MONOCYTIC LEUKAEMIA IN CHILDHOOD

BY

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In 1913 Reschad and Schilling Torgau suggested the possibility of a distinctive hyperplasia affecting the monocytic cells of the blood under the name of 'splenocytic leukaemia.' With the more accurate title of 'monocytic leukaemia,' this is now an established entity. Though still regarded as a rare disease, this condition is being increasingly recognized. In 1933 only twenty histologically authenticated cases were on record (Gittins and Hawksley, 1933). By 1937 Osgood was able to review 133 cases, of which seventeen were children. The great increase in the number of cases recognized in the last few years suggests that the disease is commoner than at one time was thought likely, and later in this paper evidence will be brought forward to show how in many cases the diagnosis may easily be missed. Only a small proportion of recorded cases has occurred in children, yet here again increasing knowledge is bringing increased recognition. In 1936 Kato could only find records of five cases in childhood, yet at the Hospital for Sick Children five cases have been discovered in the last five years. The purpose of this communication is to consider the condition in childhood from the clinical, haematological and histological standpoints and to record two further cases.

Case reports

Case 1.—Male, aged five years. Pallor, the initial symptom, was first noticed in September, 1937. By February, 1938, this was more evident and in view of the development of a cough and excessive night sweats, he was admitted to the North Middlesex Hospital (February 14, 1938). Here the child developed what appeared to be measles, together with a very severe anaemia. One or two small bruises were present on both hands. The blood picture (February 22, 1938) is interesting :

RED BLOOD CELLS : 1,680,000 per c.mm.

HAEMOGLOBIN : 30 per cent.

COLOUR INDEX : 0.93.

WHITE BLOOD CELLS : 3,125 per c.mm.

POLYMORPHS : 43 per cent.

LYMPHOCYTES : 42 per cent.

MONOCYTES : 10 per cent.

PLATELETS : scanty.

Atypical and primitive lymphocytes and monocytes were recognized in the films, but they were regarded as being secondary to an aplasia affecting the bone marrow and resulting from toxæmia.

The child was treated by one transfusion of 200 c.c. blood, and campolon 2 c.c. and sodium pentnucleotide 10 c.c. daily for sixteen days. Following this an intermittent pyrexia, which had been present since admission, subsided and the general condition improved. At no time was there any clinical enlargement of the liver, spleen or superficial lymph nodes. The final blood picture was :

RED BLOOD CELLS : 4,370,000 per c.mm.

HAEMOGLOBIN : 72 per cent.

COLOUR INDEX : 0·8.

WHITE BLOOD CELLS : 9,300 per c.mm.

POLYMORPHS : 48 per cent.

EOSINOPHILS : 6 per cent.

LYMPHOCYTES : 38 per cent.

MONOCYTES : 12 per cent.

Improvement was maintained for a month. The child then began to lose weight, appetite and energy. The cough was still present, and in the middle of June he developed abdominal pain, always followed and relieved by defæcation.

On June 30, 1938, he was admitted to the Hospital for Sick Children.

FIG. 1.—Case 1 : Photograph to show marked enlargement of the cervical lymph nodes and the scars of old furuncles on buttocks and back.

EXAMINATION : A pale child of moderate physique. A purpuric rash with a few ecchymoses was present over both lower limbs and the right arm. There was no obvious bleeding from the mucous membranes. The buttocks showed numerous scarred areas, said to be the result of a series of furuncles which occurred during the previous illness. There was well-marked, generalized enlargement of the superficial lymph nodes, most obvious in both posterior triangles of the neck (see fig. 1). The tonsils were large, but otherwise appeared normal. The liver was enlarged three fingersbreadths and the spleen two fingersbreadths below the costal margin, the former being the more striking feature. Clinical examination of the chest was negative and a skiagram revealed a slight increase in the hilar shadows.

COURSE : The child was febrile on admission and intermittent pyrexia continued. Iron, campolon, sodium pentnucleotide and one blood transfusion were given, but the course was progressively downhill. For a few days before death there was considerable increase in the glandular swellings, gross haematuria and dysuria, and a severe ulcerative stomatitis. Death occurred on July 23, 1938.

BLOOD PICTURE : The initial blood picture, before the true nature of the condition was realized, was as follows :

February 7, 1938.—RED BLOOD CELLS : 2,760,000 per c.mm.

HAEMOGLOBIN : 44 per cent.

COLOUR INDEX : 0.8.

WHITE BLOOD CELLS : 19,700 per c.mm.

NEUTROPHIL POLYMORPHS : 1 per cent.

LYMPHOCYTES : 46 per cent.

MONONUCLEARS (nature doubtful) : 51 per cent.

PRIMITIVE CELLS : 2 per cent.

MEGALOBLASTS : 1 per cent.

ANISOCYTOSIS AND POIKILOCYTOSIS.

The diagnosis of monocytic leukaemia was made from the examination of subsequent blood films and confirmed by sternal marrow puncture and biopsy of a cervical gland. Supra-vital staining of the films proved that the majority of cells were monocytes. Those classed as 'atypical,' however, did not show the typical appearances of the monocytic cells (fig. 2).

FIG. 2.—Case 1 : Leishman stain $\times 700$. Blood-film showing a monoblast with a lymphocyte beside it. There are several promonocytes and atypical cells ; two of the latter are at the bottom.

BLOOD-COUNTS

DATE	4.7.38	6.7.38	15.7.38	22.7.38
HAEMOGLOBIN, per cent.	45	—	46	18
RED BLOOD CELLS, in millions per c.mm.	3.46	—	—	1.14
COLOUR INDEX	0.65	—	—	0.78
WHITE BLOOD CELLS, per c.mm. . .	47,800	51,300	63,600	42,600
NEUTROPHIL POLYMORPHS, per cent.	0	0	9	0
METAMYELOCYTES (NEUTROPHIL), per cent.	0.5	0.5	0.5	0
MYELOCYTES (NEUTROPHIL), per cent.	0.5	0.5	0	0
LYMPHOCYTES, per cent.	11.0	18.0	13.0	5.5
MONOCYTES (MATURE), per cent. . .	0.5	0.5	8.5	0
PROMONOCYTES, per cent.	59.0	50.0	29.5	57.5
MONOBLASTS, per cent.	2.0	1.5	2.5	1.5
ATYPICAL CELLS, per cent.	26.5	29.0	37.0	35.5
NORMOBLASTS, per cent.	0	0.5	0	0
ERYTHROBLASTS, per cent.	0	0.5	0	0
MEGALOBLASTS, per cent.	1.0	0	0	0
PLATELETS, per c.mm.	46,000	—	—	41,000

SUPRA-VITAL STAINING (4.7.38)		STERNAL MARROW FILM (6.7.38)	
	PER CENT.		PER CENT.
MONOCYTES	54.5	POLYMORPHONUCLEARS	0
LYMPHOCYTES	42.5	METAMYELOCYTES (NEUTROPHIL) . .	0.3
NEUTROPHIL POLYMORPHS	0	MYELOCYTES (NEUTROPHIL)	0.3
EOSINOPHIL POLYMORPHS	0.5	„ (EOSINOPHIL)	0.3
BASOPHIL POLYMORPHS	0	„ (BASOPHIL)	0.3
DOUBTFUL CELLS	2.5	LYMPHOCYTES	7.3
		MONOCYTES	0
		PROMONOCYTES	52.0
		MONOBLASTS	6.0
		ERYTHROBLASTS	0.3
		ATYPICAL CELLS	33.0

Histological report on the lymph node.—Cursory examination of a section through the node shows that the normal appearance has been lost, but with care a few follicles, some with secondary centres, together with the lymphatic sinuses and intervening medullary tissue, can be made out. Large masses of basophilic cells, which appear to be produced by proliferation in the medulla, are compressing the rest of the medulla, follicles and sinuses. These cells have a more or less uniform appearance. They are round or oval, have scanty basophilic agranular cytoplasm, and vary in diameter from 4μ to 8μ . Their nuclei, though varying in shape with round, indented or even convoluted forms, have a similar structure. The nuclear membrane is well marked, with condensation of chromatin at the periphery. There is a fine loose chromatin network, with nodes at the intersection of the chromatin threads and one or two nucleoli. A few cells are in mitosis. The cells are to be regarded as precursors of the monocytes of the blood (case 1, fig. 3). Amongst these masses of monocytic cells small sinuses can be made out, and there are in addition a few reticulum cells with pale-staining nuclei and indefinite outlines. There are many monocytic cells infiltrating the rest of the compressed medulla. Granular leucocytes are absent. The sinuses can easily be identified; some of the littoral cells are swollen, but they have not proliferated. There is no increase in fibrous tissue, nor in the argentophil reticulin fibres. Large numbers of monocytic cells are infiltrating the capsule and peri-capsular tissues.

Autopsy.—For religious reasons a complete examination was refused, but

FIG. 3.—Case 1 : H. & E., $\times 240$. Section of lymph node to show infiltration of medulla by monocyctic cells.

portions of liver, spleen and kidney were removed through a small abdominal incision. A segment of rib was also excised.

The body was that of a well-developed, moderately nourished child. There was marked pallor but no other external abnormality apart from the scars of old furuncles, already mentioned.

SPLEEN : Moderately enlarged. Weight 270 gm. Cut surface thick and fleshy, with no Malpighian bodies or localized deposits.

LIVER : This was greatly enlarged, pale and yellow on section, and with no apparent deposits.

KIDNEYS : Extremely pale and grey in colour. A moderate-sized area of haemorrhage was present in the upper pole of the left kidney and a smaller one in the lower pole.

Histological examination.—**LIVER :** Sections showed well-marked infiltration of the portal tracts with monocyctic cells, similar to those seen in the biopsy of the lymph node ; there were in addition a few eosinophil leucocytes. There was a moderate degree of fatty infiltration of the hepatic cells, most marked at the centre of the lobules. Cells in the neighbourhood of the portal infiltrations were atrophied. The Kupffer cells showed evidence of phagocytosis of erythrocytes and monocytes, but were not increased in number, and there was no evidence of their conversion into free phagocytic cells. Free iron could be demonstrated in the hepatic and Kupffer cells but not in the monocytes.

SPLEEN : There was marked compression and atrophy of the follicles and an infiltration of the medulla with monocyctic cells. Only a few granular leucocytes and myelocytes were seen. Monocyctic cells were lying free in the sinuses. These appeared to have a more plentiful cytoplasm and some had the appearance of plasma cells. No free iron could be demonstrated by the Prussian blue reaction.

KIDNEY : The glomeruli were healthy, but the cells of the tubules showed fatty degeneration. Monocyctic cells could be seen in the blood-vessels and there were, in addition, small areas of infiltration by these cells into the interstitial tissue, particularly in the neighbourhood of the arterioles (fig. 4). This proximity to the blood-vessels is of interest, as it suggests a local origin of monocytes from the undifferentiated mesenchymal cells to be found in the

FIG. 4.—Case 1 : H. & E., $\times 550$. Section of kidney showing infiltration by monocyctic cells.

adventitia of blood-vessels (cf. Robb-Smith, 1938). A similar paravascular distribution of the infiltration in the kidney was found by Hernandez (1938) in one of his cases.

RIB : The portion of rib was examined after decalcification. Infiltration by monocyctic cells could be seen in the muscular and fatty tissue round the bone and also beneath the periosteum (fig. 5). The marrow was extremely

FIG. 5.—Case 1 : H. & E., $\times 40$. Section of rib. There is infiltration beneath the periosteum and also into the connective tissue outside the periosteum, which is shown on the left.

cellular and the majority of the cells were monocyctic. Granular leucocytes, myelocytes, erythroblasts, normoblasts and megakaryocytes were present, but in a much reduced proportion from the normal. There were, in addition, a few cells with large oval nuclei and an indefinite cell-outline.

Case 2.—Female child, aged four and a half years. Admitted to the

EXAMINATION : Well-built girl ; pale and rather quiet. Mouth and tonsillar region normal. No bleeding from the gums. Spleen moderately enlarged. Liver just palpable. Small lymphatic glands felt in the right side of the neck and in the right axilla. These did not increase in size during the course of the illness. No purpuric spots seen anywhere, but a few bruises were present in the region of both knees. Moderate pyrexia 99°-100° F.

STERNAL MARROW PUNCTURE

STERNAL MARROW FUNCTION					PER CENT.
NEUTROPHIL POLYMORPHS	..	..	..	..	2.0
EOSINOPHIL POLYMORPHS	..	..	..	..	0.5
BASOPHIL POLYMORPHS	..	..	..	..	—
NEUTROPHIL METAMYELOCYTES		..	..	..	3.5
NEUTROPHIL MYELOCYTES	..	..	..	..	3.5
LYMPHOCYTES	..	..	..	..	29.0
MONOCYTES	..	..	..	..	4.0
PROMONOCYTES	..	..	..	..	33.5
MONOBLASTS	..	..	..	..	5.5
INDEFINITE	..	..	..	..	3.5
NORMOBLASTS	..	..	..	..	6.5
ERYTHROBLASTS	..	..	..	..	3.0
MEGALOBLASTS	..	..	..	..	5.5

[illegible]

Autopsy.—The body was that of a well-developed child. Weight 35 lb. ; height 3 ft. 10 in.

THE BRAIN was pale, but otherwise normal.

THE HEART weighed 105 gm. There was marked fatty change, with the production of the thrush-breast appearance under the ventricular endocardium.

THE LUNGS were pale and oedematous and there were a few sub-pleural haemorrhages.

THE LIVER was much enlarged and weighed 900 gm. It was of a general yellow colour and was mottled with small, glistening, orange-yellow areas.

THE SPLEEN was also greatly enlarged, weighing 265 gm. ; it was dark red in colour, but on section showed stippling with small irregularly shaped areas of whitish-grey, each surrounded by a red zone of haemorrhage.

THE LYMPH-NODES were not enlarged in any part of the body.

THE KIDNEYS were extremely pale and had an average weight of 80 gm. On section the cortex appeared yellow. There were several wedge-shaped infarcts.

THE ADRENALS were normal.

THE THYMUS was moderately enlarged and pale.

THE STOMACH and INTESTINAL TRACT displayed no abnormality.

Histological examination.—LIVER : In the liver there was well-marked peri-portal infiltration, the majority of the cells being identified as monocytes or monoblasts. Many, however, were smaller than the typical monocyte and had more darkly staining nuclei and thus resembled lymphocytes ; these cells were undoubtedly similar to those seen in the blood films and termed 'atypical.' There were in addition a few granular leucocytes and myelocytes. Many of the liver cells showed a moderate degree of fatty degeneration. The sinuses contained many monocytes ; the Kupffer cells were not especially prominent, but a few showed erythrophagocytosis.

SPLEEN : The lymph-follicles of the spleen were inconspicuous and had been compressed by a marked proliferation of cells in the pulp. These consisted almost entirely of typical and atypical monocytic cells, but there were a few granular leucocytes.

BONE-MARROW : Sections of the bone-marrow showed it to be cellular and to consist mainly of monocytes. There were only scanty numbers of granular leucocytes and myelocytes, megakaryocytes and nucleated precursors of the erythrocytes. There were, however, a few large histiocytes, some of which showed evidence of phagocytosis.

THYMUS : There had also been extensive infiltration of the original lymphoid tissue of the thymus with monocytic cells, but the differentiation of the two types of cells was made difficult by the presence of the 'atypical' lymphocyte-like cells.

HEART : The heart muscle showed no obvious abnormality apart from the blood-vessels containing large numbers of cells, due to the escape of many primitive forms into the circulation before death. Many of the cells were small and darkly staining, which agrees with the last blood-count. This showed that the majority of the cells, then beginning to flood the circulation after the preceding leucopenia, were of the 'atypical' variety.

THE LUNG showed oedema and large numbers of monocytes in the capillaries of the alveolar walls, as well as in the larger blood-vessels.

KIDNEY : Similarly in the kidney there were many monocytes in the capillaries, but no interstitial infiltration. The glomeruli were normal and the cells of the tubules showed post-mortem change only.

Discussion

An increasing number of cases of monocytic leukaemia is being recorded and analysis of their features has established a clinical picture for adults. No similar attempt has been made to define the condition in childhood. In Osgood's (1937) recent review, seventeen patients were children. Hernandez (1938) has described the clinical and histological findings in two other cases. Four further examples have occurred in this hospital ; one has been reported previously (Newns and Signy, 1938, case 2), and full details of two others have been given here. A further case at this hospital, reported by Lightwood and Hawksley, is included in Osgood's collection. These twenty-three authentic cases will be analysed in this paper. The five cases from this hospital have occurred in the last five years. During this period, thirty-five children with leukaemia were admitted to the wards. Apart from the five examples of monocytic leukaemia, twenty-nine had lymphatic leukaemia and one probably myelocytic. Lymphatic leukaemia is therefore much the most common in childhood, and the twenty-nine cases mentioned above will serve for purposes of comparison in this communication.

The following clinical features will be considered.

AGE : The youngest case reported was eleven months. The average age was six years and three months. In the lymphatic series, the average age was four years and three months. Only 40 per cent. of the monocytic group were under five years of age, as compared with 64 per cent. of the lymphatic. This suggests that monocytic leukaemia tends to occur rather later in childhood than the other types. This may be contrasted with the traditional view that, in children, leukaemia as a whole tends to occur in the first four years of life (Whitby and Britton, 1937).

SEX : Males are more frequently attacked than females in the proportion of three to two. A similar ratio is found in adults.

DURATION : The average duration in the monocytic series was sixteen weeks ; the longest period was twenty-one months and the shortest ten days. In the lymphatic group the average duration was ten weeks, with a maximum period of ten months and a minimum of ten days. In four of the monocytic cases the disease lasted for six months or over, and in three of these a definite remission, extending over a period of months, occurred. During this time the clinical condition reverted towards the normal and the anaemia responded to treatment. This is well exemplified in case 1. The blood monocytes remained persistently above the normal level and were qualitatively abnormal. Whitby and Britton (1937) emphasize that relapse in almost every case is preceded by an infection usually affecting the upper respiratory tract. Though in many cases the exact onset is difficult to determine, once established the disease usually runs a rapid course. At the same time sub-acute or remittent cases occur rather more frequently than in other leukaemias. These contrasting types are excellently illustrated by the two cases reported in this paper.

ORAL LESIONS : Lesions in the mouth occurred in 52 per cent. of the monocytic, as compared with 20 per cent. of the lymphatic series. These consist of soreness, bleeding from the gingivae, swelling and necrosis of the mucous mem-

brane, which may extend on to the tonsil or soft palate. Although these lesions give rise to some of the most striking symptoms in adults, in whom necrosis of the mucous membrane may reach the degree of a diffuse cellulitis, only the milder forms occur in childhood. In only two cases has necrosis been a prominent feature. In the first cases reported by Hernandez (1938) this was the presenting feature. But in the remainder simple bleeding and superficial ulceration alone were present, and in many cases it was then only a terminal feature. Although a suggestive symptom, the claim made by Forkner (1934) that this picture of diffuse and marked swelling of the mucous membranes, particularly affecting the gingivae, with ulceration and necrosis, is characteristic of monocytic leukaemia and is usually absent in the other forms of acute leukaemia, is not substantiated by a review of monocytic leukaemia in childhood.

HAEMORRHAGIC FEATURES : Purpura was noted in 76 per cent. of the monocytic and 67 per cent. of the lymphocytic series. In the former, petechiae, often widespread, were the usual manifestation ; in the latter, ecchymoses and larger areas of bruising were more in evidence. Retinal haemorrhages were frequent. In the terminal stages bleeding from any mucous surface occurred, notably haematemesis and haematuria. However, in both cases recorded by Hernandez (1938) epistaxis, haematuria and melaena occurred in the early stages. Case 1 here reported had massive haematuria terminally, due to renal infarction, with severe colic. In the adult series purpura was only present in 37 per cent. of cases.

LYMPHADENOPATHY : This was present in 100 per cent. of the lymphatic and 76 per cent. of the monocytic series. In the former the process was generalized in 60 per cent. and in the latter in only 20 per cent. of cases. An attempt has been made by several writers, notably by Forkner (1934), to use the degree and quality of the glandular enlargement as a differentiating factor. He suggests that in the myeloid type the enlargement is slight or absent, in the lymphatic group generalized and of moderate or marked extent, and in the monocytic group moderate in the neck and slight elsewhere. We feel, however, that there is a much greater variation than this. There is no question that glandular enlargement is a more prominent feature of the lymphatic type. Nevertheless the most striking thing about the present first case was the wide distribution of the enlarged glands and the marked degree of their enlargement. Furthermore, in 26 per cent. of the lymphatic series the cervical glands were enlarged alone or were relatively greater in size. A rather higher proportion was found in the monocytic group. Mickulicz's syndrome was present in two cases, both of which were lymphatic in type. In both groups the glands were firm, discrete and painless. The extent of the enlargement would appear to vary directly with the duration of the disease.

ENLARGEMENT OF LIVER AND SPLEEN : A palpable spleen was present in 87 per cent. of the monocytic and 73 per cent. of the lymphatic series. This was rather an unexpected finding in view of the accepted idea that the spleen is always significantly enlarged in lymphatic leukaemia. Splenomegaly occurred alone in 26 per cent. of cases. Our first impression, that when enlargement of the liver occurred as well, it was the more obvious clinical feature, was not

borne out by statistics. Hepatomegaly occurred in 58 per cent. of the monocytic and 60 per cent. of the lymphatic series. In 20 per cent. of both groups enlargement of the liver was more evident than that affecting the spleen. In 13 per cent. of the monocytic and 17 per cent. of the lymphatic, neither were clinically enlarged. This clearly differs from the contention of Whitby and Britton (1937), for monocytic leukaemia as a whole, that the liver is invariably enlarged.

CUTANEOUS LESIONS : These are of some importance. They were present in 18 per cent. of the monocytic and in none of the lymphatic series. The lesions are of two types :

(a) Nodules in the skin, which are firm and painless and on histological examination show a preponderance of monocytic cells or their precursors.

(b) Widespread staphylococcal infection with boils or carbuncles. This seems to occur too frequently to be a coincidence. This feature was well illustrated by case 1.

GENERAL CONSTITUTIONAL FEATURES : These do not differ from those in other acute leukaemias. Pallor is well marked and associated with asthenia and weakness. Pyrexia is almost invariably present and may be of high degree. The presenting symptoms are many and varied ; the statement that they are usually associated with the mouth and fauces is not so true in childhood as in later life. The first thing noted is usually pallor and lack of energy. This may be accompanied by a sore throat or acute coryza. Purpura is often an early feature. Dyspnoea and abdominal pain have been noted in several cases ; the latter may be associated with melaena. Once established, the disease usually pursues a rapidly downhill course and the terminal stages are distressing. Two extremes, between which all gradations of severity exist, are represented by the two cases reported above. The first presents the subacute or remittent picture extending over a period of ten months. Glandular enlargement, splenomegaly, enlargement of the liver, purpura and, in fact, all the possible features were present to a marked degree. The child was relatively well during the earlier phases and rapid deterioration only occurred in the last three weeks. In the second case the child was apparently healthy until five weeks before death. Bleeding from the gums, enlargement of the lymph glands and purpura were never in evidence. The course was rapid and treatment failed to produce even temporary arrest of progress.

HAEMATOLOGY AND PATHOLOGY : Analysis of the clinical features suggests that there is no distinctive clinical picture in the monocytic leukaemia of childhood. This contrasts with Forkner's contention, after his study of the adult condition, that the clinical appearances are of sufficient value to allow a tentative diagnosis of acute monocytic leukaemia to be made independently of the blood picture. Similarly it fails to confirm the suggestion by Merklen and Wolff (1928) that clinically a strong presumption is possible. The striking difference between the present cases, together with a careful consideration of those reported in the literature, suggest that monocytic leukaemia shares its clinical features with other leukaemias of the acute or subacute types and cannot be diagnosed at the bedside without laboratory assistance.

During life it is possible to examine the blood and sternal marrow, and also, when an enlarged lymph node is available, this can be removed by biopsy. But leukaemia is a systematized disease of the reticulo-endothelial system, as has been stressed by one of us recently (Edward, 1938), and this can only be examined completely at autopsy. It is then possible to confirm the diagnosis of monocytic leukaemia by the distinctive histological appearances. We disagree with the statement of Beck (1938) that post-mortem findings do not materially help in the diagnosis of the type of leukaemia. Robb-Smith (1938) has pointed out that any confusion regarding the histology has arisen from the relative lack of attention paid to it, as compared with the detailed studies of the haematology. A full histological description has therefore been given of the present cases. The recognition of the histology is important because of the possibility of the hyperplasia of the reticular system occurring without escape of the newly-formed monocytes into the circulating blood (true aleukaemic monocytic reticulosis).

Special considerations

Interesting features about the two cases described in this paper are the relative scarcity of mature and immature granular leucocytes, both in the blood and in the tissues (although they were more numerous than in most cases of lymphatic leukaemia) and the stage of leucopenia in both. However, when the first case came under observation, the leucocyte count had risen and there were many typical immature monocytic cells. The blood and marrow films of these two cases have been carefully examined and compared with material derived from three other earlier cases at this hospital and from several adult cases. In both cases typical mature monocytes were scanty. The predominating cell was the promonocyte; this had a mean diameter of $10-16\mu$, frequently contained one or two nucleoli, and conformed in every way to the published descriptions of this type of cell. There were also a few more primitive cells—monoblasts—measuring $13-16\mu$. In neither case could Auer's bars be found, despite a special search for them, and azurophil granules were scanty. In addition to the promonocytes and monoblasts there has been, in all the films examined, another type of abnormal cell classified as 'atypical.' These cells differ from the promonocyte in being smaller ($8-10\mu$); their nuclei are more darkly staining and contain no nucleoli. The shape of the nucleus is circular, polygonal or occasionally reniform; the nuclear membrane is well marked and more regular than in the promonocyte. The cytoplasm is basophilic and scanty, the nucleus nearly filling the cell. In many ways these cells resemble lymphocytes, but their nuclei are larger and appear more immature. Between these cells and promonocytes and lymphocytes there are no hard-and-fast dividing lines and one group tends to merge into the other. These cells seem to have attracted little attention in the literature. Smith (1937) described abnormal cells of a third type in a case of monocytic leukaemia. These he called 'primitive cells,' as he believed them to be precursors of the monoblast. The cells studied by the present authors contain no nucleoli and do not appear highly

undifferentiated ; their appearance, in fact, differs markedly from the monoblast. On the other hand, all degrees of differentiation from the promonocyte can be made out, and it would seem likely that they are more closely related to the latter, perhaps resulting from abnormal activity of the leucopoietic system the function of which has been deranged by the leucotic process. The similarity of some of these ' atypical cells ' to lymphocytes may indicate a close relationship between lymphocytes and monocytes. But a recent paper by Rhoads and Miller (1938) on the appearances of the bone-marrow in aplastic anaemia suggests that other small mononuclear cells exist, which have a superficial resemblance to lymphocytes, but differ in their origin and function. It is thus dangerous to identify a lymphocyte by a few of its striking morphological features.

The presence of these atypical cells is of importance in diagnosis. This is well exemplified in the second patient, in whom a large percentage of the abnormal cells were of this type. There were, however, enough typical promonocytes and monoblasts to indicate the true diagnosis. In this case supra-vital staining failed because of the paucity of leucocytes at the time of the examination and because many of them were ' atypical ' cells. It would appear, from the findings in the first case, that the latter do not show the typical appearances of monocytes after supra-vital staining. It is of interest that in this patient half of the cells which flooded the circulation before death were ' atypical.' This markedly affected the histological appearances after death, because only a minority of the infiltrating cells and those in the blood-vessels were typical monocytic cells. Thus the occurrence of atypical cells confuses the diagnosis both haematologically and histologically. It is probable, therefore, that monocytic leukaemia is more common than is realized. The presence of a few typical promonocytes or monoblasts in a blood-film suggests the diagnosis, and post-mortem material must, as a routine, be carefully examined with an oil-immersion lens, especially after staining by Leishman's method, in order that this type of leukaemia is not missed.

Summary

1. Two new cases of monocytic leukaemia in childhood are described.
2. The clinical features of these and other recorded cases are analysed and compared with a similar series of the lymphatic type.
3. This analysis shows that there is no distinctive clinical picture. Certain minor differences exist, however, between the two types, notably the older age-incidence, longer duration, presence of cutaneous lesions, and, to a lesser degree, the distribution of the lymphadenopathy in the monocytic variety.
4. The diagnosis is established by haematological and histological investigation. During life examination of both blood and sternal marrow, together with a lymph gland where possible, should be carried out.
5. Attention is drawn to the presence of ' atypical ' cells. Their occurrence in large numbers may confuse the diagnosis. It is suggested, in consequence,

that monocytic leukaemia is probably more common than is generally recognized at present.

Thanks are due to Dr. Wilfred Pearson and Dr. Donald Paterson for their permission to publish the clinical details of these cases, to Dr. D. Nabarro, late Director of the Pathological Department, and to Mr. D. Martyn for help with the photography. The authorities of the North Middlesex Hospital kindly allowed access to the notes on case 1.

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