BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 3 1937

CASE OF CHRONIC MONOCYTIC LEUKAEMIA

BY

G. STEWART SMITH, M.D.

Assistant Pathologist to the Manchester City Hospitals

(WITH SPECIAL PLATE)

Although Reschad and Schilling-Torgau first described the condition in 1913, monocytic leukaemia is still a controversial subject, and it is only recently that its existence as a distinct entity has been accepted by most haematologists. It is agreed that these cases should be reported with full haematological and histological data, and the case here put on record has some features not previously described.

Clinical Notes

History.—A woman aged 48 years was admitted to Crumpsall Hospital on January 27, 1937. Three months earlier she had felt pains all over the body, especially in the neck and back, and general malaise. After resting for a month she got up, but had to return to bed as the symptoms continued. During the whole of this time she experienced frequency of micturition and thirst, and during the few weeks before admission had a feeling of heaviness in the left side of the abdomen.

Condition on Admission.—There was no pallor of the skin, but a slight cyanosis was present, and an erythematous rash appeared on the trunk. The mucous membranes were highly coloured, but nothing abnormal was found in the tongue or throat. The spleen was much enlarged, firm, and with sharply notched anterior border. The liver was slightly enlarged. The lymph glands were not palpable. No abnormality was found in the chest or the central nervous system. The urine was normal.

Progress.—Five days after admission a cough developed and catarrhal signs appeared in the chest; these persisted until death. On February 15 the general condition deteriorated and the patient became listless and semi-conscious, but there was no rise of temperature. The symptoms were thought to be due to cerebral thrombosis. Death occurred on February 17 after three weeks in hospital.

A blood count taken on February 2 showed 4,720,000 red cells per c.mm.; 70 per cent. haemoglobin; and a colour index of 0.75. The leucocytes numbered 394,000 per c.mm.: polymorphonuclears 2.5 per cent.; lymphocytes 0.5 per cent.; eosinophils 0.5 per cent.; monocytes 26 per cent.; monoblasts 11.5 per cent.; and primitive cells 59 per cent. The subsequent counts (see Table) showed little change. The Wassermann and van den Bergh reactions were negative, and the red cell fragility was within normal limits.

The monocytes, comprising 96.5 per cent. of the total count, were of three chief types, as stained by Leishman, although a rigid classification is impossible.

Table of Blood Counts

	2/2/37	12/2/37	15/2/37
Red cells per c.mm.	4,720,000	—	4,760,000
Haemoglobin per cent. of normal ..	70.0	—	75.0
Colour index	0.75	—	0.8
Leucocytes per c.mm.	394,000	461,000	341,000
Polymorphs per cent.	2.5	4.0	3.5
Lymphocytes per cent.	0.5	0.25	0.25
Eosinophils per cent.	0.5	1.0	0.25
Basophils per cent.	—	0.25	—
Monocytes per cent.	26.0	19.0	25.0
Monoblasts per cent.	11.5	14.5	9.0
"Primitive cells" per cent.	59.0	61.0	62.0

1. Monocytes, similar in many respects to the monocytes seen in normal blood, with an average diameter of 14 μ. The nuclei were large, lobulated, and often of unusual shape with slight reticulation. They had a moderate amount of pale blue "ground-glass" cytoplasm with occasional fine azur granules; but granules were not a prominent feature in any of these cells, and the variations in the shape of the nuclei were much greater than those seen in normal monocytes.

2. Monoblasts, larger than the monocytes—average diameter 18 μ—with large round or irregular pale-staining ribbed nucleus and generally two nucleoli. The cytoplasm was non-granular, and in some cells was vacuolated. Pseudopodia were seen in a few cells only.

3. So-called "primitive cells"—average diameter 9 μ. The nucleus, which was sometimes homogeneous, sometimes slightly ribbed, almost filled the cell, and was not uncommonly divided into two or three parts. The cytoplasm was slightly basophilic and non-granular, and typically formed a narrow rim around the nucleus.

The oxidase reaction (Graham's method) was negative in each of these three types. Classification may often be difficult or uncertain when a large proportion of primitive cells are present, but on examination of these films it was quite clear that the three types were all of one series. Some of the points above described are shown in the photomicrographs reproduced in the Special Plate.

Post-mortem Examination

Necropsy was performed on February 18, 1937, eighteen hours after death. There was no evidence of external injury and no rash, and no enlargement of axillary, cervical, or inguinal glands. The bone marrow of the middle of the shaft of the femur was pale creamy reddish brown. The heart (227 grammes) was extremely flaccid; the endocardium showed much post-mortem staining; and the heart muscle was greyish brown. The right ventricle was dilated and the wall very thin. There was no valvular disease and no fatty streaking. The lungs contained a few easily broken down pleural adhesions on each side; both lower lobes showed congestion and oedema. The liver (1,843 grammes) was pale and friable. The spleen (1,531 grammes, length 24 cm.) was uniform maroon in colour and the capsule thick and wrinkled; Malpighian bodies were not evident. A few slightly enlarged lymph glands were found in the gastro-hepatic omentum. The lymph glands elsewhere in the abdomen were not enlarged. The kidneys were mottled greyish yellow, with thickened capsules, which stripped leaving a finely granular surface. The thyroid (28 grammes) contained an adenomatous nodule three-quarters of an inch in diameter in the left lobe. The brain and cerebral vessels showed no abnormality. There was extensive post-mortem staining in all the body cavities.

Histology

The Bone Marrow (fixed Zenker, stained Leishman).—Fatty areas were present. The blood vessels contained many leucocytes. Erythroblasts were very plentiful and eosinophils fairly plentiful, megalokaryocytes scanty; myelocytes were found in large numbers. The other cells were: (1) Large cells, somewhat irregular in shape, with lobulated vesicular nuclei and cytoplasm which was slightly basophilic without definite granules. These were considered to be monocytes and premonocytes. (2) Small cells with deeply staining nuclei, often in two or three divisions, and a small amount of non-granular cytoplasm. These were undoubtedly "blasts." Both these types of cells corresponded well to the cells seen in the vessels in the marrow and with those seen and described in the blood films. The oxidase stain was positive for the myelocytes and eosinophils, negative for the mononuclear cells and "blasts." The presence of much erythroblastic tissue is unusual in leukaemia, but fits in well with the fact that there was no anaemia and no abnormality of the red cells as seen in blood films. The bone marrow, in fact, showed normal myeloid and erythroblastic activity, together with collections of monocytes and their precursors. A somewhat similar bone-marrow picture has been described by Doan and Wiseman (1934).

Spleen (fixed Zenker; stained Leishman).—The capsule was thickened and there was a thin subcapsular zone of red blood cells; the Malpighian bodies were not discernible. The pulp was very compact, and consisted of red blood cells and masses of mononuclear cells which were similar to those seen in the bone marrow except that cells of Type 2, with a rather darkly staining nucleus, frequently double, were more numerous in the spleen than in the portion of marrow examined. A few of the larger cells (monoblasts) had nucleoli, and mitotic figures were frequent. The cytoplasm of the mononuclears was opaque and entirely non-granular. Nucleated red cells were scanty and polymorphonuclears absent. The arrangement of the monocytes in the spleen was not suggestive of any special origin or method of formation. There was no evidence of desquamating endothelium in the sinuses as described by Clough (1932). The absence of lymphoid tissue and polymorphonuclears is important from the point of diagnosis, and will be discussed later.

Lymph Gland (from the gastro-hepatic omentum).—The normal follicular structure was absent. Lymphocytes were present in small numbers, but the tissue was largely composed of monocytes and monoblasts as seen in the other organs. The cells lining the sinuses were well defined, but there was no evidence of proliferation or desquamation. In general the picture was that of a gland which had been infiltrated by leukaemic cells and the lymphadenoid structure was grossly disturbed.

Liver.—There was pronounced central fatty change and some increase of periportal fibrous tissue. The intercellular capillaries showed a general infiltration of monocytes with denser collections in the portal areas; the capillaries around the central vein were congested. The appearances were those of chronic venous congestion with leukaemic infiltrations of "myeloid" distribution, but not as pronounced as is usual in chronic myeloid leukaemia.

Kidney.—There was a general increase in intertubular connective tissue, with many fibroblasts. A few tubules appeared to be normal, but in most the lining showed varying degrees of degeneration up to complete necrosis and shedding of the epithelium. The glomeruli were less affected, but many showed some capsular thickening, and a few complete obliteration and fibrosis of the tuft. These changes, especially as regards the tubules and intertubular connective tissue, were diffuse and advanced, and were probably the cause of death. In both kidneys there were dense infiltrations of mononuclear cells similar to those found elsewhere. The liver, spleen, and kidney contained no free iron.

Heart Muscle.—No fatty change, but there was slight leukaemic infiltration.

Lungs.—These showed oedema and congestion, with leukaemic cells in the exudates.

Discussion

It is not proposed in this article to survey the literature of monocytic leukaemia; Dameshek (1930) and Clough (1932) reviewed all the cases published up to that time, and Gittins and Hawksley (1933) gave notes on cases reported since Dameshek's paper. To date some thirty reported cases have been published, but only six in this country (Cooke, 1931; Gittins and Hawksley, 1933; Orr, 1933, two cases; Whitby and Christie, 1935; and Israëls, 1937). Most have been acute cases, with symptoms such as stomatitis and haemorrhages, common to all acute leukaemias. In the present case death occurred from nephritis.

Accepting monocytic leukaemia as a separate disease, a chronic form, as with the other leukaemias, might be expected to occur, and the features of this case seem to warrant its recognition as an example of a chronic leukaemia of monocytic type.

The spleen, which weighed 1,531 grammes and was 24 cm. long, was much larger than has been previously described in monocytic leukaemia. Mostly in this disease the spleen is not palpably enlarged, though in a few cases there is moderate enlargement. The size of the spleen in the case here described implies chronicity. The diagnosis rests between three conditions:

1. Chronic lymphatic leukaemia.—The abnormal cells in the blood were not lymphoid as regards either nucleus or cytoplasm. There was no general enlargement of the lymphatic glands, and the lymphoid tissue in the spleen

and lymph glands was not increased, but was decreased in amount and replaced by leukaemic infiltration.

2. Chronic myeloid leukaemia.—This is the condition which presents the most difficulty in differential diagnosis, since it is admitted that the cellular infiltrations in the organs are "myeloid" in distribution and the spleen is similar in size to a chronic myeloid spleen. It has been pointed out also (Gittins and Hawksley, 1933) that monocytes or monocytoid cells may appear in large numbers in the blood during the course of myeloid leukaemia. In the present case, however, the following facts are definitely against a diagnosis of chronic myeloid leukaemia: (*a*) Polymorphonuclears did not account for more than 4 per cent. of the leucocytes in the blood, and no myelocytes or myeloblasts of usual type were seen in a total of 461,000 leucocytes per c.mm. It is difficult to picture a case of myeloid leukaemia with so high a leucocyte count without at least a fair proportion of primitive cells definitely of the granular myeloid series. (*b*) The bone marrow contained normal erythroblastic and myeloblastic elements with an intermingling of mononuclear cells. The picture was not that seen in chronic myeloid leukaemia, in which the erythroblastic elements are crowded out by all types of granulocytes and their precursors. (*c*) The oxidase reaction of the monocytic cells in the blood, bone marrow, and spleen was negative. This is strong evidence against myeloid leukaemia.

3. Chronic monocytic leukaemia.—It is obvious from the literature that many different types of cells have been observed in cases considered to be monocytic leukaemia, ranging from monocytes similar to those found in normal blood to actively phagocytic histiocytes. In this case the monoblasts and monocytes (Types 1 and 2 in the differential blood count) appear to be typical as to size of cell, shape and character of nucleus, and colour and opacity of cytoplasm. Granules, although present in very few of the maturer monocytes, definitely were a rare feature. Some typical monoblasts with mitotic figures were seen in the spleen. The negative oxidase reaction, although valuable evidence against the cells being abnormal myelocytes, does not establish their identity, since monocytes may give a varied result with this method.

The cells classed as "primitive cells," Type 3, are more difficult to place. The absence of nucleoli from most of them, together with the fact that the nucleus was often divided into two or three parts, is quite unlike the picture of either myeloblasts or lymphoblasts; except for the absence of granules they are very similar to cells drawn and described by Doan and Wiseman (1934) as premonocytes in a case of monocytic leukaemia with a long history, ending in death from intercurrent disease. They state that "multinucleated cells are encountered frequently both in the blood and in the tissues in monocytic leukaemia." The name "premonocyte" suggests that they considered them to occupy a position between the monoblast and the mature monocyte. The lack of differentiation, combined with other features, however, leads me to a tentative conclusion that they are more primitive still than the large monoblasts, although of the same series. The supravital staining methods were not used in this case, but it is doubtful, in view of the contradictory findings of different workers (summarized by Hall, 1930), whether they add anything of diagnostic importance to the information obtained from dry smears.

Two features are worthy of special comment. (*a*) The fact that active erythropoiesis was going on in the bone marrow, and the corresponding absence of any anaemia in spite of a leucocytosis of 500,000 per c.mm. A progressive anaemia is almost the rule in leukaemia of this degree. (*b*) The spleen was densely infiltrated with monocytes and primitive cells, the latter being more plentiful than in the bone marrow, suggesting that the monocytes were being produced chiefly in the spleen.

Summary

1. A case of monocytic leukaemia is described, with haematological and histological findings.

2. The disease is rare, and a case with the high leucocyte count here recorded and the greatly enlarged spleen has not previously been reported.

3. It is considered that the case is one of chronic monocytic leukaemia.

I wish to thank Dr. C. S. D. Don, senior visiting physician to Crumpsall Hospital, for permission to publish this case, and Dr. G. D. Dawson and Dr. M. C. G. Israëls for helpful criticism.

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VESICAL EXTROVERSION WITH CONTROL OF MICTURITION

BY

A. RALPH THOMPSON, Ch.M., F.R.C.S.

Consulting Surgeon, Genito-Urinary Department, Guy's Hospital

(WITH SPECIAL PLATE)

The two cases of extroversion of the bladder recorded in this paper are worthy of attention in that they show the value of as complete a clinical examination in this type of case as is possible. For this purpose an anaesthetic should be given, and this has the additional advantage of allowing an artist to draw what is seen, at his leisure, and under the guidance of the surgeon. The cases also show that an operation directed towards closure of the bladder may, under the conditions which are to be noted, be of great value in leading to voluntary control of micturition, with as little disturbance of the parts as is possible. The main importance of the cases is that there was a normal proximal urethra developed in association with an extroversion of the bladder. This possibility is not generally recognized, but it is so important that no excuse need be offered for its early mention. For a very long time I have suspected that even in cases of advanced extroversion of the bladder much more of the normal urethra may be developed than authorities have apparently believed. In support of this assertion three cases of mine may be mentioned that seem to prove the occurrence of such a condition. In the absence of the two main cases which form the subject of this paper, the possibility of there being a normal proximal urethra is difficult of demonstration or conception. One of these cases, however, undoubtedly shows the presence of a normal proximal urethra. Two illustrations are here shown (Special Plate, Figs. I and 2) the originals of which are

G. STEWART SMITH: CHRONIC MONOCYTIC LEUKAEMIA

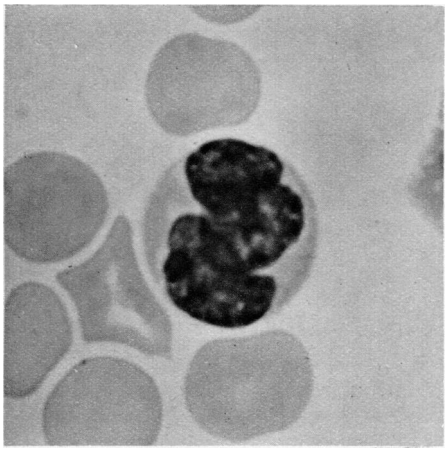
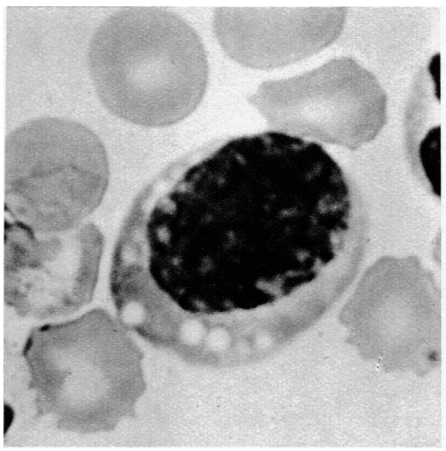
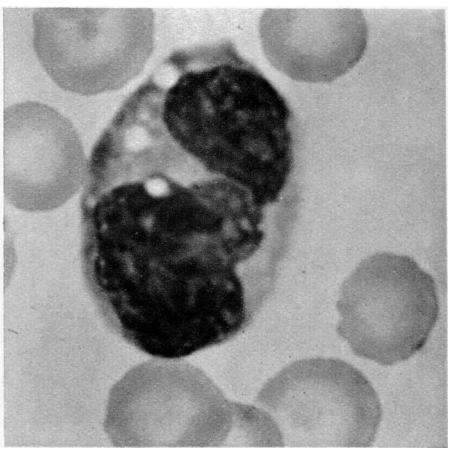
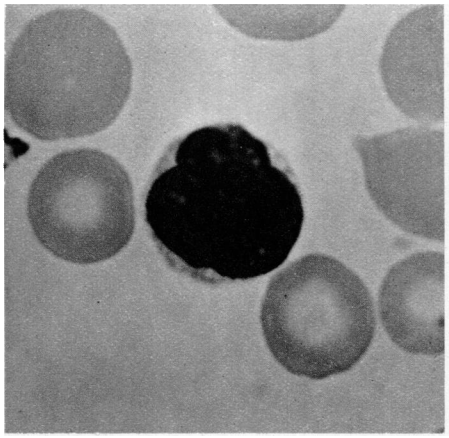


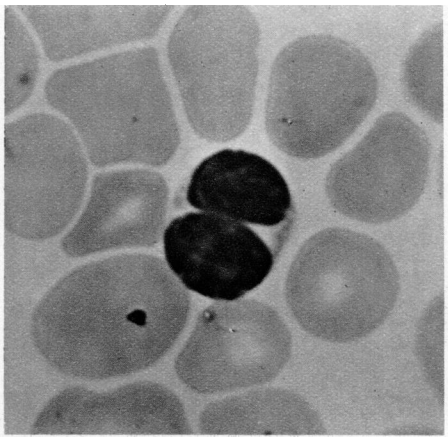
FIG. 1.—Monocyte (Type 1) showing lobulated nucleus.

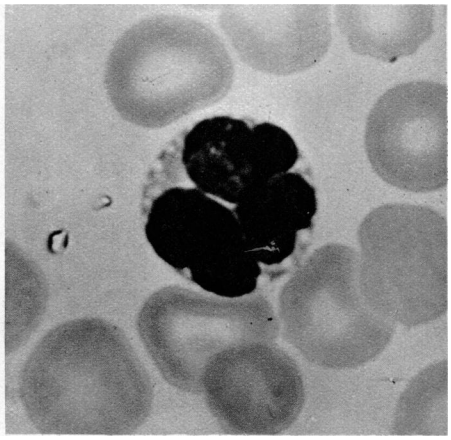




FIGS. 2 and 3.—Monoblasts (Type 2); much larger cells than the monocyte, with faintly marked nucleoli and vacuolated cytoplasm.







FIGS. 4, 5, and 6.—Primitive cells (Type 3). In Fig. 4 the nucleus is single, in Fig. 5 bipartite, and in Fig. 6 tripartite. (Magnification × 2,000.)

A. RALPH THOMPSON: VESICAL EXTROVERSION WITH CONTROL OF MICTURITION

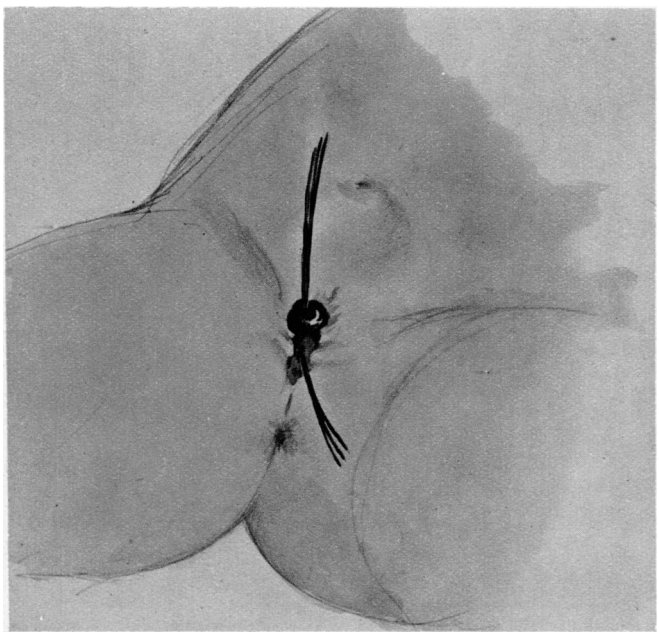


FIG. 1.—Case I. Salmon-gut probes have been passed through the proximal urethra from the bladder.

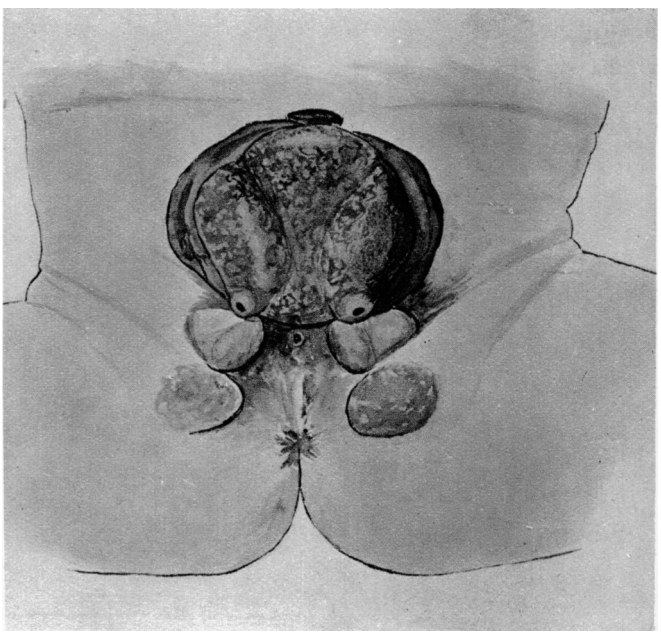


FIG. 2.—Case II. Note the large extroversion of the bladder showing the ureteric orifices, and below this the bilateral projections which represent the penis and the scrotum. The central orifice between the projections suggests a proximal urethra.