DIAGNOSIS AND TREATMENT OF SPLENIC ENLARGEMENT IN CHILDREN.*

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INTRODUCTORY.

ENLARGEMENT of the spleen is a physical sign, like jaundice, due to many causes, which in the vast majority of cases are infective, though in many instances, such as in von Jaksch's anaemia and aplastic anaemia, it may be impossible to go further than to assume such an origin. The more unstable condition, as regards response to stimulation, of the blood-forming organs in early life as compared with that in adult life makes the significance of the blood picture a difficult and therefore an interesting problem.

The spleen and the lymphadenoid tissues generally are more prone to active response and enlargement in childhood than in later life, and the spleen in particular is more distensible than in adults. In considering the subject it will be well to take conditions in which the spleen is very definitely enlarged, and not to include cases in early infancy in which the edge can be felt just below the ribs; this is of less significance in early infancy than in subsequent years. In G. Carpenter's series of 348 cases of enlarged spleen in children under 12 years of age, 94 occurred in the first six months of life and 220 under 18 months of age; it is probable that some of these were due to rickety deformity displacing the spleen downwards rather than to real splenomegaly.

A special point of interest in connexion with splenic enlargement is in the early stages of the chronic diseases in which it is recognized as occurring, when the other manifestations characteristic of the fully developed disease have not appeared. In some instances splenomegaly may constitute the chief or only clinical sign of an incomplete or fruste form of a disease—for example, in chronic haemolytic jaundice and Hanot's cirrhosis. A palpable spleen has been found as the only physical sign in a family in which other members had Hanot's hypertrophic biliary cirrhosis (Boinet).

A question deserving discussion is the probability that in some cases splenic enlargement is due to more than one factor—for example, syphilis complicated by a low grade streptococcal infection or by tuberculosis. Syphilis may well favour a secondary infection, and then (vide infra) anti-syphilitic treatment may fail to be curative.

It would no doubt be convenient to group the forms of splenomegaly under a number of inclusive headings, such as (1) those that may be familial (chronic splenomegalic haemolytic jaundice, Gaucher's disease, and congenital syphilis); (2) those associated with changes in the blood picture (anaemia, haemolysis, erythraemia, leukaemia); (3) those definitely infective, whether acute, as in enteric fever, or chronic, as in congenital syphilis and tuberculosis; (4) those of tropical origin (malaria, kala-azar); (5) mechanical (growths, cysts, infarcts); (6) associated with hepatic enlargement or cirrhosis. But though this arrangement is attempted, there is obviously such an amount of overlapping as to render it of little value, except as a means of arranging the various conditions in some order or other.

1. FAMILIAL SPLENOMEGALY.

Familial splenomegaly may be due to chronic splenomegalic haemolytic jaundice, Gaucher's disease, and congenital syphilis. In addition, it is well to bear in mind the possibility that familial splenomegaly may occur in other and undetermined conditions; De Lange and Schippers recorded a family of seven in which four children had enlarged spleens; one died from haematemesis and two others underwent splenectomy.

In chronic splenomegalic haemolytic jaundice the diagnosis depends on the examination of the blood for fragility

of the red cells; and the treatment, in cases with symptoms demanding it, is splenectomy. After splenectomy the symptoms of chronic haemolytic jaundice disappear, but the red blood cells hardly ever become normal as regards fragility, thus suggesting that the fragility is an inherent peculiarity. So far this fits in with Naegeli's suggestion that the microcytosis of the condition is evidence that these patients belong to a different type of human species. But against this interesting conception are the observations that microcytosis is confined to those members of a family with chronic haemolytic jaundice (Meulengrath), and that after splenectomy microcytosis diminishes (Whitcher).

The cholesterol content of the blood rises after splenectomy, and this might suggest that the fragility and haemolysis depend on the low cholesterol content; but an equally low content is found in some anaemias without fragility (Campbell and Warner), and it has been thought to depend on the relative proportions of cholesterol and lecithin. Thus the medicinal administration of cholesterol in chronic haemolytic jaundice does not rest on such a logical basis as might have appeared at first. X-ray exposures were recommended by Parisot and Heully as the result of benefit in two cases of the congenital form, but subsequent experience does not appear to have been confirmatory.

Gaucher's Disease.

This condition (*épithéliome primitif*), first described in 1882 as a neoplasm, is now considered to be a special change in the reticulo-endothelial system, and from its racial (Jewish), familial, sexual, and congenital characters has been regarded as a constitutional anomaly, a mutation in the human species (Naegeli; Waugh and MacIntosh). It is a striking but rare disease; in 1924 Conner referred to 24 recorded cases. It is familial, but this has not always been established—for instance, the sixth recorded case in France was the first shown to be familial (Harvier and Lebé). Though the condition involves the spleen, lymphatic glands, liver, and bone marrow probably simultaneously, it is most obvious, both in point of its chronological appearance and objectively, in the spleen, which may be larger than in any other disease suitable for splenectomy; the superficial lymphatic glands are very seldom enlarged. From the distribution of the lesion splenectomy cannot be expected to bring about a real cure, but it gives relief. In Harvier and Lebé's 13 collected cases of splenectomy (9 adults, 4 children) there were 3 deaths after operation, and among 51 collected splenectomies in patients under the age of 14 years 4 were for this condition (Bartlett). It is characterized by a peculiar yellowish wedge-shaped thickening of the conjunctivae, commonly seen on both sides of the cornea. According to Brill and Mandlebaum, the skin, though showing a peculiar brownish-yellow discoloration in areas exposed to the light, is never jaundiced. Now as the reticulo-endothelial system is concerned with the formation of bilirubin out of haemoglobin, the interesting question arises whether jaundice can occur in Gaucher's disease; observations with Hijmans van den Bergh's test should throw light on this point. It is noteworthy that in Willmore and Mackenzie Douglas's case of an adrenal tumour with extensive degeneration of the reticulo-endothelial system anaemia and jaundice were absent.

Splenic Enlargement in Congenital Syphilis.

This was first pointed out, at any rate in this country, by Gee in a paper read before, but not deemed worthy of inclusion in the *Transactions* of, the Royal Medical and Chirurgical Society. Gee found it in 25 per cent. of his cases, Still in 45 per cent., Marfan in 50 per cent., and Coutts in 63 per cent. It is an index of the severity and activity of the infection; in infants born with syphilitic manifestations it is almost always enlarged; in cases in which they appear later the spleen may enlarge before they become obvious, but usually this sequence is reversed; hence the variations in statistics may be explained.

In older children splenic enlargement associated with anaemia should always suggest syphilitic infection and the Wassermann or the therapeutic test. The imitation of

* Being the opening paper of a discussion on this subject in the Section for the Study of Disease in Children of the Royal Society of Medicine on November 27th.

splenic anaemia and the further stage of Banti's disease by delayed congenital syphilis is well known.

In children with an enlarged spleen and a positive Wassermann reaction antisyphilitic treatment may be disappointing, and there may not be any improvement until splenectomy has been performed. Farley has collected seven cases, not including Weil's, but all except French and Turner's were in adults. In such a case, reported by Osman, failure of salvarsan led to splenectomy, when the liver was seen to be cirrhotic; this was followed by apparent cure with a negative Wassermann reaction for six years, when haematemesis and cerebral symptoms proved fatal. The patient of French and Turner, a boy aged 5 years, in whom the blood picture had previously been that of von Jaksch's anaemia pseudo-leukaemica infantum, was very similar, except that cirrhosis was not recorded and that a younger sister also had splenomegaly.

The interesting question arises why antisyphilitic treatment fails to exert a curative action; Weil, indeed, suggested that the Wassermann reaction was due to an unknown parasite, but perhaps the more probable view is that syphilitic infection had been complicated by a secondary infection in the spleen, like that presumed to be responsible for the chronic splenic anaemia of adults.

2. CASES ASSOCIATED WITH CHANGES IN THE BLOOD PICTURE.

Acute Leukaemia.

In early life acute leukaemia is probably more often of the myeloid or myeloblastic than of the lymphoid type; it should be recognized by the blood examination. If acute progress occurs in cases previously latent the spleen may reach a large size. Except in the rare cases, such as Cabot, Marchand, and Arthur Hall's, which turn out to be examples of the lymphocytosis of acute infection,* and thus imitate acute lymphoid leukaemia, the prognosis is hopeless, and treatment with benzol, radium, x rays, and arsenic fails even to retard the inevitable end. Splenectomy, which W. J. Mayo carried out after preliminary x-ray exposures in 31 cases, with beneficial results in more than a third of the patients, does not appear to be suited to the acute cases in early life.

Murray H. Bass has recorded unusual eosinophilia with splenomegaly in a girl aged 6 years belonging to the small group of cases in the adult called eosinophilic leukaemia; the white count (25,600) showed 37 to 64 per cent. of eosinophils, with 6 per cent. of eosinophil myelocytes.

Pernicious Anaemia.

Pernicious anaemia is very rare in early life, but aplastic anaemia occurs, and from examination of a blood film only may suggest acute lymphoid leukaemia or the existence of the rather discredited entity leukanaemia.

Thrombocytopenic Purpura Haemorrhagica.

This may be (a) primary and constitutional, or (b) secondary to infection, such as by *Streptococcus haemolyticus*, drug poisoning (such as by benzol), and such morbid conditions as nephritis, hepatic cirrhosis, and leukaemia. It may be acute and even fulminating, or chronic and recur for years. It is characterized by a diminution in the number of the blood platelets, from the normal 250,000 to 40,000, 5,000, or lower, a normal coagulation time and a prolonged bleeding time often exceeding two hours (Dukes), and in the active stage by some enlargement of the spleen. There are various views as to the evil influence of the spleen in this condition, and as to the mechanism of the good results of splenectomy introduced by Frank of Breslau in 1915, and followed by Kaznelson of Prague (1917), Brill and Rosenthal (1923) in New York, B. Vincent (1925) in Boston, Cowen (1925) in Australia, and Sutherland and Williamson (1925) in London. Ricaldo and Albo report cures by splenectomy of chronic haemorrhagic purpura without splenomegaly. Frank suggested that the spleen inhibited the activity of the bone marrow; Kaznelson that it removed platelets from the blood; and Brill and Rosenthal that it produced a toxin.

Acute thrombocytopenic purpura haemorrhagica can be

distinguished from acute lymphoid leukaemia and aplastic anaemia by the blood count; from the haemorrhagic forms of diphtheria and the exanthemata by careful examination; from scurvy by the history, the spongy gums, and the reaction to antiscorbutic remedies. The chronic form can be differentiated from haemophilia by the absence of superficial haemorrhages, the normal platelet count, and the normal bleeding time in the hereditary disease.

In the past the chief form of treatment was transfusion, which had sometimes to be repeated. Splenectomy can now be employed as an emergency measure in acute cases when other means have failed to arrest the bleeding, and in the chronic form is regarded as the best remedy by Vincent, who found five fatal cases in almost fifty collected cases of the disease treated by splenectomy.

Infantile Splenic Anaemia.

Infantile splenic anaemia, meaning thereby von Jaksch's anaemia pseudo-leukaemica infantum (1889), also described by Luzet (1891), whose name is bracketed with von Jaksch's by the French, and also called splenomegaly with anaemia and myelaemia, should be definitely separated from the juvenile form of chronic splenic anaemia of adults, and for this reason von Jaksch's more cumbersome title perhaps has an advantage. It appears, like chlorosis, to have become rarer in recent years (Thomson). It is confined to the first three years of life, its maximum incidence falling in the middle of this period, and is characterized by great splenic enlargement, secondary anaemia with leucocytosis (30,000), some relative lymphocytic increase, the presence of nucleated reds, a constant myelaemia (up to 6 per cent.), and tendency to spontaneous recovery. It is often associated with rickets; but except for Beretervide and Bianchi modern writers do not consider that congenital syphilis, which certainly is found in a proportion (less than half) of the cases, is responsible except by diminishing the resistance to the as yet unknown cause. Marquard recorded the disease in twins, and suggested that some congenital factor is responsible, but the tendency to spontaneous recovery is rather against this view. Thursfield, who has paid special attention to this disease during this century, puts the recovery rate at 65 to 70 per cent., and doubts the suggestion that it is specially frequent in Jews. It is familial; the twins figuring in the frontispiece of Hutchison's *Lectures on Children's Diseases* when seen at the age of 12 years had recovered and their spleens were no longer palpable; but splenic enlargement may persist after the blood picture has become normal. Beretervide and Bianchi of Buenos Aires also differ from the general opinion in taking a gloomy prognostic view, and state that in ten years' experience they have not seen a cure; the possibility that the disease they describe is different from the British form in some respects, etiologically or environmentally, naturally arises. In the absence of any definite knowledge of its real cause reliance has chiefly been placed on hygienic measures; splenectomy, which would seem rather unnecessary in the light of the recovery rate, has, according to Bartlett, been carried out in five cases.

Chronic Splenic Anaemia.

That chronic splenic anaemia of the form seen in adults may occur in older children I have no doubt. There is rightly some scepticism about the existence of such a condition, and it may fairly be said that it is only cases of unknown origin which can be so labelled. But there are such cases which cannot, in the presence of a negative Wassermann reaction, be regarded as syphilitic, unless the view be taken that the splenomegaly is the legacy of a spirochaetal infection which has died out. Some young adults with chronic splenic anaemia have had an enlarged spleen from childhood; I have recorded such a case, and Leech reported a case fatal after splenectomy (spleen 426 grams, or 13 oz.) in a boy aged 9 years with a negative Wassermann reaction. It has been suggested that von Jaksch's anaemia is the infantile form of the chronic splenic anaemia of adults, and that the blood picture depends on the more active response of the blood-forming organs; but the difference in the prognosis—von Jaksch's anaemia often undergoing spontaneous cure, while chronic

* H. L. Tidy, it may be mentioned, has vigorously criticized the existence of cases of absolute lymphocytosis due to sepsis.

splenic anaemia of adults does not—makes this an improbable assumption. I have not any reference to splenic anaemia due to thrombosis of the splenic vein in a child.

Banti's Disease.

In Banti's disease and portal cirrhosis with splenomegaly removal of the spleen has sometimes been beneficial (Osman), but the general opinion is that splenectomy is most successful in cases before the liver has become cirrhotic—namely, in the stage corresponding to splenic anaemia and before Banti's disease has supervened. Among 69 collected cases of splenectomy for chronic splenic anaemia—mainly in adults as shown by the average age of 33 years, the extremes being 2½ and 69 years—Chaney found that 23.3 per cent. of the 30 cases showing hepatic cirrhosis proved fatal within forty days of the operation, whereas in cases without hepatic cirrhosis the corresponding mortality was 13 per cent. Richards and Day found that in Egyptian splenomegaly, in which hepatic cirrhosis is an early accompaniment, splenectomy was beneficial if performed before the appearance of ascites.

Erythraemia.

The spleen is nearly always enlarged in this condition, which, however, is rare in childhood. In his monograph on the subject Parkes Weber refers to about six cases in early life, two of which were probably associated with congenital syphilis. Poynton, Thursfield, and Paterson recorded a case in a girl aged 3½ years. Splenectomy is inadvisable as the spleen serves as an overflow for the excess of blood. Benzol by the mouth and x-ray exposures of the long bones may be tried, and the question of intestinal infection and toxæmia should be considered.

3. CASES OF INFECTIVE ORIGIN.

Infective Splenomegaly.

Infective splenomegaly as part of an acute general affection of the haemopoietic system is very rare. I have seen a mixed infection of the glands, which in places were breaking down, due to *B. coli* and streptococci. Osman reported a case of anaemia with splenomegaly associated with tonsillitis in a boy aged 6½ years who was in good health eight years later. Infarcts and enlargement of the spleen in malignant endocarditis, and the spleen of enteric fever, should be recognized by the special features of the causal disease.

As regards chronic infections, the field is large. Perhaps the palpable spleen sometimes present in status lymphaticus may, like that condition, be due to a low grade infection, as suggested by H. C. Cameron. In Still's disease, or the juvenile form of rheumatoid (chronic infective) arthritis, the spleen and lymphatic glands are enlarged, and amyloid change has been reported.

Tuberculosis of the Spleen.

Tuberculosis may give rise to very considerable enlargement, both in acute miliary tuberculosis and in the chronic form. In chronic tuberculosis the organ may contain comparatively large caseous masses, resembling to the naked eye lymphadenoma. There may be adhesion to the diaphragm so that the organ, though increased in size, cannot be felt. Owing to the perisplenitis there may be pain and tenderness, and Thursfield considers that tuberculosis is the only condition of the organ in which it is often distinctly tender.

Lymphadenoma.

This is not uncommon in older children, but it is very rare to find it predominantly splenic as in a boy aged 11 years, recorded by Poynton, Thursfield, and Paterson; in this case the spleen weighed 25 oz., the liver 44 oz., both being invaded with the growth; the cervical glands were practically unaffected. Among five cases of lymphadenoma recorded by these writers two had jaundice.

Hyperplastic Lymphatic Splenomegaly.

The relative value of splenectomy and x-ray exposures in disease accompanied by splenomegaly is obviously a matter of practical importance. In spite of the tendency to produce adhesions, and so render subsequent operation

more difficult, x-ray treatment would appear to be worth a trial in cases of splenomegaly of doubtful origin, as they may be examples of the condition called by Brill, Baehr, and Rosenthal "splenomegalia lymphatica hyperplastica." They record three cases, none in children; in two, one of which proved fatal, splenectomy was performed, and then it was found that radiotherapy caused complete disappearance of the general lymphatic gland enlargement and reduction of the spleen to its normal size. The condition, which may sometimes pass unrecognized, is characterized by a normal blood count, general enlargement of the lymphatic glands, and great splenomegaly. The microscopic appearances are enormous enlargement of the Malpighian bodies, which are almost entirely composed of endothelial or reticular cells, and of the follicles of the lymphatic glands which show a similar structure. The condition is not influenced by arsenic, but is rapidly cured by exposures to the x rays.

4. TROPICAL SPLENOMEGALY.

Kala-azar.

The infantile form of kala-azar may be seen in children who have come from countries where it is endemic, and the diagnosis depends on the detection of the Leishman-Donovan parasite by splenic puncture. The liver and the spleen are enlarged, but as compared with other conditions are soft to the palpating hand. It occurs in the Mediterranean littoral, Malta, Egypt, and elsewhere, and probably many cases of typical splenomegaly are due to kala-azar. The ponos* of the Greek islands Spetsia and Hydra is of this nature. This febrile splenomegaly has been reported in children in the South of France (D'Oelsnitz, Daumas, Liotard, and Puech), and Wyllie has recorded one in a child who came from Malta to England. The treatment is the intravenous injection of tartar emetic and sodium antimonyl tartrate solutions (Rogers). After failing with medical treatment Talbot and Lyon obtained a cure from splenectomy in the first reported cases of infantile kala-azar in America.

5. MECHANICAL CAUSES.

Enlargement of the spleen due to primary new growth, hydatid and simple cysts, angiomas, and abscess are very rare. Among 57 collected cases of abscess in children 14 only were recognized clinically (La Ferla).

Reference has already been made to the cases with hepatic enlargement or cirrhosis.

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*I am indebted to Dr. A. Cawadias of Athens for the following information: πόνος τῶν Σπετίας (the pain of Spetsia) is in the neighbouring island of Hydra known by the name of τσάπανι, meaning a sort of large plate from the form of the abdomen, and in Cephalonia as Απλοπινάκι, with the same meaning. These have all been proved to be kala-azar by Gabbi (1910). The disease is relatively common, and the results of treatment by tartar emetic are very good.

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THE STRENGTH OF INSULIN PREPARATIONS:

A COMPARISON BETWEEN LABORATORY AND CLINICAL MEASUREMENTS.

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I.—INTRODUCTORY.

THE decision of the discoverers of insulin and their colleagues in Toronto to indicate the strength of the preparation in "units" of activity was undoubtedly sound, and has led to a highly satisfactory precision in its dosage. So far as this country is concerned, experience may be divided roughly into three periods.

In the first no final definition of the unit had been given, and only rough methods were available for its measurement in the laboratory. On the other hand, physicians had yet to learn what regularity of effect could be obtained with a really constant preparation, so that comparatively few complaints were heard of the differences in strength between similarly labelled batches of the solution, though it can hardly be doubted that such occurred.

In the second period, though the unit had received its final physiological definition, and a representative batch of solution had been received in this country to serve as a standard of comparison, a trustworthy method for its measurement on normal animals was still being sought. Physicians, on the other hand, with time and opportunity, had found that a patient whose diet and activities were under complete control was a very constant reagent for insulin. The effect of each daily dose on such a patient, if followed with sufficient care, provided a reasonably accurate measure of the activity of the preparation. Clinical observation, for the time being, had attained a greater accuracy than laboratory methods of assay, and it was to be expected that discrepancies would be observed, such as those collected below by Drs. Harrison and Lawrence in Table III. The suggestion naturally arose that a clinical assay of each batch of insulin should supplement that made in the laboratory before the final adjustment of its strength for issue. The Insulin Committee of the Medical Research Council decided first to organize a careful and deliberate comparison between the results of laboratory and clinical assays, on a selected series of samples.

By the time this decision was taken, however, the third period had been reached. There was reason now for hope that the laboratory test had again overtaken clinical observation in accuracy. The method devised and described

below by Mr. Marks had aimed at eliminating the effect of the wide individual differences of response shown by different animals, as thoroughly as such differences were eliminated in the clinical tests on patients of known reaction. It had endeavoured to go further, and to neutralize even the day-to-day variations of sensitiveness to insulin shown by the same animals. The comparative trials now undertaken had, moreover, the advantage that clinical and laboratory measurements were to be made at the same time; whereas many of the discrepancies earlier apparent had resulted from clinical trials made many months after the laboratory assay, at a time when the preparations of insulin were less stable than the highly purified products now available. The results of this organized comparison, as shown in Table IV of the report of Drs. Harrison and Lawrence, fully realized the expectation that the laboratory method of assay, now for some time in use at the National Institute, would be able to hold its own with the most careful clinical measurements. The correspondence is so good, indeed, as to justify the conclusion that the assay on rabbits here described by Mr. Marks, if conscientiously carried out, can fix the activity of a preparation with an accuracy that no clinical test is likely to improve.

It should be added that experience in this department with preparations standardized by other methods suggests that these also are capable of an accuracy well within the range of clinical needs, when carefully carried out in comparison with the stable standard now adopted for international use.

H. H. D.

II.—THE BIOLOGICAL ASSAY OF INSULIN PREPARATIONS IN COMPARISON WITH A STABLE STANDARD.

BY

H. P. MARKS.

The original physiological unit of insulin was defined as the smallest dose which would lower the blood sugar of a 2 kilogram rabbit, starved for twenty-four hours previously, to the convulsant level of 0.045 per cent., and this unit, with the clinical unit later based on it (1 rabbit unit = 3 clinical units), has been generally accepted. The word "unit" is here used throughout to mean such a "clinical" unit, the original or "physiological" unit being now only of historical interest.

All the earlier methods of assay based on this definition, whether they involved the observation of actual convulsions or of the fall in blood sugar produced by a subconvulsive dose, aimed at determining the potency of a sample of insulin absolutely in terms of an animal reaction.

THE STANDARD OF REFERENCE.

As it became evident that such a reaction could not furnish an invariable standard, an attempt was made in this laboratory to standardize rabbits by determining their response to a given dose of a stable reference sample whose potency had been verified at Toronto. The response of these rabbits to the sample under test was then compared with their response to the standard sample, so that, in effect, the potency of the unknown sample was expressed in terms of that of the standard preparation. Such was the state of affairs at the time when the laboratory tests were performed on the batches in Table III of the clinical report. Effort was directed to improvement of the laboratory test, so as to take full advantage of direct comparison with a standard sample of constant potency. Meanwhile we had replaced the original reference sample of insulin solution by a purified, dry preparation which could be relied upon to retain its potency unchanged. A similar preparation, made at the request of the International Conference on Biological Standards, has now been accepted for international use, and the unit of insulin has been defined by the Insulin Committee of Toronto in terms of that standard preparation.

THE METHOD OF COMPARISON.

In the experience of this laboratory, as also in that of Macleod and Orr, it has been found repeatedly that, for either of two reasons, convulsions may fail to occur in a