without clinical splenomegaly.¹⁵ The cause of this cellular infiltration of the liver sinusoids is unknown. In Algeria and Calcutta, where satisfactory malaria control has been established, this syndrome has almost disappeared. Long-term antimalarial therapy results in a reduction of splenic size¹⁶ and disappearances of hepatic sinusoidal lymphocytosis.¹⁷

An increase of serum globulins in the gammaglobulin fraction is a feature of this syndrome. This is due to an increase in the IgG, and especially the IgM (macroglobulins)

fractions.¹⁸ In Kampala and New Guinea patients with splenomegaly and hepatic sinusoidal lymphocytosis have a high malarial fluorescent antibody titre.^{15 19} It has been suggested that this condition represents an abnormal immune response to malaria.

FIG. 2.—Hepatic sinusoidal lymphocytosis. There is also sinusoidal dilatation but no malaria pigment. The basic architecture is preserved and parenchymal cells are normal. ($\times 175$ approx.)

In adult patients with this condition in Kampala persistent blood film examinations showed a higher incidence of *P. malariae* parasitaemia.²⁰ This finding was not confirmed in New Guinea.¹⁵

The absence of malaria pigment in the liver and spleen of these patients has been cited as evidence against the concept that malaria might be playing a part. The length of time malaria pigment persists in the tissues of man is not known, but it may be of doubtful value in longstanding infections as a histological marker in indicating malaria infection.²¹ Not all patients with clinical malaria have pigment demonstrable on liver biopsy.²²

As in other patients with marked splenomegaly certain complications are common. A feeling of weight in the abdomen associated with the enlarged organ, which has been present for many years, is a frequent symptom. The co-existent anaemia is the compound result of an increased plasma volume, a reduction of red cell survival time, and trapping of large volumes of red cells in the splenic pool.^{23 24}

Portal hypertension is commonly associated with this condition, and occurs in the absence of obvious intra- or extra-hepatic obstruction. It may be related to increased splenic flow.²⁵

(b) Without Hepatic Sinusoidal Lymphocytosis

Even in malarious areas tropical splenomegaly syndrome occurs without hepatic sinusoidal lymphocytosis, and the aetiology is quite unknown. Whether non-cirrhotic portal fibrosis is responsible as suggested by Boyer and his colleagues¹¹ requires investigation. It is likely that the mechanism of the anaemia found in these cases is similar to that described above.

Treatment

The therapeutic approach to the tropical splenomegaly syndrome associated with hepatic sinusoidal lymphocytosis has varied from centre to centre. Antimalarial chemotherapy has been used.^{16 26} At Ibadan with a daily dose of 100 mg. proguanil a slow but progressive diminution in the size of the spleen over a matter of months was noted associated with an improvement in anaemia and general health. In such patients antimalarial chemoprophylaxis under medical surveillance should probably be continued for as long as they reside in a malarious area.

More information on the success of this therapeutic approach is needed.

There is usually an element of haemolysis in the anaemia in these cases, and folic-acid deficiency is a possibility which should be corrected. Exchange transfusion may be required in cases of acute haemolysis such as may occur in pregnancy.²⁶

In tropical splenomegaly syndrome simple splenectomy has been attended by a low initial mortality,²⁷ and markedly improves the co-existent anaemia.^{26 28} The susceptibility of splenectomized individuals to malaria and other infections makes this a risky procedure of doubtful long-term value. It is worth noting that the only three *Babesia* infections of man (a protozoon ill adapted to man) have all occurred in individuals who previously had had a splenectomy.

Conclusion

The classification used is an oversimplification. For instance, among the conditions that have not been considered hydatid disease or veno-occlusive disease of the liver may cause splenomegaly in a tropical area. In contrast to London teaching hospital practice collagen diseases and rheumatoid arthritis do not deserve consideration as important causes of splenomegaly in the tropics, although they are seen. Such conditions are swamped by the welter of other infections. Several processes may be going on in the spleen at the same time and contributing to its increase in size.

Even in centres where every diagnostic facility is available the aetiology of marked splenomegaly may remain unknown. In the tropics, where such a situation is encountered far more frequently, further research is needed.

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

New Influenza Vaccine

Q.—Some of the partners in this practice, and their staff, have had the usual injection of influenza vaccine this year. Should we also have an injection of the new vaccine against Asiatic virus?

A.—Though they were vaccinated earlier this year, the doctors and their staff should receive a dose of the new vaccine prepared from an A2 strain antigenically similar to that isolated in Hong Kong at the onset of the epidemic. The vaccine used in the early autumn had been prepared from influenza virus strains then currently endemic in this country and against which most adults already had demonstrable antibodies. The vaccine boosted antibody titres against these strains, but was less effective in stimulating antibody production against the Hong Kong strain. Only a few individuals have demonstrable antibodies against the Hong Kong strain, and, though the vaccine given in early autumn would have produced a weak antibody response in some of the recipients, a dose of the new Hong Kong strain vaccine would greatly increase the titres of these antibodies.

Risk of Spina Bifida

Q.—A girl has a half-brother (their mother is the same) with spina bifida. What is the risk of the girl having children with spina bifida?

A.—No empirical risk figures are available for this situation, but any children of the patient will be third-degree relatives of the boy with spina bifida. The risk here is probably less than 1%.¹

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Lithium and Foetal Abnormalities

Q.—Is there any risk that lithium carbonate may cause foetal abnormalities when taken in pregnancy?

A.—A systematic study, with present-day animal breeding techniques, to answer this question, has not yet been carried out. Never-

theless, it is known that lithium ions when added in sufficient concentration to the nutrient media of developing sea urchins and chick embryos may produce developmental abnormalities.^{1 2} In mammals, such as mice and rats, experiments neither implicate nor clear lithium definitely.^{3 4} For this reason very careful consideration should be given before lithium carbonate is administered to pregnant women, particularly in the first trimester. Obviously, if a patient is known to become severely psychotic in the absence of lithium, the possible harmful effects on the foetus resulting from this disturbed mental state and the possible physical concomitants must be balanced against the unknown risks of the drug. In fact, the writer has had one such case, and Schou² has reported six others when lithium was given throughout pregnancy without any complications and the delivery of normal babies.

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