STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD

(From the Children's Hospital and the Department of Diseases of Children of the University, Birmingham).

Part VIII.—Leukæmia (leucosis) in Children*

BY

ROBERT GITTINS, M.D., M.R.C.P., D.T.M. & H.

Leukæmia is a disease which has always held great attraction for the clinician and pathologist, for there are few diseases which can be studied with such simple apparatus and in which the results lead to such fascinating speculations on cellular development and function. Although these speculations have so far not led to success in treatment, the careful study of leukæmia has considerable practical value, not only in the sphere of differential diagnosis (for there is only a minority of blood diseases, in which the possibility of a leukæmic process has not to be excluded), but also in throwing light on processes which are later seen to possess analogous features. It is, therefore, somewhat surprising that only a relatively small number of papers have been written dealing with the aspects of leukæmia in childhood. The present paper has been written partly for this reason, and partly because when the present studies on anæmia were in progress it was found impossible adequately to deal with diseases of the erythron without considering diseases of the leucon (the leucocyte and its predecessors).

Many acute leukæmias are in greater or less degree 'aleukæmic,' and frequently present considerable difficulty in recognition and identification; yet it is almost exclusively this acute type which occurs in children, and the present series does not include a chronic case, nor has one been found in the records of the Hospital. Acute hæmolytic (erythronoclastic) anæmia, von Jaksch's anæmia, infective mononucleosis, some infective and septic conditions, and even severe nutritional anæmia may simulate leukæmia, and without hæmatological investigation, may for a time be indistinguishable from it. Too much emphasis can scarcely be laid on the acuteness of leukæmia, and the frequency of aleukæmia in children, and the consequent difficulties in hæmatological examination. Moreover, such an examination

* This communication is based on the personal study of fourteen cases, the detailed records of which have had to be omitted for reasons of space. Editors, A.D.C.
does not always reveal unequivocally the nature of the process, and the complete study must include also a histological examination. For these reasons it has been decided to include in this study only those cases which during the past three years have come to autopsy and of which the blood films and sections have been preserved for comparative examination.

Nomenclature.—The disease, which has been known for many years as leukæmia, was so christened because of the large number of leucocytes found in the blood stream. This invasion of the blood stream is accompanied by definite histological features, which typically are not reproduced by other disease processes. As leukæmia was further studied it became apparent that while the histological features remained more or less constant, increase of the total leucocytes in the peripheral blood was not an essential feature. Such a condition was labelled 'aleukæmic leukæmia,' although these cases usually showed definite qualitative changes in the leucocytes, similar to those in the leukæmic group. A few rare cases, showing the histological features, but with not even qualitative changes in the leucocytes of the peripheral blood have been claimed. The underlying process of the disease is one affecting the leucopoietic tissues, and for it leucosis is a more suitable term than leukæmia.

Leucosis may be divided into two chief forms—myelosis and lymphadenosis. We may then speak of:—

Leukæmic myelosis: myelosis, with an increase in total leucocytes which show also qualitative changes of leukæmia.

Aleucocythæmic myelosis: myelosis, without definite increase in total leucocytes, but with qualitative changes of leukæmia.

Aleukæmic myelosis: myelosis, with neither an increase in total leucocytes nor any qualitative change.

Similarly we may speak of leukæmic, aleucocythæmic and aleukæmic varieties of lymphadenosis, and possibly also of reticulo-endotheliosis.

Most of the present series of 14 cases fall into the category of aleucocythæmic lymphadenosis, although one case, which displayed equivocal signs, appeared to be an example of the rare condition of acute aleukæmic lymphadenosis; there were only two examples of myelosis.

Symptoms.—Although the maximum incidence of acute leucosis occurs in the first five years of life, Stransky1 quotes Adler as stating that from the time of the discovery of leukæmia in 1845 to 1914 only seventeen cases in infants were reported of which, excluding cases of alleged congenital leukæmia, ten have been accepted. In our series the age varied from 10 months to 12 years. The onset is often insidious and anaemia develops; the presenting symptom in one of our cases was glandular swelling (myelosis), in another abdominal enlargement (myelosis) and in yet another jaundice. Pallor, except at the onset, is striking, and is often waxy in type. Nutrition is frequently good and wasting is not a feature. In three cases of lymphadenosis no glandular enlargement was noted either during life or at autopsy; indeed only one case showed more than slight enlargement,
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during life, and at autopsy the glands rarely appeared of more than normal size. Splenomegaly was present in all, but only marked in one of the cases of lymphadenosis; it was definitely greater in both the cases of myelosis. The presence of a large spleen (three or more finger-breadths below the costal margin) may be taken as a point in favour of the myeloid as against the lymphatic form. The size of the spleen has been observed to vary: notably in one instance of lymphadenosis, in which splenic thrombosis was suspected, but not found at autopsy. Hepatomegaly is variable and was clinically absent in two cases of lymphadenosis. Gingivitis, stomatitis, and enlargement of the tonsils have not been features in our series.

Hæmorrhagic retinitis of mild degree has been found in only one or two instances. Exudate was not observed, and the hæmorrhage took the form of small scattered flecks. According to Borgeson and Wagener the eye-ground have been found to be normal in leukæmia with white cells as high as 582,000 and red cells as low as 1-4 million per c.mm. Baar and Stransky state that changes in the fundi may be absent, even when affection of the skin is widespread. It is curious that in a disease with such an outstanding tendency to widespread, though usually small, hæmorrhages, the retina should not be more frequently affected.

Except for petechie and purpura lesions of the skin have not been seen. Infiltration of the skin, sometimes seen in adults, particularly in chronic lymphadenosis, is extremely rare in childhood and in a series of one hundred cases in children Ramsay recorded only one instance. The mucous membranes and submucous tissues of the mouth and pharynx may show similar changes as the skin, and extensive lesions may occur, but none were observed in our series. Infiltration may occur in the tonsils and this, if necrosis or infection supervene, may lead to confusion with anginal conditions of the throat: according to Opitz such changes have been mistakenly interpreted as evidence for the infectious origin of leukæmia.

Considering the extensive changes in the marrow it is surprising that bone changes are such a rare manifestation of leukæmia in childhood. Radiograms, however, may show osteoporosis, cortical thinning, and elevation of the periosteum with layering. Karshner has reported six such cases, but we have met with the condition only once, and the changes are well seen in Fig. 19 from this case. Occasionally pain in the bones may be complained of and even tenderness and swelling of the joints may occur, thus simulating acute rheumatism. In the case just referred to, lymphadenosis definitely supervened after an attack of acute rheumatism.

Fever, either continuous or intermittent, of an irregular type was usually present. In one instance the temperature reached 106°, owing to pontine infiltration. Dypsnoea was present terminally in some cases.

It is only to be anticipated that a disease such as leucosis may occasionally produce rare and unusual features: thus, infiltration of different areas of the nervous system may produce various symptoms and signs. For instance, Bass has recorded cases of acute leukæmia in children showing symptoms of cerebral hæmorrhage and a case simulating cerebro-spinal
meningitis; and according to Baar and Stransky, even peripheral paresis may be produced. One case in our series showed a pontine lesion, and reports of a variety of rare lesions may be found in the literature.

**Course.**—The course of the disease is usually short. Of our cases one lasted 19 weeks, two for 8 months and the remainder under 2 months. Reckoning the duration from the time of the first complaint, it is surprising, as several observers have noted, that the degree of enlargement of liver, spleen and lymph glands does not form a reliable guide to the rapidity of the course. It is possible, however, that these enlargements preceded the first obvious symptoms and thus the duration of such cases was actually longer. Occasionally remissions have been reported: Schirnitz has recorded one in a child, aged 14, following blood transfusions, and Baar and Stransky state that regression of leukæmic symptoms has occurred in a few cases under the influence of an acute infection.

Chronic leucosis is rare in children, and, when it does occur, the condition is almost always a myelosis. Maternowska and Redlich in publishing two cases of lymphatic leukaemia which they regarded as chronic, state that Berghans recorded the first case in 1926. The durations in Maternowska’s and Redlich’s cases were not more than eight and four months. In Opitz’s series the durations of three of his seven cases of myelosis were 5, 8 and 2½ years.

**Haematology.**—The foregoing clinical manifestations may be produced in whole or in part by other pathological processes, and constitute only presumptive evidence of leukæmia, and therefore an examination of the blood is essential. As already pointed out acute leucosis is often aleucocythaemic in children, and the most common type is the lymphatic; in only one of our cases was the white count over 40,000 per c.mm., and a common figure was about 20,000. In myelosis, however, low total leucocyte counts are rare, the lowest count in Opitz’s series being 15,000 per c.mm., while one of our two cases showed over 100,000, the other over 80,000 per c.mm.

Many of the cases in Ramsay’s series displayed much higher white cell counts, even up to 300,000, but unfortunately autopsies on these cases were not obtained, and it is not possible to be certain of the type of leukæmia from the details given. Numerous cases of acute leukæmia in children have been recorded, in which the leucocyte count was high, running into hundreds of thousands. In fact the recognition that many cases in children are aleucocythaemic, is of comparatively recent occurrence.

**Red cells.**—Except in the early stages there is always a hypochromic anemia, with a colour index which is often quite low. By the time complaint is made of the child’s condition, the red cells have frequently been reduced to two millions or less per c.mm., and the hemoglobin to 40 per cent. or less. At this time the platelets are almost invariably seriously reduced in numbers, usually to figures well under 100,000. The volume of the red cells measured by the haematocrit is small.
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(Wintrobe\textsuperscript{15}); for instance, one case of lymphadenosis showed a volume index of the red cells of 0.74 and a saturation index of 0.96, and another (lymphadenosis) a volume index of 0.6. The normal value for these indices is unity. While aniso- and poikilo-ctytosis, polychromasia, normoblasts and megaloblasts are more often found in myelosis, they are almost uniformly absent in acute lymphadenosis except in the early stages when infiltration of the marrow is commencing: a state of affairs which might be expected from our knowledge of the mode of production of the erythrocyte. In a paper on leukæmia by Hunter\textsuperscript{14} the presence or absence of nucleated red cells was reported throughout; of the cases in which the diagnosis of leukæmia seemed most secure, the majority showed no nucleated red cells and the remainder a few only. It appears, then, that nucleated red cells are rare in acute leucosis in children, and their presence in any number should at once raise suspicion that the alleged leucotic process is actually an erythronoclastic (hæmolytic) one: a point of great importance since the latter is often amenable to treatment.

The white cells.—The close examination of the leucocytes is, of course, the one essential feature of the blood examination. No consideration of total numbers must outweigh the verdict on the presence or absence of great and widespread immaturity of these cells. It is still necessary to lay emphasis on this fact in regard to the lymphadenoses of children, since they are, as already emphasized, usually acute and aleucocythaemic. In lymphadenosis the proportion of lymphocytes and lymphoblasts is usually high, even up to 98.7 per cent. (Stransky\textsuperscript{12}), and all other types of cells are absolutely reduced. One of our cases of lymphadenosis showed relatively few definite lymphoblasts, most of the cells being small lymphocytes of somewhat immature general appearance, and another case, probably the most interesting of any, appeared to be aleukæmic.

In myelosis especially, the variations in the differential count of the white cells are so wide, that hard and fast limits can scarcely be defined. Myeloblasts are rarely absent and promyelocytes and myelocytes are common. Baar and Stransky\textsuperscript{1} state that in acute myelosis, although myeloblasts usually preponderate, cases showing chiefly myelocytes and even polymorphonuclear cells are sometimes met, and that the latter cells may show degenerative changes. Several of Opitz's cases of myelosis showed striking basophilia, even up to 11 per cent., and the eosinophils also were higher than in lymphadenosis. Three of the cases in his series were of chronic myelosis and in this condition there may be little anaemia, the platelets may be normal or even increased, and the more mature myeloid elements preponderate over myeloblasts.

It is to be noted that the monocytes are usually low in lymphadenosis and myelosis: a surprising feature in the latter group if Naegeli's view of their myeloid origin is correct.

As has been shown, the acute leucoses of children often show extremely immature non-granular cells in the peripheral blood; in the early cases these
were regarded as types of lymphocytes. Naegeli, however, showed that the precursor of the myelocytes, i.e., mother cell of the myeloid series, is a non-granular cell which he designated the myeloblast. The oxydase reaction was found to be positive in all granulocytes and some myeloblasts, though some of the latter were oxydase negative and hence regarded as the most immature myeloid cells. As a result of Naegeli's contribution on the characters of the myeloblast, there followed a tendency to regard non-granular cell leukæmias as myeloblastic, for it was argued that even oxydase negative cells were perhaps myeloblasts. However, more recently it has been realized from histological investigations that most leukæmias in children are truly lymphatic in type. The details of cytological differentiation in blood films and tissues are dealt with in a later section. Cases are sometimes encountered in which it is almost, if not quite, impossible to diagnose the type of leukæmia from an examination of blood films. Nevertheless, the histological differentiation on the basis of architecture and the cytological features of sections, is invariably clear—at least, such has been the lesson learned by the present study.

**Interpretation of the blood picture.**—The general features of the blood picture and the effect on the erythron may now be considered. Focal deposits of 'foreign' cells in the marrow, such as those of lymphadenoma, chronic lymphadenosis and carcinoma, may easily give rise to large numbers of nucleated red cells in the blood stream; a picture which has been delineated by Piney and which is presumably due to irritation of the marrow. We have, then, in leucosis the possibility of the presence of abnormal cells, arising in two different ways: (1) the fundamental process (e.g. lymphadenosis), (2) irritation of normal marrow (or other tissues, such as reticulo-endothelium), leading to the emigration of immature forms (e.g. myelocytes, normoblasts or even monocytes). It is probably the operation of these two factors, which has lead to the conception of 'mixed' leukæmias; but as will be suggested in another section, histological investigation of our cases has shown that, although the blood picture may reveal signs of immaturity of both myeloid and lymphatic series of cells, the type of the leukæmic process in the tissues is single and remarkably pure.

It appears that in the early stages of acute lymphadenosis or in subacute cases, the early infiltration of the marrow by the foreign cells may result in stimulation, with emigration into the blood stream, of immature forms of the myeloid cells and erythron. Evidence in favour of this was found in an example of lymphadenosis of three months' duration, but from the considerable enlargement of the organs judged to be of longer standing; and in another which developed under observation and was examined early in the process. However, by the time the majority of instances of lymphadenosis in children are examined, the invasion and infiltration of the marrow have proceeded far beyond the stage of irritation and no response is possible: in fact, the condition revealed is one of aplasia of the granular leucon, platelets and erythron, while the leukæmic picture becomes pure.
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In myelosis there is more variability in the number of nucleated red cells in the peripheral blood. The more chronic of our two cases showed a good many normoblasts, while the acute one did not. It appears that in the more acute cases, where anaplasia is extreme, the formation and emigration of normoblasts is less marked.

The blood picture may be summarized as follows:

1. Acute lymphadenosis: there is usually a moderate increase in white cells, but both high and low counts may be encountered; lymphoblasts are numerous, but occasionally only few are found; platelets are diminished when the disease is well established; there is severe anæmia in the later stages; abnormalities of the erythron are found only in the early stages; microcytosis is usual.

2. Myelosis: higher total leucocyte counts are the rule; all forms of immature myeloid cells may be present, with sometimes a high proportion of myeloblasts in the more acute types; eosinophil and basophil cells are more frequent than in lymphadenosis, and may be pronounced in chronic cases; platelets are diminished in the acute forms; anæmia is severe in the later stages; abnormalities of the erythron are more common than in lymphadenosis.

Diagnosis.—The most interesting aspect of our study of leucosis has been that concerned with diagnosis. The acute nature of the illness, the frequency of aleucocytesæmic forms, the similarity of clinical features, and the occurrence of leukæmoid conditions of the blood in other diseases, frequently render the differentiation by no means easy. In this differentiation the haematological and histo-pathological features have to be studied intensively, and for this reason the characters of the distinctive cells, as they appear both in blood films and tissues, are described in detail later in this paper. Here only the chief conditions which may mimic leucosis are briefly dealt with.

Acute hæmolytic (erythronoclastic) anæmia.—The clinical features of the acute hæmolytic anæmia of Lederer were dealt with in Part V of this series, where it was suggested that, since the disease exerts its harmful influence not only on the mature red cell but also on its immature precursors, i.e., on the whole erythron, the term erythronoclastic would designate the anæmia better than hæmolytic. This condition may closely simulate acute leucosis; indeed, it is more than probable that the examples of recovery from acute leukæmia which occur in the literature, are in reality instances of recovery from erythronoclastic anæmia. The onset of this anæmia is usually sudden and dramatic, although, if the process is subacute, it may resemble the insidious onset of leukæmia. Typically acute erythronoclastic anæmia is a rapidly developing anæmia in a previously healthy child, and splenomegaly may develop. Lazarus\(^{13}\) states that hepato- and spleno-megaly develop after remission in acute, or later, in sub-acute cases. The absence of enlarged lymph glands will not eliminate acute leucosis. Marked jaundice is not common in either, but slight icterus is more frequent in
erythronoclastic anæmia. In the early stages the blood may show a neutrophilia (twenty to forty thousand) with some immaturity of the white cells, which is of less degree than in acute myelosis: one of our cases showed 8 per cent. myelocytes, 7 per cent. immature metamyelocytes and 15 per cent. mature metamyelocytes, and Lazarus has recorded 16 per cent. myelocytes. Myeloblasts are usually absent and, in any case, scanty. The leucocytosis may, however, be extreme, and higher than found in some acute leucoses in children, e.g., 108,000 and 76,000 white cells per c.mm. (Lazarus). Sometimes, and often in subacute and chronic cases, a relative or absolute lymphocytosis may occur, which may give confusion with that of acute lymphatic leukæmia; careful examination of the lymphocytes will reveal their mature characters, as opposed to those of the lymphoblast. The colour index is often above unity and marked aniso- and poikilo-cytosis and polychromasia, many reticulocytes, normoblasts, macro-normoblasts and megaloblasts are found much more frequently in acute erythronoclastic anæmia and generally when remission, often as a result of blood transfusion, sets in; in acute lymphadenosis these are rarely seen.

ANÆMIA PSEUDOLEUKÆMICA INFANTUM (VON JAKSCH).—The disease most likely to cause confusion with leukæmia is that form of anæmia which we have described as subchronic erythronoclastic anæmia: the so-called von Jaksch's anæmia. Confusion is liable to arise on account of the immaturity of the white cells, which include a fair proportion of myelocytes and even a few myeloblasts. Lymphocytosis also may occur, and this, if marked, is differentiated from the lymphoblastosis of lymphadenosis by the mature characters of the lymphocytes. Although aniso- and poikilo-cytosis and polychromasia with an occasional normoblast may be found in acute myelosis, these features are pronounced in von Jaksch's syndrome, and normo- and megaloblasts may reach very high numbers. Baar and Stransky mention that embryonal blood-forming foci may be found in this disease, and also in other severe anæmias, and produce some resemblance to the histological features of leukæmia—an aspect of the subject which we have stressed in a later section (Part IX).

ERYTHROBLASTOSIS.—The erythroblastic changes found, especially in the liver in which there is the embryonic type of blood formation, may lead to confusion with myeloid metaplasia. When such histological changes accompany severe erythronoclastic anæmia of the new born, the similarity to leucosis becomes even closer. The clinical features are dealt with in another article of this series (Part IV), and the morphology of the cells in another section of this paper.

COOLEY'S ANÆMIA.—This form of erythroblastæmia can be partly differentiated from leukæmia by its racial incidence, being confined to children of Mediterranean races; by the bony changes as revealed by radiography; and by blood examination, which shows an enormous number of normoblasts and some megaloblasts in the blood stream.

CONDITIONS WITH LEUKÆMOID BLOOD PICTURES.—A large number of conditions give blood pictures which may closely simulate those of leukæmia.
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Septic granulocytosis.—In severe sepsis, extreme degrees of immaturity of the white cells may be rarely encountered, and even myeloblasts may be present (Krumbhaar17, and Herz18), a condition which resembles one of our examples of myelosis in which myeloblasts were few.

Septic lymphocytosis.—Sepsis and infective conditions have also long been regarded as occasionally causing absolute lymphocytosis. Tidy19 has reviewed most of the records of such cases and has concluded that the case for lymphocytosis in inflammatory conditions is not proven and that many, if not all, of the alleged cases were really examples of infective mononucleosis or glandular fever. However, it appears that not uncommonly an infective process may lead to a relative lymphocytosis on account of an overwhelming depression of the myeloid series (Talley Griffith20). Piney has pointed out that eosinophils and platelets are often not reduced, and considers that this indicates a defect in emigration rather than an aplasia.

Glandular fever.—Owing to the swelling of the lymph glands, this disease may closely simulate leucosis. In contrast, it shows little or no anaemia and no diminution of platelets. The characteristic mononucleosis consists usually of an absolute increase in lymphocytes and more rarely of monocytes. The all important point again is the mature nature of the mononuclear cells. In this condition remission may occur and the mononucleosis may persist after clinical recovery; thus the accidental finding of a lymphocytosis may be explained by a previous attack of the disease.

Post-infective and post-hæmorrhagic lymphocytosis.—On recovery from infective conditions which have produced a granulocytosis, a relative lymphocytosis, with return of eosinophils may occur, but because of the mature character of the cells and the presence of eosinophils, and a good number of platelets, this will only rarely simulate lymphatic leukæmia.

Hæmorrhages of long duration may also be a cause of relative lymphocytosis and increase in eosinophil cells, the red cells showing changes including polychromasia and microcytosis. It should be emphasized that the lymphocytosis here is relative; absolute lymphocytosis occurs in few conditions, examples of which have been given.

Other specific infections.—Leukæmoid blood pictures may be associated with specific infections such as measles, whooping cough, diphtheria, chicken-pox. The following example of such a condition in congenital syphilis illustrates the difficulty of diagnosis.

T. C., aged 3 months. Complaint was made of epistaxis two days before admission and of a rash on the legs and arms. Bleeding from the rectum had occurred three weeks before. On examination:—intense anaemia; a brownish, slightly raised rash on both legs and pemphigoid eruption on the left side of the scalp; spleen enlarged one inch; liver enlarged. The course in hospital was afebrile. Blood examination: R.B.C. 1,600,000; Hb. 18 per cent.; C.I. .96; W.B.C. 20,100; platelets 29,000. Differential count: neutrophil p.m.n. 15 per cent.; eosinophil p.m.n. 3-5; basophil p.m.n. 5; n. meta. 2-5; large lymphocytes 72-5; small lymphocytes 0; Törek cells 1-0; monocytes 5. Red cells pale, aniso- and poikilo-cytosis, slight polychromasia, one normoblast found, platelets few in the film. Wassermann reactions of child and both parents were strongly positive.
Though there were clinical features which suggested the true diagnosis, from the haematological standpoint the only clue was the definitely mature character of practically every one of the lymphatic cells present. As against all other features, the characters of the suspicious cells cannot be over-emphasized. A drawing of these cells is found in Fig. 18.

**Agranulocytic Angina and Aplastic Anaemia.**—In aplastic anaemia, there are anaemia, thrombopenia, usually leucopenia with relative lymphocytosis, and sometimes splenomegaly. The mature characters of the lymphocytes should distinguish this condition from aleucocythaemic lymphadenosis, but difficulty would occur in differentiation from aleukæmic lymphadenosis. The latter would tend to have a normal or slightly increased total of white cells, and probably a more acute course. Aplastic anæmia may be a phase of an erythroclastic anæmia, and aplastic blood pictures of the erythron are often seen in the leucoses, especially in the later stages. According to the conception of Lescher and Hubble, only one of the three elements (erythron, white cell and blood platelet systems) of the haemopoietic apparatus may be damaged and, in this way, aplastic anæmia, agranulocytic angina and thrombo-cytopenic purpura may arise. Bigler and Brennemann have collected cases of agranulocytic angina in children, where the severe leucopenia of even 800 leucocytes, would distinguish the condition from aleucocythaemic lymphadenosis. In the event of severe haemorrhage, causing anæmia, thrombo-cytopenic purpura might simulate aleucocythaemic leucosis.

**Banti's Disease.**—Splenic anæmia of the adult type, though rare, is occasionally met in children, and it has been seen as early as two-and-a-half years (Parsons). Haematemesis and leucopenia are usual, and together with the histological findings of fine cirrhosis distinguish the condition from leucosis.

**Osteosclerosis Fragilis Generalisata (Albers-Schönberg's Disease).**—This rare disease usually shows blood changes of leukæmic type and therefore may lead to diagnostic difficulties; the following is an instance which came under our observation:

A girl of 8 months, who had always been pale, developed double proptosis and rotary movements of the eye. Examination revealed a large head with distended veins, marked anæmia, splenomegaly, slight glandular enlargement and optic atrophy with 'pepper and salt' fundi. The blood examination showed: R.B.C. 3,900,000; Hb. 65 per cent.; W.B.C. 50,000. Differential count: 19 per cent. myelocytes, 18 per cent. myeloblasts, 11 per cent. fractured immature cells; 7 normoblasts and 8 megaloblasts per 100 W.B.C. Radiograms of all the bones showed typical changes: normal contour, except for fractures, but all spongy bone and marrow transformed into compact bone. Death occurred at the age of 11 months. At autopsy the outstanding feature was the replacement of spongy bone by dense bone and the absence macroscopically of marrow; at the ends of the long bones osteoid tissue was found. Histologically the bones showed small islets of myeloid tissue, which often surrounded the blood vessels and were present also in the cartilage; myeloid metaplasia was present in the liver and lymph glands. The
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immaturity of the granulocytes in the peripheral blood and the myeloid metaplasia suggest a relationship with myelosis. It is interesting to speculate whether the blood changes preceded and caused the bone changes, or vice versa.

Reticulo-endothelioses.—There is a group of somewhat widely differing diseases, of which the commonest is Hodgkin’s disease, which may be grouped under this heading. Hodgkin’s disease is accompanied by a more pronounced glandular enlargement than the leucoses and the blood picture is not leucæmic in character. The so-called storage reticulo-endothelioses—Gaucher’s, Niemann-Pick’s, and Christian’s diseases—may, on account of anaemia and spleno- and hepato-megaly, clinically resemble leukæmia, but the blood picture is entirely different.

Of recent years several cases of reticulo-endotheliosis in children have been reported, mainly by German workers, and we have recently observed four cases, with somewhat similar features. A full description of these cases will be given in Part IX, and it is evident that many features: anaemia, enlargement of liver, spleen and/or lymph glands, may cause confusion with leucosis, but neither lymphatic nor myeloid leukaemic cells are found in the blood stream.

Other forms of leukæmia.—There are certain other forms of leucosis which may be mentioned. Lymphosarcoma simulates lymphadenosis in many ways and the process seems to differ only in the lesions being more focal in distribution; the blood counts may be similar to those of acute lymphatic leukæmia. A case of leucosarcomatosis was described by Parkes Weber22 in a boy aged 7. The blood picture showed 108,000 white cells, of which 94·5 per cent. were myeloblasts. Histological investigation showed myeloid interacinous infiltration in the liver, myeloid metaplasia, including the presence of megakaryocytes, in the hilus of the kidney. Chloroma occurs most frequently in childhood; there is usually a blood picture of myelosis, and, though immature cells may be absent from the peripheral blood, the condition may be regarded as essentially the same as the ordinary leucoses.

Eosinophilic leukæmia is very rare (Hay and Evans25) and, according to Bass24, only three cases in children have been reported.

The present study of leukæmia does not lend support to the conception of a mixed type, though immature cells of both the chief series may be found in the same case. As explained elsewhere, the cause of this is probably irritation of marrow by the invasion of foreign cells. Our cases have been remarkably pure in their hæmatological and histological features. However, many, e.g., Türek, Hirschfeld, Herz, Baar and Downey, have believed in the occurrence, though no doubt rarely, of true mixed leukæmias, and Logefeil25, in reporting a case which he claims as an example, has carefully reviewed the literature.

Morbid anatomy of acute leucosis.—As a rule, naked-eye examination reveals no diagnostic feature. Extreme pallor with sometimes a few petechiae; an inconstant degree of enlargement of the liver, but often much fatty change; considerable, slight or even no increase in the size of the spleen
with little alteration in texture or appearance; congestion with little or no swelling of lymphoid tissue; an atrophied or normal-sized thymus; frequent ecchymoses and a thrush-breast appearance of the myocardium; terminal broncho-pneumonia and scattered small irregular hemorrhages into the pleura; a light or dark red cellular marrow: such are among the usual findings in infants and children. Nor could myelosis be differentiated from lymphadenosis with certainty, though our two cases of the former type showed greater enlargement of the lymph glands and spleen than some of the lymphatic cases, and they both displayed a slightly grey tint in the red colouring of the marrow, which was not noted in the lymphatic cases.

A point of interest is that none of our cases has shown enlargement of the thymus gland, nor have histological abnormalities been present where this organ has been examined. This suggests that the small thymic cells are not lymphocytes and are of different origin.

**Microscopic Morphology.**—The morphology of the leucotic cells as seen in films of the peripheral blood and in the tissues is of the utmost importance in the study of leukosis, both from a diagnostic and an aetiological point of view. In this study blood films have usually been made on cover slips, and Leishman's and Panoptic stains have been used. In the examination of tissues, to define the cytological features, the thinnest possible sections, not exceeding 4μ, and preferably 3μ, thick have been necessary and the use of a one-twelfth oil immersion lens almost essential. An ocular micrometer has proved a useful adjunct. Oxydase staining has sometimes been employed, but, before its use, the type of the leukæmia has usually been fairly clear from the examination of the blood films. Except in special circumstances, when obviously unusual forms are present, vital staining does not appear to assist very much; indeed, Hall, after an extensive review of recent papers, concluded that polychrome stains assisted more than vital staining in the differentiation of blood cells.

**Blood Films and Sections.**—A real difficulty in the study of the blood and its formative tissues is the difference in appearances of cells in the blood films and in sections of tissues, however fixed and stained. Again, films made from pieces of tissue provide a picture of cells different from that of films made from the peripheral blood. The characters of the cells of the peripheral blood have been described by numerous workers, and a large number of drawings have been published, but far less attention has been paid to appearances of blood cells in sections and to their correlation with those of blood film preparations; indeed, the majority of authors fail to provide illustrations of cells in sections, comparable with those of the peripheral blood film. No doubt a great cause of the different appearances between the tissues and blood films is due to changes in the cells following death, for frequently even films made from the heart's blood within a few minutes of death are surprisingly disappointing in their staining properties. The lack of clear staining of the neutrophil granules in sections is one of the great obstacles. A good many methods have been tried to overcome this and so far the best results have been obtained with fixation by Helly-
Maximow solution, and subsequent treatment with iodine, followed by hyposulphite of soda. Jenner's or Panoptic stains (Jenner followed by Giemsa) have given definitely better revelation of neutrophil granules than Giemsa alone, although the latter is often recommended for this purpose.

In these studies an attempt has been made to correlate these different cytological appearances. Drawings of the cells under discussion are given in Fig. 1.

**Lymphadenosis.**—In this condition in children the condition is so acute that lymphoblasts are rarely absent from the blood-stream and thus the diagnosis is easier than in the chronic forms of adults, where frequently only mature lymphocytes may be found. The results of our observations have indicated the necessity of modification of some of the published descriptions.

The lymphoblasts in the peripheral blood have generally been smaller than 12–18μ (the measurements given by Pinney27): the smaller ones have measured 7 to 9μ, and the larger 9 to 14μ, with an occasional case showing forms up to 18μ; the cytoplasm has almost invariably been small in bulk, often scarcely discernible. A feature has been the irregularity of the nuclear contour: indentation has been present in many of the cells, while blunt lobulation has frequently been seen. The texture of the basi-chromatin has usually been finer than distinct stippling, though slightly coarser than that of the myeloblasts in one of our two cases of myelosis: the texture might be described as of a matt appearance, with fairly fine stippling in the more mature forms; condensation of the chromatins has not been marked round the nucleoli or nuclear membrane, but it was more than in the myeloblasts. Nucleoli have frequently not been easy to find, although some cells have shown one or two and rarely even four or five; small vacuoles in the cytoplasm of the cells with a more bulky cytoplasm have often been present. Türeck cells have commonly been found, but the larger plasma cells have not been frequent in lymphadenosis.

Tissues have been fixed by formalin, neutral formalin and Helly-Maximow methods in different cases. No definite differences in cytological appearances have been noted by these various methods, except that there was more shrinking in the formalin-fixed tissues, proportionately to the length of time of fixation, and the myeloid cells in the marrow sections showed granulation better with the last method. In sections from cases of lymphadenosis, lymphoblasts, like other cells, have uniformly appeared much smaller than those in the blood films, their diameters being half to two-thirds in diameter, and their total cell area about one-quarter to one-half of the lymphoblasts in the blood films. The diameter of the cells has been fairly constant, being between 5 and 8μ, whereas typical lymphocytes in the same cases measured 3 to 5μ. Again irregularity of nuclear contour has been present, and its extreme degree has occasionally given some difficulty in identification. On careful focussing it is seen that this irregularity is sometimes complex and not merely the jutting off of a lobe. The appearance may be similar to that of a cigarette paper fairly loosely crumpled: the
twisting margin of the nucleus being comparable with the irregular folds of the crumpled paper. It is possible that this appearance may be partly due to some shrinking during fixation, but in sections, fixed in Helly-Maximow's solution and showing no shrinking, irregularity of nuclear shape has sometimes been well marked. In most of the sections the lymphoblasts have shown this crumpled appearance more than myeloblasts. The cytoplasm has been small in amount and the nuclei have stained a fairly dark blue throughout, overlaid by irregular and indefinite dots and threads of chromatin. Compared with the myelocyte, the nuclear size has been smaller, the colour darker, the nuclear margin heavier but less delicate and so less prominent and more irregular, and the chromatin deposits less sharply defined; granules have, of course, been absent. The cell is less vesicular in appearance and less conspicuous in the tissues.

**Myelosis.**—In blood films, the two cases of myelosis did not show many myeloblasts, most of the young cells being slightly granular, i.e. promyelocytes. The myeloblasts and promyelocytes were larger than lymphoblasts and measured 11 to 18 μ with nuclei of 7 to 15 μ in diameter. The cytoplasm was more bulky than in lymphoblasts, but in some cells was small in amount; in some cells the cytoplasm was paler near and round the nucleus. On the whole there was less irregularity of nuclear outline, the texture was finer and somewhat sponge-like, and sometimes showed a faintly staining delicate network and streaking; nucleoli were more frequent than in lymphoblasts. Rarely mitoses were found in the peripheral blood. Monocytoid myeloblasts have been described fairly frequently in myelosis; and these, with other forms of monocytosis in myelogenous leukaemia have been referred to in Part VII. On the whole the above characteristics apply to a large number of cells, though individual cells are not always capable of identification as myeloblasts or lymphoblasts. It is, of course, rare for the blood picture of a myelosis to fail to show any signs of granulation in some of the cells, especially when oxydase staining is used.

In the tissues myeloblasts appear smaller than in blood films though larger than lymphoblasts as indicated in Fig. 1 (22, 23, 81 to 86). The cell usually appears round or oval with a definite amount of cytoplasm, surrounding a round or oval nucleus of which the margin is more regular and delicately cut than in the lymphoblast. This clearness of the nuclear margin is largely due to the paler staining of the interior, which shows less well marked dots, threads and irregular masses of chromatin than the lymphoblast; some cells show nucleoli and smaller deposits of karyomitome. These features are displayed better in the myelocyte and promyelocyte. In a normal marrow, if neutrophil granule staining is successful, it will be found that most of the cells with the above-mentioned characters are in fact promyelocytes, whereas a smaller number of cells, which have less well defined features and stain more palely, are myeloblasts. Probably the outstanding point in the differentiation of young myeloid
cells from lymphoblasts is that of their paller "vesicular" appearance and larger size. In the lymphoblast and lymphocyte, the oxy- and basichromatin are not so well defined one from the other, and combine to give a nucleus more deeply stained and with indefinite darker markings, whereas the nuclei of the myeloblast and myelocyte show a paller groundwork with one or two nucleoli and a few clearly defined condensations of chromatin in their interior. An attempt has been made to depict these characters to scale, in Fig. 1.

Possibly of equal help in cytological diagnosis is the determination of the direction of maturation: whether towards the lymphocytic or myeloid series of older cells. Only rarely do acute cases fail to show adolescent, if not older cells, indicating the family to which the young forms belong.

**Differentiation of myelopoietic from erythropoietic foci.**—In the tissues immature forms of hemoglobin-containing cells, i.e., erythroblasts, are sometimes difficult to differentiate from myeloblasts and myelocytes; indeed, this may be impossible with the most immature forms of the pro-erythroblast. However, the differentiation of foci of erythropoiesis, such as are seen in the liver in premature infants, in icterus gravis, in hydrops fœtalis and in hæmolytic anæmia of the new born, is important both from a cytological point of view and in relation to the study of leukæmia. Pinkerton states 'it must be admitted that there is no positive method of distinguishing in fixed tissues between the myeloblast and the early megaloblasts,' and with this we would agree. Ellermann and Petri give the angle of mitosis of myeloblasts as 60 and that of the erythrogonium as 20. Megaloblasts are scanty in normal bone marrow and frequently, though erythropoiesis is active, cannot be definitely identified. Working on smears of bone marrow, prepared according to Isaacs' technique we have found only three or four megaloblasts after searching through preparations from a number of different cases. Even the finding of this small number, however, would appear to exclude their restriction solely to a type of embryonic hæmatopoiesis in the liver and spleen, as is claimed by some. In cases of erythroblastosis, however, cells are often found in the hepatic sinusoids which have characters suggesting that, in stained films of the peripheral blood, they would give the appearance of the typical megaloblast.

The term erythroblast appears a suitable term to connote any stem cell which appears to be a maturing hemoglobiniferous cell, and in this paper this term is used for any immature cell which appears to be a precursor of an erythrocyte, i.e., it includes both megaloblasts and normoblasts. In sections of erythropoietic foci some cells are found which, allowing for the difference in appearances of sections and blood films, appear to correspond with the megaloblasts of the blood stream whereas some cells appear to be more immature. The latter probably correspond to erythrogonia of some writers and have been called by us 'pro-erythroblasts.' Sabin, however, uses the term erythroblast to designate only early and late types.
of normoblast, and megaloblast for cells which are more immature than these. The terms used here may be arranged as follows—

```
Pro-erythroblast (Erythrogonium)
  | megaloblast
  | young normoblast
Erythroblast
  | normoblast
  | macro-normoblast
  | micro-normoblast
Erythrocyte
```

Normoblasts, if large, are termed macro-normoblasts, and, if small, micro-normoblasts. It is not certain that the above arrangement necessarily represents the sequence of maturation, for it is possible that, for example, a megaloblast may develop into an erythrocyte without passing through a normoblastic stage.

In erythroblastosis of infants (see Part IV) it is usually seen that erythropoiesis in the liver preponderates over, and even excludes, leucopoiesis. Apart from a few myeloid cells, the cells found in extra-medullary embryonic erythropoietic foci may be described as follows.

The most immature cells, which are usually not numerous, are fairly large pale cells with lightly staining nuclei and a rather lightly staining cytoplasm. We have called these pro-erythroblasts or erythrogonia. The next cells in the series are more numerous and prominent; they are fairly large oval or round cells, 8–10μ in diameter with a moderate amount of cytoplasm, which frequently stains more deeply with hematoxylin or methylene blue than does that of myeloblasts. The nuclei are about 7μ in diameter, vesicular and similar to myelocytic nuclei, though there is a tendency for the knots of karyomitome to be fewer, larger and more distinct and to lie nearer to the nuclear membrane. On the whole, as compared with promyelocytes and myelocytes, the cytoplasm and nuclear chromatin stain more darkly, or stand out in greater contrast against a rather paler karyoplasm. It is not certain whether these cells emigrate into the blood stream; if so, they would no doubt appear as that kind of megaloblast with a fairly streaked nucleus and basophilic cytoplasm; if not, we may include them with the pro-erythroblast.

The cell which appears to correspond most closely with the megaloblast of the blood stream is slightly smaller (about 7μ) and definitely darker in the staining of all its components: the cytoplasm is darker blue, the nuclear membrane heavier and the karyoplasm darker. But the striking difference is the heavy dark stippling, distributed evenly throughout the nuclear area, similar to the appearance in blood films.

The young normoblasts are often more numerous than any of the foregoing and their characters form a transition to the normoblasts. These young normoblasts are smaller than megaloblasts, dark, and show in their round nuclei a few indistinct heavy masses of chromatin, sometimes arranged in cart-wheel fashion; their cytoplasm is small in amount and
more eosinophilic than the foregoing cells. The remaining normoblasts are older and display a small round blue-black nucleus, devoid of markings, in a thin or thick rim of eosinophilic cytoplasm. Some of these may show marked degrees of pyknosis, even simulating polymorph granulocytes in their shape, but can be differentiated from them by the deep-staining properties of the nuclei and their smaller size. Scattered whole nuclei and nuclear fragments are also usually to be found. In some sections it has at times been difficult to differentiate young normoblasts from normal lymphocytes on individual cytological features alone. As described above, the young normoblasts show some dark chromatinic markings as does the lymphocyte: nevertheless, by comparing specimens of the two, from regions where there was little doubt as to their identity, it has usually been found that the young normoblast is slightly smaller (about 4μ as against 5μ), its cytoplasm more eosinophilic (yet small in amount), its nucleus darker and the chromatin deposits fewer and more deeply stained than is the case with the lymphocytes. In somewhat over-stained sections these differences will be more or less obliterated.

The cytological features of embryonic erythroblasts have been dealt with in some detail because of the importance of differentiating them from myeloid metaplasia in myelosis. Sometimes the proportion of pro-erythroblasts is so high that differentiation from myelosis on the examination of one section may be impossible; indeed, it is probable that not a few cases of leukæmia reported in young infants have in fact been cases of anaemia showing erythroblastosis in response to a hæmolytic process.

The reticulo-endothelial system in leukæmia.—Practically all our cases have shown activity on the part of the reticulo-endothelial system, in the form of swelling and loosening of Kupffer cells; proliferation in the splenic reticulum, sometimes with the production of many reticulum fibres and at other times with the multiplication of cells with blunter processes; proliferation and freeing of the endothelium of venous sinuses of the spleen, and of the sinuses of lymph glands. Without going into the question of the origin of the histiocyte, which has been dealt with elsewhere, it appears probable that they arise from the reticulo-endothelium. Our cases have shown an increased number of histiocytes, particularly in the hepatic sinusoids. Typically these cells have a bulky and faintly eosinophilic cytoplasm as stained by hæmatoxylin and eosin; their shape is polygonal, caudate or irregular and their measurements vary greatly from 12 to 30μ in fixed sections. Their nuclei are usually faintly stained, often indented or bean-shaped and not uncommonly lobulated or bulbous; the interior possesses few markings, mainly some faint streaks and a few dots, but the latter are less numerous and distinct than in fibroblasts, which often show dotted or dusted nuclei. The nuclei are similar to those of swollen Kupffer cells, which are frequently seen and, if they are still partially attached to the walls of the sinusoids, may be identified with certainty. In fact, the study of our cases supports the conception that histiocytes arise
in part from endothelium in the liver, reticulum cells of the spleen and lymph glands, and probably from so-called germ centre cells of lymph glands. Some swollen cells will be found, however, with similar cytoplasmic and nuclear characteristics which suggest that they too are histiocytes. These cells may be as small as the average polymorphonuclear granulocyte—in the region of 6 or 7 μ in sections—and owing to the fact that the nuclei are sometimes lobulated (in contra-distinction to segmented), they may closely simulate the granulocyte. The latter has typically, however, a darker nucleus with a heavier nuclear margin and well defined oxy- and basi-chromatin. The larger histiocytes will sometimes be seen to have ingested other cells and fragments, but phagocytosis has varied much in our different cases. Cells entirely similar to these histiocytes have been observed in large numbers in cases of anaemia with reticulo-endothelial reaction (Part IX).

Histopathology of leukæmia.—Passing on from purely cytological features, the architecture of the various leukæmic tissues is easier to describe and its features in the two chief forms easier to recognize.

Lymphadenosis. Liver.—The differences between the two types of leucosis are well shown. All the cases of lymphadenosis show definite infiltration of the portal tracts; these lymphomatæ may be small or large and they may also be accompanied by extensive permeation of the sinusoids. The combination with sinusoidal infiltration is shown well in Fig. 6. The sinusoids are swollen and loosened endothelial cells, with some histiocytes, often phagocytic, may be prominent. Fatty degeneration, especially of the central areas, is a feature.

Spleen.—This organ may show surprisingly little infiltration, though sometimes this is marked in both the capsule and pulp. The chief changes are fibrosis, hyaline change in arterioles, and a definite increase in reticulum cells. The nuclei of the latter are often paler and larger, and their cytoplasm has shown blunter processes than normal; the endothelial cells lining the sinuses show less proliferation than in myelosis. Some phagocytosis may be seen. The lymphatic cells of the follicles and in the meshes of the pulp are increased in number and often show the characters of lymphoblasts described above. The increase in size of the spleen is partly due to infiltration, but also to fibrosis and reticular proliferation, which appear to be reactive in nature. Preparations in which the reticulum is stained by Bielchowsky's silver method show an increase of reticulum fibres in some cases, but not in all.

Lymph glands.—The outstanding feature is packing of the whole tissue with lymphatic cells, so that it is difficult to pick out germ centres and sinuses. Some cases show some swelling of reticulum cell nuclei. One, which
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was of longer duration than the majority of the cases, displayed considerable proliferation of endothelial cells of the sinuses and phagocytic histiocytes were numerous. A few eosinophil cells have been seen in some cases. Mitoses are found more easily in glands, but are somewhat less frequent than might be expected. The germ centres do not show evidence of any great activity. The lymphoblasts appear to reproduce themselves and not to arise de novo from the endothelium either of the germ centres or the reticulum.

Bone marrow.—This is usually diffusely infiltrated by lymphatic cells, most marked round the blood vessels. Reticulum and myeloid cells may be difficult to find. However, in the less acute cases, and in some acute ones, sections of marrow may show no infiltration; presumably the degree of infiltration may vary considerably in different parts of the marrow.

Kidneys.—Interstitial infiltrations, usually small and scattered, are frequently found, but the sections of some of our cases have failed to show them.

Lungs.—Areas of terminal broncho-pneumonia, collapse and compensatory emphysema are common. One or two cases showed consolidation with the alveoli filled with mucinous material, some red cells and large pigment-carrying cells. The sections of those cases examined did not show leukæmic infiltrations.

Other tissues.—No characteristic changes were found, apart from the infiltration of the brain substance in one case. Usually where small accumulations of leukæmic cells are encountered, it is seen that they are grouped around blood-vessels or lymph sinuses.

Preparations by the Turnbull-Hueck process for the demonstration of hæmosiderin, have shown much variation in the amount and distribution of the iron: generally it has been most marked in the liver cells on the periphery of the lobules, but in the spleen it has been scattered in an irregular manner and not obviously included in any particular cells.

MYELOSIS. Liver.—Fatty degeneration of the central areas of the lobules is more or less severe, even proceeding to small focal necroses. The sinusoids are widened, and throughout are scattered cells of various types. Two cases in the present series, and one recorded in Part VII, have not shown such prominent groups of cells as cases of erythroblastosis, nor so much myeloid metaplasia as in adults. The cells scattered throughout the widened sinusoids are myeloblasts; more mature cells of the granular series; erythroblasts; loosened endothelial (Küpffer) cells and histiocytes which are often observed to be in phagocytosis. It is thus evident that prominent areas of metaplasia are not an essential feature in the liver. The picture is somewhat similar to that of the cases of reticulo-endotheliosis which will

B2
be reported in Part IX, except that more myeloid cells have been found, and proliferation of Küpffer cells and the number of histiocytes have been less.

Spleen.—The prominent features are a diminution of lymph follicles which contrasts with the increase in lymphadenosis, and proliferation of the reticulum cells and fibres, in the meshes of which are numbers of scattered myeloblasts, myelocytes, metamyelocytes and erythroblasts. Eosinophil cells may be plentiful. The nuclei of many reticular and sinus cells are swollen and some of the cells are wholly or partially free. On the whole the cases showed a more cellular type of proliferation on the part of the reticulum than the more reticular one in the lymphatic cases. One case showed marked proliferation and liberation of cells lining and venous sinuses.

Lymph glands—The general picture is similar to that of the spleen, though lymphocytes are more numerous throughout the tissue.

Marrow.—It is here that histological diagnosis may be most difficult, for although, especially in acute cases, it may be easy to discern the immaturity, yet it may not be easy to differentiate a less anaplastic myelosis from the response of a marrow to an acute infection. In both these conditions the degree of immaturity displayed may be very similar. Probably the most trustworthy indication is given by the state of erythropoiesis, which is not so suppressed in the great majority of acute infections as in a subacute myelosis. In adults, where the shafts of the long bones consist so largely of fat, the wide extension of myeloid tissue is in favour of myelosis rather than a reaction to infection, but in young children this criterion cannot be applied. At the same time, it is true that in myelosis there is always definite increase in cellularity, packing together of the cells and a striking failure to develop mature granulocytes: changes which although present in severe reaction to infection are not so well marked. However, in the case of a less anaplastic myelosis it may be impossible absolutely to exclude the possibility of a purely infective reaction. The importance of this fact is obvious in biopsies of the marrow for diagnostic purposes. In myelosis degrees of anaplasia of the myeloid tissue are found. In the most acute cases all the cells appear to be myeloblasts or the slightly larger pro-myelocytes, and erythropoiesis is at a minimum. In less acute cases fewer of these cells, but more myelocytes are found, while polymorphonuclear granulocytes are few. Reticulum cells are often seen. Eosinophil cells are frequently plentiful in less acute cases.

Other organs.—Such organs as the adrenal and pituitary glands may show areas of myeloid metaplasia, but this was not found in our cases. Turnbull-Huecke preparations did not show any characteristic distribution of the iron, which was, however, increased in quantity.

Treatment.—There is unfortunately little to record with regard to the treatment of leucosis in children. The disease is so uniformly acute that measures which have delayed the progress of chronic leukæmia in adults,
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such as treatment with benzol, arsenic, application of X-rays, etc., have usually no time to be effective.

Various attempts to treat the condition are recorded in the literature. Vedel, Vidal and Laux31 used radiotherapy with liver treatment, their idea being to stay the inhibitive action of the X-rays on erythropoiesis by the administration of liver. A suggestive paper on the use of arsenic was published by Forkener and Scott32, who recalled the observations of Cutler and Bradford33 in 1878 on the effect of potassium arsenite in reducing the blood cells in two normal cases, two cases of anaemia and one of leukæmia. Forkener and Scott obtained good results by using Fowler’s solution 30 to 50 minims daily, but all their cases were of chronic myelosis. The idea of administering liver along with treatment by arsenic was adopted in the last case of acute lymphadenosis which we have had under treatment, but without any apparent effect on the rapid development of the disease.

Conclusions.

This study of cases of both types of leucosis in children has shown that: (1) macroscopic focal leukæmic deposits in the viscera in children rarely occur, the infiltration being of a diffuse nature; (2) the cytological characteristics are different but relatively constant in the two types, and the architecture is distinctive in various regions.

The histology of the third rare type of leukæmia—monocytic or histiocytic—has been dealt with elsewhere35.

Although certain features of myelosis can be imitated by severe myeloid reaction in inflammatory disease, the profound anaplasia of myelosis, often obliterating all erythropoietic function, is an outstanding feature. Lymphadenosis is not imitated by any known process of infectious disease in man. The impression left, after cytological and histological study, is uniformly that leucosis is a neoplastic process. Leucocytosis and leucosis appear to be respectively hyperplastic and neoplastic phenomena and analogous to reparative processes and malignant focal new growths.

Baar and Stransky1 favour Sternberg’s view that acute leukæmia is infectious in origin and different in nature from chronic leukæmia. They point out that leukæmic changes, i.e., in the pharynx, provide a more ready means of entrance to pathogenic bacteria and that the immature leukæmic cells show less phagocytic activity than normal polymorphonuclear cells. Hence great caution must be exercised in assessing the part, which any infection accompanying leukæmia, plays in its causation. Here and there infectious processes occur in the course of some cases of leukæmia, yet isolated instances are not convincing evidence that the infections are not incidental but causal.
ARCHIVES OF DISEASE IN CHILDHOOD

Summary.

1. A study of 14 cases of leukaemia in children is presented, which includes brief reference to two cases previously published elsewhere. Only cases in which autopsy has been obtained have been included.

2. All the cases were relatively acute; there were 11 cases of the lymphatic, two of the myeloid and one of the monocytic type.

3. The clinical, haematological and histological features have been detailed and special attention paid to cytological appearances in blood films and tissues. Support is given to the view that types of leukaemia are distinct and can be distinguished by various criteria.

4. The differential diagnosis of a variety of somewhat similar diseases, with special reference to erythroblastosis of infants, has been dealt with.

5. The bearing of a few outstanding features of the study on the question of the aetiology is briefly discussed.

It is a pleasure to express my appreciation of the help of my technical assistant, Mr. J. T. Hall, who has especially assisted me by the skilful preparation of a large number of thin histological sections, involving much painstaking work.

REFERENCES.

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[For illustrations see pp. 314-322.]
Fig. 1.
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Fig. 1.—No. 1 to 18 inclusive. Drawings of cells found in blood films of cases referred to. Magnification approximately 1,000 in all.

(Naegeli = Blutkrankheiten und Blutdiagnostik, O. Naegeli, Berlin, 1923.)

2.  
3. Promyelocyte.  
5. Myelocyte or young immature metamyelocyte in D. W., Leishman.
7.  
9.  
10. G. M.  
11. K. W. Subacute aleukæmic  
12. L. P. Subacute lymphadenosis. Leishman.
13.  
15. Lymphoblasts.
16.  
17. in K. W.
18. Lymphocyte, showing some immaturity of nuclear structure.

N.B.—The constantly small size of the lymphoblasts as compared with the myeloblasts and their greater tendency to irregularity of nuclear contour. Such lobed cells are often termed Rieder cells—see Naegeli, Tafel IX, 7. The nuclear texture, though fine, is slightly coarser, the nuclear staining somewhat deeper, the nuclear margin more heavily defined, and the cytoplasm less bulky than in myeloblasts. These characters do not necessarily apply to each and every cell, but obtain over a number. In myeloid leukæmia, a few, if not more, promyelocytes (No. 3, but perhaps with only a very few granules) will be found, especially if over staining or oxydase staining is employed.

20. Case E. B. Acute lymphadenosis. Lymphoblast in section of liver, stained H.E., fixed in neutral formalin 17 hours after death in November.
21. Ditto
23. Case T. W. Acute myelosis. Myeloblast in section of marrow, stained H.E.
24. Case K. W. Subacute aleukæmic lymphadenosis. Lymphoblast in section of liver, fixed in formalin 10 hours after death in February.
26. Case Cus. Icterus gravis. Pro-erythroblast in section of liver, fixed in neutral formalin 38 hours after death in October. Stain H.E.
27. Case Wa. Severe anæmia of newborn. Pro-erythroblast in section of liver, fixed in formalin 4 hours after death in January.
28. Case Car. Icterus gravis. Megaloblast in liver, fixed in formalin 14 hours after death in December.
29.  
30. (Cells 28 appeared to constitute transition forms between 27 (pro-erythroblast) and 30 (normoblast), c.f. tafel XVI, Naegeli.)
32. Ditto
33. Ditto from marrow  
34. Ditto
36. Case D. W. Acute myelosis. Myeloblast from marrow, stained H.E.
FIG. 2.—Projection drawing of liver in case K. W., acute aleucocythæmic lymphadenosis, showing a liver sinusoid, packed with dark cells with unusually irregular nuclei, the edges of which were rather indistinct (see Fig. 1 (11 and 17) and Fig. 7). The swelling of the endothelial (Küpffer) cells is well shown. × 1000. Fixed in formalin 10 hours after death in February.
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FIG. 3.—L. P. Subacute lymphadenosis. Blood film × 700. Leishman. Two lymphoblasts, top left cell showing 2 clear nucleoli, and bottom cell one. Note tendency to irregularity of nuclear contour.

FIG. 4.—G. M. Acute aleucocythaemic lymphadenosis. Blood film × 700. Leishman. Two lymphoblasts and a darkly staining small lymphocyte. The top lymphoblast shows a tendency to somewhat larger masses of basi- and oxy-chromatin in the nucleus than do myeloblasts (see Fig. 12 and 13). Nuclear irregularity again apparent.

FIG. 5.—Acute lymphadenosis. Blood film × 700. Leishman stain. This case was remarkable in showing a mature type of cell: the cells shown do not apparently differ from lymphocytes.

FIG. 7.—K. W. Acute aleukæmic lymphadenosis. Liver × 700. Stain H.E. Fixed in formalin 10 hours p.m. in February. Liver sinusoids packed with dark cells with remarkably irregular nuclei, of which the edges are not sharply defined. Compare Fig. 2, 1 (24). The nuclear irregularity was a striking feature of the lymphoblasts in the tissues in this case, but the other cellular features and the distribution of the infiltrations in the tissues revealed the type of the process.

FIG. 8.—L. P. Acute lymphadenosis. Lymph gland × 525. Stain H.E. Fixed in formalin 30 hours p.m. in December. The irregular contours of the immature lymphoblasts are well shown.

FIG. 9.—S. M. Acute lymphadenosis. Kidney × 90. Fixed in formalin 27 hours p.m. in April. Typical interstitial infiltration.

FIG. 10.—S. M. Acute lymphadenosis. Kidney pelvis × 700. Fixed in formalin 27 hours p.m. in April. While searching section 9, this small group of cells of a character entirely different from those infiltrations elsewhere in the tissues in this case, was found. The photograph shows the myeloid character: cells MY, appeared to be myeloblasts or promyelocytes, while normoblasts and macronormoblasts, N. are scattered throughout the focus. The myeloid focus is probably an extramedullary embryonic hematopoietic 'rest,' (as described by Shaw Dunn and others) called into activity by the severe anæmia accompanying the lymphadenosis.
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Fig. 11.—K. W. Subacute aleukaemic lymphadenosis. Marrow × 725. Stain H.E. Fixed in formalin 10 hours p.m. in February. The irregular contours of the nuclei of the lymphatic cells in this case are well shown. Practically no myeloid cells were found in this section. Macroscopically the marrow did not show any leucotie deposits.

Fig. 12.—Acute myelosis. Blood film × 700. Stain Leishman. Two myeloblasts are shown in which the nucleoli appear faintly. The nuclear network and membrane are slightly more delicate than in the cases of lymphadenosis.

Fig. 13.—T. W. Acute myelosis. Blood film × 700. Panoptic stain. Note tendency for threading in the nuclei. Some of the cells showed slight granulation in the cytoplasm—promyelocytes.

Fig. 14.—D. W. Acute myelosis. Liver × 90. Stain H.E. Fixed in formalin 12 hours p.m. in July. Liver sinusoids wide and containing infiltrating cells, some appearing large—myeloblasts. No periportal infiltration.
Fig. 15.—T. W. Acute myelosis. Liver × 700. Stain H.E. Fixed in formalin. Two histiocytes, H, one containing an ingested nucleus in a vacuole, and one swollen Kupffer cell K, shown. The cells N show appearances, suggesting they are immature normoblasts.

Fig. 16.—T. W. Acute myelosis. Spleen × 700. Stain H.E. Fixed in formalin. The endothelium of the venous sinuses was throughout much swollen and proliferated, as shown at E. Most cells in the reticulum appeared to be lymphocytes, but M may be a young myeloblast and Me a metamyelocyte.

Fig. 17.—D. W. Acute myelosis. Marrow × 700. Stain H.E. Fixed in formalin 12 hours p.m. in July, after decalcification. Cells consist of myeloblasts, M, and myelocytes, My, the latter sometimes showing indefinite granulations; scarcely any erythroblasts, a few scattered erythrocytes.
Fig. 18.—Composite drawing of blood film of Case T. O. Leukæmoid reaction in congenital syphilis. The entirely mature characters of the lymphocytes is noteworthy and contrasts with their appearance in lymphatic leukæmia.

Red cells, 1,600,000; Hb., 18 per cent.; white cells, 20,000; lymphocytes, 72-75 per cent.; platelets, 20,000.
Fig. 19.—Lymphadenosis (J. B.). Cortical thinning and periosteal elevation with layering.
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