ON SPLENO-MEDULLARY LEUKAEMIA AND SPLENIC ANAEMIA (BANTI'S DISEASE).

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These two cases of enlarged spleen are, I think, worthy of record, because in neither case could a correct diagnosis have been made without an examination of the blood.

Dr. Frederick Taylor has shown in his Lumleian Lectures[1] that the following are the commonest causes of splenic enlargement: Taking spleens of over 30 oz. in weight, the largest occurred in cirrhosis of the liver, next in malaria, and then in infective endocarditis. Taking 379 spleens over 10 oz. in weight, he showed that, excepting in cirrhosis, the largest occurred in infective endocarditis, tubercle, typhoid, then heart disease and cancer of the spleen. Malaria came very low in this list, but probably, taking the whole world over, it is the commonest cause of splenic enlargement. The striking thing about Dr. Taylor's list is the very high position occupied by infective diseases, and particularly by infective endocarditis and tubercle; for among the 379 cases there were 52 due to the former and 42 to the latter disease. Among less common causes it is not possible to arrange any order, as they are so infrequent. They are leukaemia, especially spleno-medullary; splenic anaemia, which in its later stages is known as splenomegalic cirrhosis, or Banti's disease; and anaemia pseudo-leukaemia infantum, in all of which the spleen is enormous. The spleen is enlarged also, though not enormously so, in lymphatic leukaemia, Hodgkin's disease, and in pernicious anaemia.

Spleno-medullary Leukaemia.

I first saw this patient on March 1st, 1905, when she complained of increasing weakness, shortness of breath and gradual swelling of the abdomen during the previous five months. Three or four times recently she had had "bruises" occurring spontaneously on her legs. She was anaemic-looking, but with a flush over the malar bones. Physical examination revealed an enormously enlarged spleen extending as far as the middle-line, and well below the umbilicus. There was no tenderness on pressure, or when lying down, but when standing or walking she complained of a dragging sensation. The other abdominal and the thoracic organs revealed nothing abnormal. The fundus of the eyes was normal. She had never had any haemorrhages except the spontaneous "bruising." She had no ascites, though this occasionally occurs in spleno-medullary leukaemia.

Splenic Anaemia.

Superficially this case is not unlike the first. I saw him first with Dr. Richard Williams in Wrexham Infirmary on November 1st, 1905, and I have to thank him for permission to report this case. The patient was 30 years old, and he complained of feeling unwell, but nothing definite, for three years or so, on and off. The onset was vague. Previously he had been a healthy man. At times he had had nose bleeding and a few attacks of haematemesis. Three weeks previously he had been tapped for ascites, not for the first time. Physical examination revealed a spleen which extended just below the umbilicus. Nothing abnormal could be detected in any other organ.

An examination of the blood showed marked differences in the two cases, and at once settled the diagnosis in the first case, in which the condition of the blood was as follows: Haemoglobin 65 per cent.. red corpuscles, 4 230 000 per c.mm., white corpuscles 248,000 per c.mm; the differential count showed 47.2 per cent. of polymorphonuclears, 4.1 per cent. of lymphocytes, 4 6 per cent. of eosinophiles, 42.1 per cent. of myelocytes, and 2 per cent. of basophiles; the enormous excess of white cells at once settling that this was a case of leukaemia, and the large percentage of myelocytes present showing that it was the spleno-medullary form. The blood condition in the second case was as follows: Haemoglobin 24 per cent., red corpuscles 2,000,000 per c.mm., white corpuscles 900 per c.mm.—that is, the blood was chlorotic in type, with marked leucopenia. From this alone it is not possible to make a diagnosis, but without it it is also impossible to say what is the cause of the splenomegaly. To this I shall return later.

The first case was treated with arsenic, and rapidly improved. In about three months the haemoglobin had risen to 70 per cent., the red corpuscles to 5 960 000 per c.mm., and the white corpuscles had fallen to 7,500 per c.mm. Very few myelocytes were present, and the spleen was much less. As the result of taking arsenic very dark pigmentation was produced, fairly universal, but most marked on the abdomen. The arsenic therefore was stopped at the end of May, 1905. Towards the end of July she was feeling much weaker, and on August 1st the white corpuscles had risen again to 30 300 per c.mm.; she now began treatment with the *x* rays applied over the spleen. Under this she said she felt better, but her blood certainly did not improve, for on October 24th the white corpuscles had risen to 55 600 per c.mm., the percentage of myelocytes being 15.5. During treatment with Roentgen rays she took no arsenic. In the volume for 1905 of Byrom Bramwell's *Clinical Studies*[2] there is described the treatment of a case of spleno-medullary leukaemia by *x* rays in which the white corpuscles fell from 590 000 per c.mm. to 12,000 during four and a-half months. Byrom Bramwell says: "There cannot, I think, be the slightest doubt that in her case the *x*-ray treatment has been beneficial." In the next paragraph he says "that it is only right to say that this patient was taking arsenic at the same time the *x* rays were being applied." Professor Dock,[3] in his conclusions as to the *x*-ray treatment of leukaemia, says: "Roentgen-ray treatment of leukaemia is dangerous on account of the usual risk of dermatitis and burns, but probably also on account of toxic processes, as yet impossible to explain . . . . but it may prove more certain in its action than arsenic." This was certainly not so in this case.

By January, 1906, the white corpuscles had risen to just over 100,000 per c.mm., but as she was feeling fairly well she was very unwilling to have the *x* rays again, or to take arsenic, as the pigmentation was still bad. In September she was feeling very weak, and asked for *x* rays again; these, however, did no good, and in November they were stopped, and she was again put on arsenic. By the end of January, 1907, the white corpuscles had dropped to 26,400 per c.mm. from 200,000 per c.mm., which they were when she started the arsenic in the previous November.

The second case I take to be one of that very rare disease, splenic anaemia. Professor Osler, who has collected and published 15 cases, defines it thus:

> A chronic infection, probably an intoxication of unknown origin, characterized by a progressive enlargement of the spleen, which cannot be correlated with any known cause, as malaria, leukaemia, syphilis, cirrhosis of the liver, etc. (primary splenomegaly); anaemia of a secondary or chlorotic type, leucopenia; a marked tendency to haemorrhage, particularly from the stomach, and in many cases a terminal stage, with cirrhosis of the liver, jaundice, and ascites (Banti's disease).[4]

The patient complained two years ago of having been unwell for about three years—that is to say, there is a history now of five years. He had had epistaxis and haematemesis, and he had been tapped for ascites. Practically the only physical sign is an enlarged spleen. If we go through the chief causes of enlarged spleen it is clear that not one of them exist. The case is evidently not malaria; he has never been out of England, and there have been no shivering attacks. In alcoholic cirrhosis the history, the faeces, the more moderate enlargement of the spleen, and the whole course of the disease should make this diagnosis clear.

Infective endocarditis is another cause of an enormous spleen; here again the length of the history excludes this disease. In Hanot's cirrhosis of the liver there is an enlarged spleen, and haemorrhages also may occur; but the blood shows a leucocytosis and not a leucopenia, there is pigmentation of the skin and glycosuria, so clearly this is not a case of Hanot's disease. From leukaemia it is distinguished at once by the condition of the blood.

In addition Professor Osler gives pernicious anaemia, and Hodgkin's disease with enlarged spleen as causing difficulty in diagnosis. A few months ago I saw a case of pernicious anaemia in which the spleen was enlarged, there was marked anaemia, and in which there had been haemorrhages, with a history extending over two years. The blood, however, was typical of pernicious anaemia, for the red corpuscles were very irregular in shape, and large in size, and during the differential counts of 500 white corpuscles 13 megaloblasts were noted. This case has since improved in an extraordinary manner by taking arsenic.

As to Hodgkin's disease with an enlarged spleen, not

one of Professor Osler's cases of splenic anaemia had any enlarged glands; and the enlargement of the spleen, though not uncommon, is slight in Hodgkin's disease, while in splenic anaemia it is enormous.

As to the etiology, very little or nothing is known, every one seems to be agreed that it is commoner in males than females. Heredity has been noted in a few instances. Splenic anaemia seems to be characterized by great chronicity, for among Osler's 15 cases, 7 were of more than ten years' duration; the duration of the symptoms in this patient is five years. Probably in no disease, except spleno-medullary leukaemia is the spleen so large, in 12 cases collected by Rolleston[5] the average weight was 61 oz., and Hale White reports a case in which the spleen weighed 2 lb. 9 oz.[6]

Haematemesis is the next symptom; eight of Osler's cases vomited blood. In 26 cases collected by the Association of American Physicians, 7 had attacks of haematemesis; and this seems not to be due to cirrhosis of the liver, but either to some condition associated with the spleen, or to some blood condition, for in two cases in which the spleen was removed by operation the liver was found to be normal.[7] They may also bleed from other parts. This patient, in addition to haematemesis, also suffers from severe epistaxis. He always feels better after a haematemesis. Various suggestions as to the cause of the haematemesis have been made—namely, that it is due to:

1. A general diapedesis from the gastric mucous membrane.
2. Small erosions of the gastric mucous membrane.
3. Rupture of a varicose vein of the oesophageal plexus.
4. Rolleston[5] suggests that the large wandering spleen may pull on the gastro-splenic omentum, and give rise to torsion of the veins, or cause a kink in the splenic vein, and so induce venous engorgement of the stomach.

Probably there is no other condition except the so-called cases of gastric ulcer in young women, in which haematemesis may go on for so long a time. One sees young women who year after year suffer from haematemesis, and are treated for gastric ulcer. Personally, I do not believe that a large majority of these cases are gastric ulcer at all, but cases of chlorosis with haematemesis, due to a diapedesis from the gastric mucous membrane, possibly the result of the blood condition. *Post-mortem* evidence, evidence from operations, and the result of treatment by mild iron preparations, and feeding, whereby great improvement is noticed in many cases in about a fortnight, are all against these young womeen suffering from gastric ulcer.

To turn now to the blood, which is of a chlorotic type. The red corpuscles are now reduced to 2,300,000 per c.mm.; two years ago they were as low as 2,000,000 per c.mm. The average number in 26 cases collected by the American Association of Physicians was 3,300,000 per c.mm.; the lowest in Osler's series was 2,187,000 per c.mm. The percentage of haemoglobin is low; in fact, lower than usual in secondary anaemia—in this case 30 per cent.—while the percentage of red corpuscles is 46, so that the colour index is 0.6. A striking feature is the leucopenia. In this case, two years ago the leucocytes numbered 900 per c.mm.; in July, 1907, when last examined, they were only 1,500 per c.mm. There are no nucleated red corpuscles, and the proportions of the various kinds of leucocytes are about normal.

There is undoubtedly a large group of cases of splenomegaly with secondary anaemia, but in these there is usually an obvious cause, such as malaria, tubercle, or rickets. The anaemia and splenic enlargement yield to treatment, or the patient dies of the cause; at any rate, they do not exhibit the same chronicity as the cases of splenic anaemia. The spleen is not as a rule so large, nor the sequence of events so characteristic, as in splenic anaemia. Again, in most cases the blood shows the ordinary chlorotic changes, and in place of leucopenia there is leucocytosis. I might mention a case such as this which I saw in August, 1905.

Mrs. S. complained of weakness and abdominal swelling, which had lasted about a year. There were no physical signs of any disease except an enlarged spleen. In this case the blood showed 4,700,000 red corpuscles and 13,400 white corpuscles per c.mm., and 45 per cent. of haemoglobin. She died a few months later, and tubercle was shown *post mortem* to be the disease she was suffering from.

Here was a case of splenomegaly with secondary anaemia, but except for the splenic enlargement and the chlorosis it did not resemble splenic anaemia. It was of comparatively short duration, the spleen, though large, was not colossal; and the blood, instead of a leucopenia, showed a leucocytosis.

Pigmentation of the skin occurs in a certain number of cases of splenic anaemia. It is not present in this case. On the other hand, the case of spleno-medullary leukaemia shows marked brown pigmentation; this is definitely due to arsenic. Arsenic is so frequently given to cases with enlarged spleen that it is necessary to exclude this as a cause of pigmentation before assuming that the spleen is the cause. The pigmentation may be due to irritation of the abdominal sympathetic by the large spleen, as suggested by Rolleston, for it has been observed to disappear after splenectomy has been performed.

Coming now to the hepatic features of the disease. In the later stages, when the symptoms due to the hepatic changes occur, it is known as splenomegalic cirrhosis or Banti's disease. The symptoms are ascites and jaundice. In Osler's series of 15 cases 4 had ascites and in 2 jaundice occurred. The haematemesis occurs before the cirrhotic changes begin in the liver and is of splenic origin; in my case haematemesis has now been going on for more than three years. Haematemesis is of course one of the early symptoms of alcoholic cirrhosis of the liver, but in this disease it is quite unusual to have attacks of haematemesis going on for so many years as in splenic anaemia, and there are also other symptoms, such as morning sickness. This patient has had no jaundice, but he has been periodically tapped for ascites for more than two years. It is rather doubtful whether the ascites is really due to hepatic changes. It is, I think, more probable that the large spleen mechanically causes a chronic peritonitis, to which in turn the ascites is due, for *post mortem* on the surface of the spleen tags of fibrous tissue are sometimes found, and the capsule is thickened by changes due to perisplenitis. Also I think a case in which ascites calls for frequent tapping would not live so long as this man if cirrhotic changes in the liver were the causes of the ascites. Again, one would expect to find some physical signs of cirrhosis of the liver if it had existed for two years. In this man no physical signs of any liver change could be detected either two years ago or in July of last year.

The morbid anatomy does not throw much light on the disease. In the spleen there are two marked changes. One is a large increase in the fibrous tissue. This is composed chiefly of thickened trabeculae, though much of the normal splenic pulp is also replaced by fibrous tissue. The other change is noticed in the blood spaces, lining these are great numbers of large endothelial cells. These cells contain one or more nuclei, and occasionally completely fill up the blood spaces, so that the appearance is not unlike a new growth, so much so, indeed, that it has been described both as a carcinoma and an endothelioma of the spleen. Later in the disease fibrous changes take place in the liver. In two cases very fully reported by Dock and Warthin[8] in addition to the fibrosis of the spleen and liver there was stenosis and calcification of the portal vein. With reference to this they ask, "Is the latter the primary condition, to which the splenic fibrosis follows secondarily, or is it the result of a portal or general intoxication, to which the splenic and hepatic fibrosis are also due?" As cure of splenic anaemia may follow removal of the spleen it rather looks as if the spleen were the seat of a toxic or infective process, and that the blood conveyed from it by the portal vein to the liver carried a morbid agent causing secondary fibrosis of the liver and portal vein.

As to treatment very little is known. Byrom Bramwell[9] reports a case in which good results were obtained by giving boracic acid, and also one in which *x* rays were very beneficial. Armstrong[10] has collected from literature 32 cases which have been operated upon: there were nine deaths, the remaining 23 recovered, and apparently were cured; for instance, No. 5 in his list was operated on in 1898, and in July, 1906, was reported as "still living and well, having had no return of the haemorrhage since that time." At the end of Armstrong's article there is a note by Dr. Atherton, in which he reports great improvement in a case of what he takes to be splenic anaemia under treatment by arsenic and *x*-ray applications twice a week; and he considers that before the operation of splenectomy the *x* rays should be given a trial. The great danger of operation seems to be from haemorrhage, either during

the operation or within a few hours afterwards, and most of the deaths in operation cases have been from this cause.

REFERENCES.

[1] F. Taylor, the Lumleian Lecture, *Lancet*, 1904, vol. 1. [2] Byrom Bramwell, *Clin. Stud.*, vol. iii, 1905, p. 403. [3] Dock, *American Med.*, vol. viii, 1904. [4] Osler, *Trans. Assoc. Amer. Phys.*, vol. xvii, 1902; *Amer. Jour. Med. Sci.*, vol. cxix, 1900. [5] Rolleston, *Splenic Anaemia*, 1902. [6] Hale White, *Guy's Hosp. Gaz.*, December 1st, 1906. [7] Harris and Hertzog, *Annals of Surgery*, 1904. [8] Dock and Warthin, *Amer. Jour. Med. Sci.*, 1904. [9] Byrom Bramwell, *Clin. Stud.*, vol. iv, 1906. [10] Armstrong, BRITISH MEDICAL JOURNAL, 1906, vol. ii, p. 1273.

SOME EXPERIENCES IN THE TESTING OF TINCTURE OF DIGITALIS.

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ATTENTION has recently been drawn to the importance of standardizing the drugs of the digitalis group, and as no chemical method of testing the strength of these drugs is at present available, attempts are being made to devise some reliable system of physiological testing. Of possible methods, two in particular have been suggested as of suitable application. By one of these the drug is injected in given amount into the circulatory system of a living animal, either frog or mammal, and the strength of the drug is shown by its capacity to cause death within a given time, death being brought about by arrest of the heart in so-called systole. Employing this method on frogs, and using "good average samples" of the drug, that is to say, samples prepared with all due precaution and known to produce certain well-recognized physiological effects, Dixon has worked out a standard unit for tincture of digitalis.[1] A tincture, before being injected into the dorsal lymph sac of the frog, is diluted with an equal amount of water, and if the tincture be of standard strength, 6 minims of this solution should kill a frog of 25 grams weight in one hour.

The other method of testing is to use in place of an intact animal an isolated heart, perfused with Ringer's or Locke's solution, the drug being in this case exhibited by introducing it diluted to known extent with the perfusing fluid. Then, as in the first method mentioned, the arrest of the heart within a given time may be taken as an indication of the potency of the drug, while during the course of the experiment observation can also be made of the effects produced before arrest takes place. In the experiments of which particulars are given below this latter method was used to test a number of samples of tincture of digitalis. It is thought that it may be of use to give an account of the results obtained, as the experiments made were sufficiently numerous to afford some basis upon which to discuss the advantages or the drawbacks of the method.

The mammalian heart was used, the animals selected being young rabbits weighing usually from 3 to 4 lb. The heart was perfused through the coronary vessels with a Ringer's solution, after the manner made familiar by Langendorff, Locke, and others, and the contractions were recorded.* The recording lever was connected with the right ventricle, and throughout the experiments by the expression "arrest of the heart-beat" is meant arrest of the contractions of the right ventricle. The procedure was in all cases the same. A steady heart-beat having been established and an even series of contractions recorded, the undrugged Ringer's solution was replaced by a supply of similar solution containing a given percentage of tincture of digitalis and this supply was maintained until the heart succumbed to the action of the drug.

The question of a suitable percentage is of some importance if manageable results are to be obtained. Low percentages, which would be suitable in a detailed study of the physiological effects of digitalis on the heart, are found to work too slowly for convenience where the object is to test the relative strengths of many different samples, the gradual dying out of the heart-beat being with low percentages often very protracted. After some preliminary trials the strength adopted in these experiments was 1 in 200. Usually three experiments were made with the sample of the drug and the average time required to arrest the heart was taken to indicate the potency of the sample. When a number of samples had been tested the question arose as to how they should be rated; within what limits might one sample legitimately differ from another. In a preliminary review of results obtained with the first eighteen samples, these were arranged in tabular form according to their potency, beginning with the strongest, that is to say the sample which arrested the heart in the shortest average time. (See Table I.)

No. 13 was a tincture prepared with special care by an expert pharmacist,† and it is considered here as a "good average sample." Nos. 7 to 16 might be considered as approximately equal in strength to the good sample, the average time of arrest with all these tinctures being over twenty-five minutes and under forty-five minutes. This group is marked II in the table.

Samples 17 and 18 made a weaker group, marked III, as in some of the experiments with these tinctures the heart was not arrested within one hour, which was the limit of time adopted.

Samples 1 to 6 appeared to fall into a "strong" group, I, their average times of arrest being all under twenty-five minutes. But the placing of these six samples apart had been decided upon with hesitation. Judged by their short average time of arrest, they were "strong"; and a study of the column of maximal values showed that their maximal times also were shorter than any maximal time recorded for a sample under group II. In the minimal column, however, the distinction between "strong" and

TABLE I.—*Showing the Average Time Required to Arrest the Heart in the Case of each Tincture, with Maximal and Minimal Times: also the Median Time of Arrest.*

Tentative Grouping	Tincture No.	Average Time of Arrest in Minutes.	Maximal Time.	Minimal Time.	Median Time of Arrest in Minutes.	Final Grouping: Average.
I. Strong.	1	19	21	16	16	Average.
	2	19	26	13	19	
	3 (x)	20	26	11	20	
	4 (x)	20	30	10	22	
	5	21	28	14	—	
	6 (x)	23	24	21	23	
II. Average.	7	26	36	19	23	
	8	27	46	14	20	
	9	27	32	25	25	
	10	28	34	21	30	
	11	30	38	19	32	
	12 (x)	30	52	14	24	
	13	33	42	25	31	
	14	33	48	25	26	
	15	37	46	24	41	
	16 (x)	43	50	39	41	
III. Weak.	17	?	Over 1 hr.	25	?	Weak.
	18	?	Over 1 hr.	37	—	
	X (17 expts.)	27	52	10	23	—
	19	26	33	13	32	Average.
	20	23	28	15	25	"
	21	48	54	40	49	Weak.
	22	50	60	31	60	"
	23	19	24	15	19	Average.
	24*	27	33	22		"
	25*	29	33	25		"
	26*	23	21	24		"

* Are not included in the chart.

* For a description of the apparatus see Report of Special Chloroform Committee, BRITISH MEDICAL JOURNAL, July 18th, 1903, p. cxlvii; and more fully in Thompson Yates Laboratories Report, Part I, 1903, "On the Dosage of the Mammalian Heart by Chloroform," Sherrington and Sowton.

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