A CASE OF CHRONIC LYMPHATIC LEUKÆMIA IN AN INFANT.

WITH SOME OBSERVATIONS ON THE BLOOD CONDITION IN
OTHER CASES OF SPLENIC TUMOR.

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Our knowledge of the blood condition in many of the diseases of infants and children is at present hazy. Each individual case of anemia in children carefully observed and studied may add something to our knowledge. It is with this hope that the present case is reported.

Peter M., an Italian boy, aged nine months, first came under the observation of Dr. Henry M. Fisher on May 20, 1900. The child's parents are both living and healthy; they present no indications of disease, though living in poor and squalid surroundings in the southern part of Philadelphia. There are three girls in the family, aged, respectively, twelve, ten, and three years. The eldest, who lives in Italy, is said to have had an enlarged spleen, with anemia, from early infancy. She is still a delicate child. The other two children are healthy.

The parents said the boy presented no striking peculiarity until he was one month old, when it was noticed that he was unnaturally pale. Since that time he suffered frequently from recurring attacks of intestinal catarrh, with green stools containing much mucus. His mother was and still is nursing him at seventeen months, though her milk is scanty and is reinforced by other baby foods. Head was symmetrical; fontanelles almost closed; teeth were cut with normal rapidity. No evidence of rickets. At the first visit the spleen was enlarged extending fully four inches below the costal margin. There was no marked enlargement of either the liver or the external lymphatic glands. The heart and lungs were normal. The urine was non-albuminous and contained urates in excess. Blood smears were prepared and first examined on May 29th, though no blood count was made at that time. The slide showed a marked poikilocytosis, with many microcytes and macrocytes and a decided leucocytosis in which the lymphocytes were proportionately high. There was a considerable number of nucleated reds (normoblasts). There were no malaria parasites. The blood was subsequently examined, counted on June 15th, 25th, July 6th, November 23d, January 7, 1901, and May 23d. The results of these examinations will be found in the table on opposite page.

The child was placed upon quinine by suppository, and was also given one-half drop of Fowler's solution three times a day. During the latter part of May there was considerable diarrhea, with green stools containing mucus. During July there was a slight improvement in the patient's condition, which seemed to follow the use of oil injections and exsuxine, 2 grains given every two hours. The child was advised to be given as much as possible the benefit of fresh air, and was at times taken to the sanitarium at Red Bank. The spleen had enlarged during this interval, and could now be felt to within one finger's breadth of the iliac crest, and posteriorly two fingers' breadth below

the costal margin. He was not seen again until November 21st, when the child had frequent stools, with considerable bronchial catarrh. At that time he was put upon $\frac{1}{2}$ a grain of glycerin-phosphate of soda in solution with dilute phosphoric acid, $\frac{1}{2}$ minim of Fowler's solution and 2 grains of protosein, i. e., which treatment was continued through December.

BLOOD TABLE.

	1900.					1901.	
	May 21.	June 15.	June 27.	July 6.	Nov. 23.	Jan. 7.	May 23.
Erythrocytes,		3,120,000	3,060,000	Not count'd	3,850,000		3,670,000
Leucocytes,		105,000	54,000	" "	18,000	35,700	10,700
Hæmoglobin,		20 per cent.	22 per cent.	" "	20 per cent.	30 per cent.	15 per cent.
Polynuclear,	11 per cent.	27.5 "	30 "	28 per cent.	25 "	47 "	15 "
Small lymphocytes,	63 "	27 "	17 "	41 "	44 "	23.4 "	66.9 "
Large lymphocytes,	18 "	30 "	44 "	18.4 "	9.6 "	20.6 "	13.8 "
Eosinophiles,	3 "	7.5 "	2 "	4.8 "	8.6 "	5.6 "	2.2 "
Myelocytes,	0 "	8 "	7 "	1 "	2.7 "	3.4 "	2.1 "
Normoblasts,	33	92	39	46	Many	35	155
Megaloblasts,	8	2		5		18	8
Microblasts,	3	0		1		3	2
Polychromatophilic	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number counted,	200	200	255	250	185	160	100

On November 30th Dr. Charles A. Oliver examined the eye-grounds and reported "a neuroretinitis, with engorgement of both the retinal arteries and veins, with extremely pallid blood; there were no hemorrhages." When last seen, May 23d, the child had suffered a relapse, for it had improved considerably during the early winter months. It presented a peculiar clayish pallor, the lips colorless, with but little emaciation, the abdomen enlarged and protuberant, the spleen hard and very much enlarged, with no enlargement of the superficial lymphatic glands, and the edge of the liver just palpable. Since the beginning of the illness he has never had any nose-bleed. Once, in January, he coughed up a small amount of blood. There have never been intestinal or gastric hemorrhages. The child died about ten days (June 2d) after the last blood examination, from asthenia; no autopsy could be secured, as Dr. Fisher was unfortunately not in Philadelphia at the time.

A brief résumé of the appearance of the blood slides is, I think, necessary at this time. The first film prepared by Dr. Fisher and sent to me for diagnosis showed many changes in the size and form of the red, with much loss of hæmoglobin and decided leucocytosis, the percentage of lymphocytes being comparatively high, some few myelocytes present, and nucleated reds in plenty, some undergoing mitotic change. During June there was a great increase in the number of leucocytes, reaching over 100,000 per cubic mm. There were again numbers of microcytes with very pale macrocytes, with large numbers of both young and old normoblasts, many of them mitotic. There were many polychromatophilic cells; degenerative changes in the reds were common, especially in the old normoblasts. At this time the proportion of large lymphocytes was rather high. In July there was little change to note in the blood except the reduction of the total number of the leucocytes, which continued to fall until, November 23d, they were but 18,600, with a proportionate increase in small lymphocytes. In January the

leucocytes again began to rise, the count at this time being 37,600, and when last seen in May, after a lapse of some four months, during which time treatment had ceased through neglect of the parents, the white count reached 80,000. During this period of almost a year the erythrocyte count has remained almost stationary (about 3,000,000), while the hæmaglobin has been low. The last differential counts are of considerable interest. They show a distinct increase in the lymphatic elements of the blood; in fact, the last films made, as can be seen by consulting the table, showed over 80 per cent. of lymphocytes. Over 66 per cent. of these are small, while but 13 per cent. are large lymphocytes; many of them, however, resemble nucleated reds, the nucleus remaining rather reticulated. Some of the red corpuscles show a basophilic granulation; some of the lymphocytes are undergoing segmentation, and three or four were observed with bipolar nuclei. Myelocytes are present but in rather scanty numbers; almost 50 per cent. of the eosinophiles are myelocytic.

DIAGNOSIS. In children enlargement of the spleen is common; the usual causes may be briefly stated as malaria, typhoid fever, congenital syphilis, rickets, v. Jaksch's disease, splenic anemia, leukemia, and acute and chronic infections. A differential diagnosis between two of these diseases at times becomes extremely difficult unless we carefully bear in mind the characteristic reaction of the infant and the child's blood in various diseases—i. e., the ready response of the leucocytes, and especially the lymphocytes, to any call made upon them.

Thus *malaria* in the infant or child is usually associated with definite clinical symptoms, enlargement of the spleen, the absence of leucocytosis, the presence of the specific parasite. In chronic paludism this picture may be somewhat changed. The degree of anemia may be severe, and corresponding changes may occur in the red cells, but there is no marked alteration in the leucocytes except a tendency to a lymphocytosis.

In *congenital syphilis* there is always anemia. The hæmaglobin is reduced to the lowest figure. There is a great diminution in the reds, nucleated reds are seen in abundance, and the white cells, especially the lymphocytes, are increased. Loos reports a fatal case in which the leucocytes reached 58,000.¹ Cabot reports a case of syphilis with leucocytosis of 100,000, and Monti, Baginsky, and others have also reported excessive leucocytosis. If the skin lesions are severe there may be an excess of eosinophiles. The spleen is usually decidedly enlarged.

In *rickets* there is usually a simple chlorotic anemia. The leucocytes may rise to 30,000. (Luzet, however, believes that all grades of leucocytosis, even to a true leukemia, exist in rickets, and there is a decided belief among many observers that both syphilis and rickets not infrequently lead to leukemia; a lymphocytosis is usually the result.) In complicated cases the blood picture becomes not unlike that of v. Jaksch's disease—that is, there are unusual numbers of nucleated reds with

¹ Ewing, p. 297.

many poikilocytes. In such cases Ewing states the hæmoglobin index is unusually high. The spleen in these cases is enlarged, and there are usually other evidences of rickets, such as the bending of the ribs and changes in the other bony structures.

In *v. Jaksch's disease*, which is supposed to be peculiar to infants and young children, the following changes in the blood are considered characteristic: There is a great and unusual diminution in the number of red corpuscles. There is always a leucocytosis, which, however, is not so great or progressive as in leucæmia. There is a remarkable variety of the forms and sizes of the leucocytes. The reds show great poikilocytosis; there are numerous nucleated reds to be seen. The clinical characteristics of the disease are the great enlargement of the spleen without marked enlargement of the liver, the edge of which is sharp, and without marked glandular enlargement. The prognosis is relatively good. Three cases which came to post-mortem presented no evidences of leucæmic infiltration. The disease has an anatomical basis, though Monti and Buggram, in analyzing twenty cases, found evidences of rickets and syphilis in sixteen. It is also to be remembered that prior to 1892 (*v. Jaksch's disease*) was described in 1889) there is no case on record, according to Fischl, where a differential count was made.

Splenic Anæmia. A disease not common in children, though recently numerous observers have reported cases in infants. In this condition the blood shows no pathognomonic changes. There is usually but little change in the form and size of the red corpuscles, while the hæmoglobin is much reduced—a chlorotic anæmia. There is usually but little or no increase in the leucocytes unless high temperature has been associated with the disease; indeed, in Osler's fifteen cases—all adults—a leukopenia was the rule.¹ Nucleated reds are rather scanty, and may not be found at all. The spleen is usually enlarged and tender; this enlargement precedes the anæmia,² the liver is often slightly enlarged, while there is sometimes slight jaundice present. The digestive symptoms are probably the most prominent. There is a tendency to hemorrhage either from the stomach or bowels, not infrequently from the nose. The duration of the disease is protracted, its cause is unknown, recovery has been seen.

Leukæmia. A disease which is rather uncommon in infancy, though the literature now contains quite numerous reports of cases occurring from one month up to extreme old age. For purposes of brevity we can assume an acute and chronic variety. The chronic variety, or myelogenous type, is the more frequent. The blood picture

¹ THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, JANUARY, 1900, p. 51.

² Osler. *Ibid.*

is typical. The leucocytes are increased to astounding proportions, sometimes one to two, four or six. A large proportion of these cells are myelocytes; mast cells are present in considerable quantities, as are also nucleated reds; the mast cells Ewing considered almost pathognomonic. Eosinophilic myelocytes are numerous. The disease is chronic in its duration, we do not know its cause, and cure is almost unknown.

Lowit has described a protozoon, and many others have found similar bodies in leukemic blood, but no one has been able to verify or follow up his findings. The lymphatic variety is more rare, and the acute cases are usually of this type, the majority of these cases occurring before the age of twenty-five. Thus, Muir states that of the seventeen cases reported by Ebstein, but seven were over thirty, and Muir's four were all under twenty-six. The blood picture is here almost characteristic. The leucocytosis is usually about 200,000. A large proportion, 85 per cent. to 95 per cent. of them, are lymphocytes. Myelocytes are found but in very scanty numbers. Nucleated reds are also extremely scarce, but are sometimes found. Segmenting lymphocytes and the nuclei of large lymphocytes, without cytoplasm, are frequently seen. Vacuolated and degenerated or disintegrating leucocytes are frequent. There is no marked reduction of the red corpuscles, nor is there much change in size or shape. The hæmoglobin keeps pace with the reds. The clinical symptoms depend to some slight extent upon the variety of the disease. In the spleno-myelogenous form the onset is gradual; epistaxis is a more common symptom; diarrhœa is usual; there is increasing weakness, a peculiar grayish pallor, with decided splenic enlargement. The latter is often noticed by the patient himself. In the lymphatic variety there is usually enlargement of the entire superficial lymphatic apparatus. The glands are rather elastic, but become soft. At times the superficial glands are not affected, though the blood picture remains the same as before stated. Under such cases there is usually a leukemic infiltration of either the glands along the intestinal canal or in the viscera. The spleen is not usually affected, though sometimes it is slightly enlarged. Thus Muir¹ cites a recent case of his own in which the liver, kidneys, and adrenals were infiltrated, while the glands were almost unaffected. Lymphatic leukemia, therefore, in infants is not common. Morse² gathers twenty cases of leukemia; but one of these, however, was accompanied with a differential count, and as the diagnosis in some of the cases was made by clinical signs, without study of the blood, many of these cases must be thrown out. Morse's case was of mixed variety. A. E. Taylor in his studies on leukemia³ reports six-

¹ Allbutt's System, vol. vi. p. 656.

² Boston Medical and Surgical Journal, August 9, 1891.

³ Pepper. Clinical Laboratory, vol. II. p. 143.

teen cases of leukaemia, four of which are lymphatic, but none in patients under eleven years of age. Morze, again in 1898,¹ quotes seven acute cases in children from the literature, and describes his own case, in which but one blood examination was made. McCrao² reports an acute case of leukaemia occurring in a boy of three years, and includes thirteen previous cases from literature. Ewing (page 201) states that Andeod has observed leukaemia in fifty-six children; eleven times in the first year, twelve times from the second to the fourth year, twelve times from the fifth to the ninth year, and twenty-one times from the tenth to the fifteenth year.³

The blood picture in my own case corresponds accurately to the description given of pseudoleukaemia anæmia infantum, or v. Jaksch's disease,⁴ and the clinical picture also coincides with its description. In none of the cases, however, of v. Jaksch's disease have I been able to find a careful report with differential counting of the blood, and many of the cases reported as such have been based upon the presence of a leucocytosis, sometimes quite small, with evidences of anæmia and decided enlargement of the spleen. The differential counting of the leucocytes, it seems, must be practised in these cases before an accurate diagnosis can be made. This fact leads me to this query: "Does our knowledge of the blood at the present day allow us to acknowledge that the disease described by v. Jaksch is an entity?" If it is not, in what group of diseases can it be placed?

In order to discuss this question, let us briefly consider the effect upon the blood: First, of simple splenic enlargement. Second, removal of the spleen: (a) for injury, (b) in splenic anæmia, (c) in myelogenous leukaemia. Simple splenomegaly in acute diseases, such as typhoid fever, malaria, etc., is accompanied by a secondary anæmia, which is probably induced by the disease. The leucocytes are usually diminished in number (leukopenia). In the more chronic enlargements, such as malaria or splenic anæmia, there is again a leukopenia, or a mild grade of leucocytosis, as in rickets and syphilis; thus the most marked effect upon the blood seems to be a relative reduction in leucocytes. But this is relative, for with the onset of complications a decided leucocytosis takes place, showing that the leucocytes are present in the body, though not in the peripheral blood. This leukopenia I have also seen in cirrhosis of the liver, accompanied with marked ascites and splenic enlargement, and also in another case of simple splenomegaly whose blood showed an intense chloro-anæmia. This latter case was classed as a splenic anæmia for want of better diagnosis, though he presented none of the ordinary symptoms of the disease.

¹ Archives of Pediatrics, 1898, vol. xv, p. 130.

² Johns Hopkins Bulletin, May, 1900, p. 102.

³ Traité de Malade d'Enfance, t. II., p. 112.

Bovaird has reported two cases of chronically enlarged spleen with the pathological diagnosis of endothelioma, in which the blood changes were but slight. In the first case, a child, aged three years, the erythrocytes numbered 4,100,000; the leucocytes 9000. In the second case, a child, aged thirteen years, the erythrocytes numbered 2,880,000, and the leucocytes 4000.

Sailer, in a recent paper, has reported six cases of enlargement of the liver and spleen—with enlargement of the lymph glands—in which the presence of tubercle bacilli was demonstrated; in these cases the blood showed no special changes, there was no leucocytosis, and the differential count was normal.

The total removal of the spleen has a decided effect upon the blood. In comparatively healthy subjects Ewing states (page 241) that the spleen may be removed without affecting the blood more than any other laparotomy. Such an operation is usually followed by a leucocytosis ranging from 15 to 50,000, which may persist from two to six weeks, or even longer. In traumatic cases the blood may resemble an acute leukemia, although this does not always follow. The spleen has also been removed for diseases such as malaria (ague cake), splenic anemia (Osler only so advises when hemorrhages are recurrent), and myelogenous leukemia. In the latter the result usually is fatal, and no blood counts of value, subsequent to the operation, are to be found. Warren, however, has included in his article on "Surgery of the Spleen," a case of myelogenous leukemia, operated upon by Richardson, with recovery.

In splenic anemia the results of operation are better. Osler, Warren, and Malcolm L. Harris, with Max Herzog, and others have reported cases of removal of the spleen for this disease. In Warren's case the leucocytes after operation remained up for three months, the highest count being 24,000. Harris and Herzog's two cases showed a leucocytosis of 28,000 before operation, with no subsequent increase after the removal of the spleen. They noted, however, a great increase in the eosinophiles, after four months to 14.4 per cent. This change in the differential count is said not to occur until some months subsequent to the operation. They also noted a decided increase in the mononuclear cells.

For malaria the spleen has frequently been removed. Hoggan quotes sixty-four cases since 1890, with a mortality of 23.4 per cent. No statements are to be found as to its effect upon the blood. From the above it can be seen, therefore, that no one effect upon the blood is produced by simple enlargement of the spleen, or by its removal in health or in disease. Observers differ as to whether splenic enlargement precedes, as in splenic anemia, the blood condition, or whether the latter produces the splenomegaly. In splenic anemia Dr. Osler considers the

enlargement antedates the anemia, and is not its cause. Harris and Herzog consider the splenomegaly the cause of the anemia, and call attention to the good results of operation to support their contention.

In the case above considered there was present a typical clinical picture of chronic splenomegaly, with a leucocytosis of a slowly increasing lymphatic type; the presence of nucleated reds of all sizes and ages, degenerative changes in the reds, the same changes in the leucocytes, the presence of a few myelocytes, with death from asthenia, and, alas, no autopsy. That these cases exist without leukæmic infiltration of tissues is true, for in two cases coming to autopsy, Ewing has failed to find any such pathological change. The duration, the course, the blood picture, and the termination of this case are in common with the leukæmias of adult life; at the present time one cannot predict how long the leukæmias will be permitted to remain in the class of primary or essential anemias; they present many of the characteristics of true secondary anemias, and not a few observers consider that in the secondary anemias, splenic anemia and pseudoleukæmia anemia infantum have their proper position. I am inclined to support this view.

[NOTE.—Since writing this article there has been published in the *Boston Medical and Surgical Journal* a comprehensive and elaborate article on the "Association of Anemia with Chronic Enlargement of the Spleen," by Arthur H. Wentworth (concluded in the number of October 31, 1901). The conclusions reached in the article are valuable, while the entire literature from 1879 to 1900 is appended. Stengel, as early as 1896, in his article in the *Twentieth Century Practice*, contended that pseudoleukæmia anemia infantum was not an independent disease.]

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 Moore has collected the cases from 1861 to 1891 of infantile leukæmia.
 McCrae to 1900, with full bibliography attached.
 In Ewing's book will also be found a full bibliography.