# Tropical Splenomegaly Syndrome

In many tropical countries "all spleens are big; some spleens are bigger than others." Necropsy studies in Nigeria[1] and Uganda[2] showed that the mean spleen weight in adults was considerably greater than in temperate countries. The tropical splenomegaly syndrome, the term for big spleens of undetermined aetiology in a tropical environment, appears to be applicable to spleens at the upper end of a continuous distribution. Any cut-off point is likely to be arbitrary. There have been several excellent reviews of the problem,[3-5] and recent studies bring us nearer to a better identification of the disorder.

In general the tropical splenomegaly syndrome is common where malaria is endemic and is rare where malaria is controlled or absent. The disease is well known in Nigeria, Uganda, New Guinea, and the Congo, and there are also reports from South Arabia, Zambia, and the Sudan. In these areas it is probably caused either directly or indirectly by malaria, and no other factor has consistently been implicated. Whether the gross splenomegaly seen in Hong Kong[6] and Calcutta[7] represents the same problem is not clear, as severe liver disease is also common in these two areas, and some evidence suggests that splenic enlargement may precede the hepatic disorder. Only a small proportion of people exposed to malaria get tropical splenomegaly syndrome, so that additional factors are involved or the host is responding in some unusual way. There is no evidence to suggest any genetic or racial predisposition or impairment in cellular or humoral immunity; the intense lymphoreticular proliferation observed in this disorder is not associated with an immunological deficiency.[8] One of the studies in Uganda pointed to *Plasmodium malariae* as a causal factor,[9] but this has not been confirmed by studies in Nigeria[10] or New Guinea,[11] and there have been no additional reports from Uganda to support this earlier finding.

The interplay of malaria and migration has aroused interest in the immunological aspects of tropical splenomegaly syndrome. In the Kampala region of Uganda the people originating from the malaria-free highlands of Rwanda to the south have greater mean spleen weights at necropsy[2] and a far higher frequency of splenomegaly than the indigenous Baganda people.[12] The Rwandans also show an immunological syndrome with high titres of malarial antibody and high levels of IgM, rheumatoid factor, and circulating autoantibodies to heart, thyroid, and gastric parietal cells. This syndrome is seen far less frequently in the people indigenous to the Kampala region.[13] It has been suggested that exposure to malaria in later life in those coming from areas of low malarial endemicity may result in this immunological syndrome, of which splenomegaly may be a constituent manifestation. However, tropical splenomegaly syndrome may occur in some areas where migration is infrequent, and then it is possible that intermittent exposure to malaria (or intermittent protection from it) may be the cause. The story of malaria, migration, and macroglobulins is attractive but not completely satisfactory; many Rwandans with splenomegaly have been born and brought up in Buganda.

From Zambia has come the first report of tropical splenomegaly syndrome in a white (Caucasian) person resident in Africa.[14] The patient had spent the first 15 years of her life in the malaria-free Kenya highlands and had then lived for several years on Lake Victoria (Kampala and then Mwanza) before moving to the rural part of Zambia. After 17 years in Zambia gross splenomegaly was incidentally discovered on admission to hospital for cholecystitis. The patient resembles the Rwandans in Uganda in having moved from a malaria-free area, and the case shows that the condition does not depend on ethnic origin, malnutrition, or severe overt malaria, while it points to the possibility of an unusual response to malaria in people exposed to the disease in later life.

The tropical splenomegaly syndrome most commonly presents in young adults, though it has appeared as early as four years of age. The patient usually has a feeling of discomfort in the abdomen, occasional fever, and general debility. The liver is also usually enlarged, and portal hypertension is a feature of gross splenomegaly. Serum albumin is reduced and serum globulin raised. The IgM level is high, and this is almost invariably associated with a high malarial antibody titre. The patient usually has anaemia, leucopenia, and thrombocytopenia, but spontaneous bleeding is unusual. The anaemia is the combined result of an increased plasma volume, a reduced red cell survival time, and an increased proportion (up to 40%) of the red cell mass in the spleen. While leucopenia is usual, a number of cases show an absolute lymphocytosis, which may reach leukaemoid proportions. In pregnant women severe haemolytic crisis with deep jaundice may occur.

The diagnosis of tropical splenomegaly syndrome has traditionally been by exclusion of all disorders known to cause splenomegaly, and in any particular tropical area the list of diseases to be considered will be ranked according to frequency in that area. Where the disease is endemic, as much as two-thirds of gross splenomegaly may be of uncertain origin. Typhoid, chronic brucellosis, acute malaria in young persons, schistosomiasis, hepatic cirrhosis with portal hypertension, kala-azar, and sickle-cell anaemia must all be included on most tropical lists. Chronic lymphatic leukaemia and malignant lymphoma are among the most likely diseases of the lymphoreticular system with which it might be confused.

A study from Nigeria by Dr. A.-S. Sagoe, published in the *B.M.J.* this week (page 378) provides further positive criteria for the diagnosis of tropical splenomegaly syndrome. Forty-three adult patients with an initial diagnosis of the disease were put on long-term treatment with proguanil. In 32 patients ("responders") the spleen diminished by the end of six months. In these patients IgM values before treatment were very high and phytohaemagglutinin lymphocyte-transformation scores were normal. During treatment the IgM values fell gradually, closely paralleling the decrease in spleen size. In the 11 patients who failed to respond to proguanil ("non-responders") initial IgM values were not raised and phytohaemagglutinin lymphocyte-transformation scores were abnormally low. Three of the 11 defaulted and two of these


[1] Bruce-Chwatt, L. J., *Bulletin of the World Health Organization*, 1956, **15**, 513.
[2] Shaper, A. G., *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1969, **63**, 206.
[3] Pitney, W. R., *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1969, **62**, 717.
[4] Marsden, P. D., and Hamilton, P. J. S., *British Medical Journal*, 1969, **1**, 99.
[5] *British Medical Journal*, 1969, **4**, 4.
[6] Cook, J., McFadzean, A. J. S., and Todd, D., *British Medical Journal* 1963, **2**, 337.
[7] Basu, A. K., and Aikat, B. K., *Tropical Splenomegaly*. London, Butterworths, 1963.
[8] Ziegler, J. L., Cohen, M. H., and Hutt, M. S. R., *British Medical Journal*, 1969, **4**, 15.
[9] Marsden, P. D., *et al.*, *British Medical Journal*, 1965, **1**, 89.
[10] Watson-Williams, E. J., Allan, N. C., and Fleming, A. F., *British Medical Journal*, 1967, **4**, 416.
[11] Marsden, P. D., *et al.*, *Bulletin of the World Health Organization*, 1967, **36**, 901.
[12] Hamilton, P. J. S., *et al.*, *East African Medical Journal*, 1965, **42**, 191.
[13] Shaper, A. G., Kaplan, M. H., Mody, N. J., and McIntyre, P. A., *Lancet*, 1968, **1**, 1342.
[14] Lowenthal, M. N., and Hutt, M. S. R., *British Medical Journal*, 1970, **3**, 262.

were reported to have died. Definite diagnoses of chronic lymphatic leukaemia (3), Hodgkin's sarcoma (1), and lymphoma (1) were made, and three other patients developed autoimmune haemolytic anaemia and were considered to have lymphoma.

By the end of four to six months every patient in this Nigerian series could be classified as belonging to the responders or non-responders, and it would appear retrospectively that the differential diagnosis could have been initially made on the IgM level and the phytohaemagglutinin lymphocyte-transformation score. This represents a major advance in the diagnosis and management of tropical splenomegaly syndrome.

## Diet and Athletics

Athletes have always had a great interest in diet and often believe in the peculiar efficiency of some particular additive. But J. V. G. A. Durnin[1] has stated that "There is still no sphere of nutrition in which faddism and ignorance are more obvious than in athletics," and he goes on, "With slight qualifications, I do not think that physical fitness is influenced by diet." The subject has also been well summarized.[2 3]

A recent study[4] of 80 Australian Olympic athletes shows that their average daily intake of calories varied from about 2,000 kcal. to 6,000 kcal. Protein intake also varied widely, from 60 to 300 g., the mean being 1·8 g. per kg. body weight for men and 1·9 g. per kg. for women. On the average the proportion of calories derived from protein, fat, and carbohydrate was similar to that of usual Australian diets, but intake of minerals and vitamins was generally higher. The belief still persists, says the author, "that the consumption of large quantities of meat is necessary for athletes taking part in competitions requiring muscular strength and stamina." She also notes that a group of athletes who performed well at the Olympic Games had a higher intake of thiamine than another group whose performance at the games was indifferent.

Studies in Sweden have shown[5] that the muscle glycogen drops steadily during moderately heavy exercise. This fall is confined to the exercising muscles,[6] and the time for which muscles can work is directly related to the glycogen store in them.[7] J. Bergström and colleagues[8] have shown that changes in diet can alter the glycogen content of muscle. The average glycogen content was 1·75 g. per 100 g. muscle after a normal mixed diet, 0·63 g. after a protein-fat diet, but 3·3 g. after a diet which was almost wholly carbohydrate. Tolerance for moderately heavy work was directly related to the initial level of muscle glycogen and averaged 59 minutes for the protein-fat diet, 126 for the normal diet, and 189 for a predominantly carbohydrate diet.

On the basis of these results P. Åstrand[5] has recommended that athletes should first exhaust their stores of the muscle glycogen by moderately heavy work and then, after a short period on a high protein-fat diet, should feed almost exclusively on carbohydrate. This appears to be the most effective way of building up a large store of muscle glycogen. In this way, it is claimed, the athlete can perform exhausting work for much longer than usual. However, athletes seem to have been reluctant to carry out the treatment, and so no evidence in terms of success in athletic events is yet available. The use of anabolic steroids is another matter. Despite the official ban on their use some athletes engaged in power events, such as throwing and weight-lifting, are believed to take them.

In general Durnin is probably right that diet plays little part in athletic performance provided the athlete eats an ordinary balanced diet without any particular additives. But the work of Åstrand[5] and his colleagues certainly suggests that there may be special cases in which dietary alteration can be allied with training methods.


1 Durnin, J. V. G. A., *Canadian Medical Association Journal*, 1967, **96**, 715.
2 Van Itallie, T. B., Sinisterra, L., and Stare, F. J., *Journal of the American Medical Association*, 1956, **162**, 1120.
3 Mayer, J., and Bullen, B., *Physiological Reviews*, 1960, **40**, 369.
4 Steel, J. E., *Medical Journal of Australia*, 1970, **2**, 119.
5 Astrand, P.-O., *Federation Proceedings*, 1967, **26**, 1772.
6 Ahlborg, B., Bergström, J., Ekelund, L.-G., and Hultman, E., *Acta Physiologica Scandinavica*, 1967, **70**, 129.
7 Hermansen, L., Hultman, E., and Saltin, B., *Acta Physiologica Scandinavica*, 1967, **71**, 129.
8 Bergström, J., Hermansen, L., Hultman, E., and Saltin, B., *Acta Physiologica Scandinavica*, 1967, **71**, 140.


## Cotton-wool Spots in the Eyes

Cotton-wool spots in the retina were described in diabetes by T. Leber in 1875. They consist of localized swelling of the deeper layer of nerve fibres due to proliferative changes in the axoplasm. Lesions of similar appearance occur in such varied conditions as accelerated hypertension, embolic disorders, acute loss of blood, severe anaemia, scleroderma, dysproteinaemias, and terminal carcinoma, in all of which anoxia from focal circulatory failure appears to be the underlying cause.[2]

The cotton-wool spots in diabetes were for a long time thought to be uncommon and, when present, to be due to associated hypertension. However, V. Esmann and colleagues[3] found them in 32% of their patients with diabetic retinopathy and noted that their presence was unrelated to arterial pressure.

E. M. Kohner and colleagues[4] have compared the natural history of the cotton-wool spots in diabetes with those in accelerated hypertension. Their 136 diabetic patients were studied by serial colour and fluorescein photography, and 19 of these were also studied by fluorescein cine-angiography. Cotton-wool spots were observed in 36 of 71 patients with asymptomatic diabetic retinopathy and in 25 of 65 patients with impaired vision due to severe diabetic retinopathy. Arterial pressures were seldom raised above normal, and only five patients had diastolic pressures of over 110 mm. Hg. The spots were usually distributed within three disc diameters of the papilla and varied in size from 0·1 to 1 mm. The presence of six or more spots heralded rapidly progressive retinopathy, but, once new vessel systems developed, cotton-wool spots were uncommon.

In appearance the established spots were often like those in hypertension, but they differed in their rate of evolution and disappearance. Whereas in hypertension they developed a shiny white appearance within 24 hours, in diabetes they evolved more slowly, frequently persisting as ill-defined greyish-white discolorations in the nerve fibre layer. The average time for the spots to diminish by 50% in size in diabetes was 8 months in patients under 40 and 17 months in patients over 40, whereas in treated hypertensive patients the lesions disappeared in 1½ to 3 months.

Fluorescein angiography showed areas of capillary non-


1 Leber, T., *Albrecht von Graefes Archiv für Ophthalomolgie*, 1875, **21**, 206.
2 Ashton, N., *British Medical Bulletin*, 1970, **26**, 143.
3 Esmann, V., Lundbaeck, K., and Madsen, P. H., *Acta Medica Scandinavica*, 1963, **174**, 375.
4 Kohner, E. M., Dollery, C. T., and Bulpitt, C. J., *Diabetes*, 1969, **18**, 691.
5 Hardy, J., Panisset, A., Marchildon, A., and Lanthier, A., *Canadian Medical Association Journal*, 1969, **100**, 785.
6 Joplin, G. F., *et al.*, *Quarterly Journal of Medicine*, 1965, **34**, 443.