AMŒBOID MOVEMENTS
OF THE
COLOURLESS BLOOD-CORPUSCLES IN
LEUCHÆMIA.

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THE patient on whose blood the following observations were made, was admitted into St. George's Hospital on April 30th, 1879, under the care of Dr. Whipham, to whom I am much indebted for permission to make use of the case.

William W—, æt. 26, grocer, with a good family history, stated that he himself had been healthy with the exception of occasional attacks of sick headache and bilious vomiting, to which he had been subject from childhood. During the last four years the headaches had diminished in frequency and severity, but there had been some dyspepsia, which was always easily controlled by attention to diet. For the last month he had felt very languid and weak, and had frequent attacks of vomiting which were not accompanied by headache. His complexion had always been pale, and he had not noticed that his pallor had increased lately. Three weeks before

admission he got a cough, which did not trouble him much till April 24th, when he awoke in the night with a violent fit of coughing, followed by severe retching, during which he felt as if "his eyes were going to jump out of his head." The next morning he found both his eyes much blood-stained, and a few red spots on his body. As he felt very weak and ill, he came to the hospital a few days later, and was admitted in the following condition :

He was a stout, flabby, pale man, of middle height, with light brown hair and eyes. There were extensive ecchymoses under the palpebral and ocular conjunctivæ of both eyes, and a few small purpuric spots scattered over the chest, and on the right wrist, left knee, and ankle. Mucous râles were heard over both lungs, and a very soft systolic murmur was audible at the base of the heart. In both axillæ, over the right clavicle, and in the right groin, there were soft painless enlarged lymphatic glands, which had not previously attracted his attention. The liver dulness was normal, and no enlargement of the spleen could be made out on careful examination. The blood, on microscopical investigation, showed a great increase in the number of the colourless corpuscles, which were to the coloured in the proportion of 1 to 6. The tongue was clean and pale. Pulse 130, and temperature 101.4° .

He remained in the hospital for a little more than two months and a half, leaving at his own request on July 18th. During this time he got gradually worse, with occasional short intervals of apparent improvement. He continued to suffer from cough and dyspnœa, with great languor and loss of appetite. There was an attack of epistaxis on May 3rd, and fresh hæmorrhage took place in the conjunctivæ on May 24th and 26th after vomiting; and again on June 19th and July 8th, after severe coughing and retching. On these latter occasions multiple small spots of extravasation appeared over the chest and abdomen, and a large blood-patch on the left cheek.

The enlargement of the lymphatic glands ran a somewhat irregular course ; they decreased in size at first, especially those in the axillæ, but later they again became swollen, and fresh ones appeared in the groins, the neck, and especially near the angles of the lower jaw, the latter attaining a considerable size. Splenic enlargement was first unmistakably detected early in June, and increased rapidly until the whole left side of the abdomen was occupied by the tumour ; it was always tender on palpation or percussion. The liver also became somewhat increased in size. On June 21st he complained of slight sore throat, and on examination both tonsils were found much enlarged; nearly meeting in the middle line ; they were not, however, inflamed, and troubled him chiefly by the mechanical impediment they opposed to swallowing. They remained in the same state until he left the hospital. The temperature was nearly always above normal, the highest reached being 102.8° on the morning of July 12th ; by the following morning it had fallen to 98° , which was about its lowest ; it was most frequently about 100° , with very irregular rises and falls, apparently unconnected with any change in his condition. The pulse was always quick, and averaged 120, the lowest rate being 108, and the highest 142. The urine was frequently examined and occasionally found to contain a trace of albumen ; it often became turbid from urates, and once deposited crystals of uric acid.

After leaving the hospital, the patient came under the care of Mr. W. J. Hamlin, of Bow, who was kind enough to give an account of the further course of his illness. There was at first an apparent improvement, so that he was able for a short time to attend in some measure to his business ; but the disease steadily increased, the glands in the neck became of enormous size, and numerous cutaneous hæmorrhages appeared from time to time. He became gradually weaker, and died early in October, 1879, the disease having lasted nearly seven months from the date to which he attributed its commencement. No

post-mortem examination was made, but the case presents no difficulties in diagnosis, being obviously well marked lympho-splenic leuchæmia, and the appearances after death are of little moment for my present purpose.

The observations on the blood recorded in this paper were made with the object of determining how far the amœboid movements, which are so markedly characteristic of the colourless corpuscles in health, were preserved. They were made with a Stricker's hot stage, a drop of blood being placed between two cover-glasses with their margins oiled, so as to prevent evaporation. Twelve observations were made in all, the first ten by myself, Dr. Whipham being present at all except the sixth, which was witnessed by Dr. Pye-Smith; the last two were made by Dr. Whipham during my absence. In every case the same magnifying power was used (oc. 3, obj. 8, Hartnack, about 400 diams.), and the procedure was as follows:—The total number of colourless corpuscles in the field was first counted as nearly as possible, and then the number which exhibited amœboid movements was noted at intervals of about ten minutes, the temperature of the stage being taken at the same time. Three observations were usually made in this way on each occasion, and of these I have taken the mean and calculated the percentage in the accompanying table:

Obs.	Date 1879.	Total colourless.	Amœboid (Mean).	Per cent.	Temperature of stage.	Temperature of patient.	Duration of observation.
1	May 16	46	6	Over 13	96·8 to 104°	100·5°	Minutes.
2	" 19	104	25	"	24 93·2 to 107·6°	99°	25
3	" 23	212	24	"	11 93·2 to 107·6°	99·6°	30
4	" 26	177	17	Under 10	104°	100°	35
5	" 30	102	10	"	10 104 to 105·8°	99·2°	30
6	June 3	230	10	"	5 98·6 to 107·6°	100°	40
7	" 7	300	27	"	9 98·6 to 111·2°	99·8°	30
8	" 16	480	16	"	4 98·6 to 100·4°	98·4°	30
9	" 23	210	17	Over	8 98·6 to 104°	Not noted	30
10	" 30	136	7	"	5 98·6 to 104°	"	30
11	July 7	310	18	"	5 93·2 to 104°	"	60
12	" 14	195	10	"	5 93·2 to 104°	100·6°	20

¹ Mean of six observations.

In determining whether a corpuscle was or was not amœboid, the very smallest departure from the spheroidal shape was taken as sufficient; although, in some cases when the corpuscles were only slightly oval, or less regularly rounded than those in which no movements occurred, I think it probable that other observers might have felt disposed to attribute the very slight change of form to accidental causes, such as pressure. If this be the case, the proportion of amœboid corpuscles would be still smaller than that recorded in the table. The character of the movements, when they were unmistakable, differed remarkably from that seen in health; although the observations were made mostly at febrile, and even hyperpyrexial, temperatures, which stimulate the movements in healthy corpuscles to an extreme degree, they were almost invariably very sluggish and ill marked, one or two short, blunt processes being very slowly protruded and as slowly retracted. It now and then happened that one or two corpuscles were found in a specimen which moved more actively than the remainder, although they still fell far short of normal heated examples. These relatively active corpuscles, which were only met with in a few of the observations, were distinguished by a bright, strongly-refracting aspect from the remainder, which were of a dull greyish appearance.

Three kinds of colourless corpuscles were found: small corpuscles of the size of a coloured corpuscle or less, consisting of a large nucleus with a narrow protoplasmic zone (lymphoid cells); ordinary colourless corpuscles, a little larger than a coloured one; and large, strongly granular cells, with the granules usually accumulated at one side of the periphery. Of these large cells only one or two were seen occasionally. All the above corpuscles have been found in normal blood, and amœboid examples of each kind were met with in the case under consideration. The most active, or rather the least sluggish, were found among the ordinary corpuscles, while the lymphoid, and especially the large granular cells, showed the merest

traces of movement. The lymphoid cells were most numerous in the first five or six observations, before the spleen had become markedly enlarged; after this had occurred the somewhat larger ordinary corpuscles were found to be most plentiful. No intermediate forms between coloured and colourless corpuscles were found. One point of some interest is, that coagulation took place much more rapidly in the later than in the earlier specimens, the field becoming very quickly covered with threads of fibrin which started from, or, at any rate, were connected with, the colourless corpuscles.

It will be seen on reference to the table that only a very small proportion of the corpuscles exhibited even the sluggish movements which I have described, the highest number being a little over 24 per cent. (Obs. 2), and the lowest under 4 per cent. (Obs. 8). Further, that with the progress of the disease during the time the patient was under observation there was a very distinct diminution in the proportion of amœboid corpuscles, the mean of the first six observations being about 12 per cent., while that of the last six is not more than 6 per cent. Although there is thus an unmistakable decline in the total number for the whole period, it will be seen that the numbers in successive observations often do not show a regular downward course; there is sometimes a decrease, but at others an increase in the percentage (compare Obs. 1, 2, and 3, and also 5, 6, 7, 8, and 9). I am not able to associate this fluctuation with any obvious change in the patient's condition, and suppose that it is merely an expression of the unexplained temporary improvements and deteriorations which occur so frequently in this disease.

It is a question of some interest whether the loss of amœboid movement takes place at the earliest onset of leuchæmia; on this point I cannot speak with certainty, as my first observation was made when the disease was already well marked, and had existed for at least six weeks, according to the patient's statement of the time at

which he began to feel out of health; but I think we are justified in assuming a longer duration than this would give us, as hæmorrhages, which are among the later occurrences of leuchæmia, had already taken place before admission; further observations are necessary, therefore, to determine this point. It is, however, very probable, in my opinion, that loss of contractility in a large proportion of the colourless corpuscles will be found among the earliest phenomena.

Whether, and how far, amœboid movements are affected in various other diseases, is a not unimportant question which remains to be solved by future observations, and will, I think, repay investigation. I may here state that, for purposes of comparison, I examined the blood in two cases of chloro-anæmia, and one of anæmia from cancer of the stomach. The colourless corpuscles in these three cases were all amœboid at ordinary temperatures.

The earliest observations on the point I have brought before the Society were, so far as I have been able to find, made by Dr. Laking in 1873, at St. George's Hospital, with very similar results. They were not published, however, and, unfortunately, no record of them has been preserved.¹ In 1878 the absence of amœboid movement was communicated to the Pathological Society on April 16th, during the discussion on leuchæmia, by Dr. Pye-Smith,² to whom I had mentioned it, and was again shortly described by myself in a letter to the 'Lancet,' dated April 27th.³ It was, however, stated at the same discussion by Dr. Moxon,⁴ that Mr. Golding-Bird had found the leucocytes in leuchæmic blood to have active

¹ Since this paper was read, Dr. Bastian has pointed out that he has long been familiar with "the sluggishness of the white blood-corpuscles in this disease," and has informed me that the fact has been known to him since the latter part of 1868. Priority of observation on this point, therefore, belongs to him. (See 'Brit. Med. Journ.,' Nov. 27, 1880, p. 845, and ditto, Dec. 4, 1880, p. 881.)

² See report in 'Lancet,' vol. i, 1878, p. 607.

³ Loc. cit., p. 662.

⁴ Loc. cit. p. 607.

amœboid movements. The next observation with which I am acquainted was published in 1878 by E. Neumann,¹ and is of considerable interest. He examined the blood of a leuchæmic patient, and found it to contain chiefly small lymphoid cells, with a certain proportion of ordinary colourless corpuscles. No detailed account of his observations is given, but he states that the former showed no amœboid movement, and that the latter were extremely sluggish, even at high temperatures. He then examined the pus-cells obtained by blistering from the same individual, and found them all amœboid at ordinary temperatures, and very active on the hot stage. He concludes that the cells found in the blister-fluid cannot have migrated from the blood, but must have had some other origin, such as proliferation of connective-tissue corpuscles.

The observations I have brought forward warrant, I believe, the following conclusions :

I. The great majority of the colourless corpuscles in leuchæmia are dead or dying, and hence obviously incapable of further development.

II. As amœboid movement is practically lost, emigration from the blood-vessels is rendered impossible.

III. Coagulation, and hence the formation of capillary and other thrombi, is largely favoured.

The characteristic accumulations of lymphoid cells and colourless corpuscles which are found after death from leuchæmia in various organs and tissues, are attributed by Mosler² and Rindfleisch,³ partly to extravasation by hæmorrhage, but they consider that a true *emigration* of colourless corpuscles, in the sense of Cohnheim, has a large share in their production. Further, Mosler accepts the doctrine of lymphatic new growth as accounting for a

¹ "Farblose Blut- und Eiterzellen," 'Berlin. Klin. Wochenschrift,' 1878, p. 607.

² Art. "Leukämie," Ziemssen's 'Handbuch d. Speciellen Pathol. u. Therapie,' Bd. viii, 2te Hälfte, 1875, pp. 155—162.

³ 'Handbuch d. Pathol. Gewebelehre,' ed. 4, 1875, p. 153.

portion, at least, of the secondary infiltrations, but this view is considered incorrect by Rindfleisch. Now, as the power of amœboid movement, on which emigration depends, is nearly lost, we must reject this process as capable of explaining the presence of more than an extremely minute proportion of colourless corpuscles or lymphoid cells outside the blood-vessels. The vast majority must have escaped by rupture, but it is, I think, probable that an accumulation of lymph-cells in perivascular and other lymphatic channels has also much to do with their origin. It is a warrantable supposition that many of the cells shed directly into the lymphatic system have remained there without ever penetrating as far as the blood-vessels. In support of this view I may adduce the important part played by the colourless corpuscles in coagulation, and the production of the fibrin factors.¹ The researches of A. Schmidt and later observers render it extremely probable that the components of fibrin, especially the fibrin-ferment, are contained in the colourless corpuscles, from which they are discharged on their death and disintegration; if, then, the vast majority of these corpuscles in leuchæmia are dead or dying, the fibrin generators must be liberated in large quantity and thus give rise to the formation of clots, coagulation being doubtless favoured by textural changes in the vessels and tissues due to mal-nutrition. In this way thrombi will be formed, not only in blood-vessels, but also in lymphatics, and an effectual obstacle opposed to further circulation through the plugged vessels. In the case of the lymphatics it is theoretically probable that many corpuscles would thus be prevented from entering the blood. So far as the blood-vessels are concerned, the investigations of Cohnheim² have shown what an important part is played by embolism and thrombosis in the production of extravasations. I believe that the majority of secondary leuchæmic nodules is to be explained by these two

¹ See, On Coagulation, Foster, 'Text-book of Physiology,' ed. 3, pp. 12—16; Landois, 'Lehrbuch d. Physiologie,' pp. 49—57.

² 'Untersuchungen über die Embolischen Processe,' 1872.

processes, extravasation and lymphatic accumulation, and that emigration has only a very minute share in their production. With regard to lymphatic new growth we must be sure that the so-called "stroma" to be seen in pencilled or washed sections is a true adenoid reticulum, and not simply composed of a network of threads of fibrin,¹ a point which requires further histological investigation.

In conclusion, I may point out that the absence of amœboid movement has a bearing on diagnosis as well as pathology. It is known that cases of early leuchæmia often present great difficulties, which cannot be at once settled by a simple examination of the blood. The colourless corpuscles may be found largely increased, and still it may not be by any means easy to decide whether we have to do with leuchæmia, or with simple leucocytosis, especially as cases occur in which a splenic tumour, arising from causes other than leuchæmia, is accompanied by a temporary increase in the colourless corpuscles.² If the absence of amœboid movement be, as I believe, an essential character of true leuchæmia, it is plain that attention to this point may prove of great value in doubtful cases. I have already referred to a case of cancer of the stomach³ in which I examined the blood; there was in this instance a very large increase in the colourless corpuscles, but they were all actively amœboid, even at ordinary temperatures. I mention this only as an illustration of the fact that leucocytosis may occur without loss of amœboid movement; and although it is perhaps too early to draw a final conclusion, I think we may reasonably expect that its presence, or absence, will prove of primary importance when we are called upon to distinguish between leuchæmia and increase of colourless corpuscles from other causes.

¹ Greenfield, 'Path. Trans.,' vol. xxix, 1878, p. 303.

² Mosler, 'Pathol. u. Therapie d. Leukämie,' 1872, pp. 204, 222, 224.

³ Communicated to the Clinical Society by Dr. Whipple, on May 28th, 1880.