The increasing number of cases reported is due undoubtedly to the greater frequency of routine blood work. The cases usually suggest an acute infection. If the throat symptoms be severe at onset there seems enough to explain the condition, and there may be no suspicion of the grave malady. In the cases with swelling and bleeding of the gums scurvy may be suggested. If there be many haemorrhages, either externally or into the skin, purpura naturally seems a proper diagnosis. As Kelly suggests, many of the cases have probably been mistaken for typhoid fever.

There are some cases which suggest features of the group suggested by Leube. Future work is necessary to determine their exact classification. Some may give difficulty in diagnosis between pernicious anaemia and leukaemia.

ETIOLOGY.

Discussion on this must be more or less theoretical. Neither hereditary conditions nor the previous health of the patient can be said to have any definite influence. The association of severe throat and mouth lesions may be causal or secondary. In some instances an etiological influence is strongly suggested. The frequent finding of streptococci and staphylococci may be regarded as perhaps of significance, but it seems more reasonable to regard these as terminal infections. The whole clinical picture suggests a severe infection, and also the possibility that acute leukaemia may be quite a distinct process from the chronic type. The observations of Löwit are as yet unconfirmed.

In conclusion, the following points may be emphasized:

1. That in the majority of the cases of acute leukaemia there is a rapid destruction of the red cells with the blood features of a severe primary anaemia.
2. That the essential changes in acute leukaemia are in the bone marrow.
3. That certain cases seem to justify the term of "leuk-anaemia" suggested by Leube.
4. That in the study of future cases more attention should be paid to the changes in the red cells and the probable similarity to pernicious anaemia definitely decided.
5. That the clinical features of acute leukaemia suggest its being an acute infection, and perhaps a distinct disease from chronic leukaemia.

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A CASE OF ACUTE LYMPHATIC LEUKAEMIA.

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THE subject of this note was a boy, aged 12 years, as fine a sample of coming manhood as one could wish to see. He had always enjoyed good health, and I would only note in passing that he was an old man's child, his father being now nearly 90 years of age, although in vigorous health.

The boy was at a public school in England, and when he returned home for the Easter holidays last year his mother noticed a spotty rash on his chest, which he attributed to forcing his way through a hedge during a paper chase. It had also been observed that he was a little more languid than usual, and became rather short of breath after any exercise. As he was to return to school next day, I was called to see him on April 28th, 1903.

He expressed himself as quite well. There was distinct anaemia, showing especially in the mucous membrane of the lips and palate. The tongue was coated. A petechial rash was present on the chest and trunk, and particularly well marked on the legs. The heart appeared normal. The spleen could just be felt under the costal margin at the end of a deep inspiration.

For a fortnight he remained in bed with a slight rise of temperature, not exceeding 100°. He had some pain and

swelling in one knee, and the petechiae came out in crops, each set fading in a few days. The tongue remained coated, and constipation was present.

As the anaemia appeared to be deepening and the parents were dissatisfied with the slow progress of the patient, I recommended a blood count, and on May 12th Dr. Houston kindly came down. The result of the count was as follows:

Red cells ...	...	1,600,000 per c.mm.
White cells ...	...	40,000 "
Haemoglobin ...	...	30 per cent.
Differential count of white cells:		
Polymorphonuclears ...	...	0.8 per cent.
Small lymphocytes ...	...	7.4 "
Large lymphocytes ...	...	91.5 "
Transitionals ...	...	0.3 "

That is, 99 per cent. of the leucocytes were lymphocytes. This at once revealed the true nature of the malady, and only too clearly resolved our doubts. I am much indebted to Dr. Houston for his promptitude in completing the examination. He only got home after 8 p.m., and telephoned the result by 10.30 the same evening. I immediately put the boy on Fowler's solution (m.v.).

On May 14th he was seen in consultation with Sir William Whitla. The spleen was distinctly larger and could be felt easily well under the costal arch. There was no lymphatic enlargement. A fresh crop of petechiae had come out. Arsenic increased to m.vijss.

The after-history of the case was as follows:

May 15th.—Temperature 101°, pulse 128. The rise of pulse and temperature evidently portend fresh developments, and this was borne out by the occurrence of a sharp attack of epistaxis in the afternoon, recurring again in the evening.

May 16th.—Morning temperature 100.4°, pulse 136. Bleeding from nostril continues; right nostril packed with lint saturated in solution of adrenalin (1 in 1,000). Apparently as the result of the haemorrhage the spleen is much reduced in size, and can just be felt under the costal region. Has had intense pain in left ear, for which one-eighth of a grain of morphine given hypodermically. Put on 15 gr. of calcium chloride, and 10 minims of adrenalin every three hours. Evening temperature 103.4°, pulse 152. Slept several hours after morphine.

May 17th.—Morning temperature 101.6°, pulse 156. Bleeding again when plug removed. Evening temperature 103.4°, pulse 164. Fairly well all day; no return of bleeding, and has taken food well.

May 18th.—Morning temperature 101.5°, pulse 160. Fresh bleeding from nose. Seen again with Sir William Whitla. Ol. terebinth., m.v in capsule, ordered. Evening temperature 103°, pulse 168. Some mental confusion. Breathing slightly stertorous. Respirations 24.

May 19th.—Morning temperature 98.8°, pulse 176. Delirious. Pil. morph. 1 gr. In afternoon wildly delirious for a time, but quieted by another 1 gr. of morphine. Bleeding again when plug removed. Nostril packed with puff ball.

May 20th.—Temperature subnormal, pulse 180, and very feeble. Respirations 40. Had a fairly quiet night. Evacuations involuntary. Died at 8.15 p.m.

REMARKS.

The points of interest in this case are:

1. The age of the patient—namely, 12 years.
2. The complete absence of any palpable lymphatic enlargement, coupled with a moderate amount of splenic hyperplasia. The considerable increase in the size of the spleen only lasted a few days, and was reduced again rapidly by the nasal haemorrhage. The non-involvement of the glands appears to be rather the rule in the very acute cases, and is explained by the fact that the bone marrow is first invaded by lymphoid tissue, and the patient dies before the glands have time to react. The absence of this sign adds greatly to the difficulties of diagnosis.

3. Its exceedingly rapid course, so that one cannot help comparing it to a specific fever or septicæmic process. If we date its onset from three weeks before he was seen, the fell malady ran its course in six weeks, and the symptoms were only acute from the first epistaxis—that is, six days before death. As his mother remarked, she absolutely refused to believe the contents of my note, informing her of the result of the blood count and of the fatal nature of the disease, when she looked at him sitting up in bed chattering to his brothers and sisters, and yet he was dead eight days later.

4. The absolute necessity for a blood count in every case where anaemia is a feature and the symptoms obscure. As Ehrlich says, "the microscopic examination of the blood alone, on dry preparations, without the assistance of any other clinical method, can decide whether a patient suffers from leukaemia, and whether it belongs to the lymphatic or myelogenic variety."

5. The profound anaemia, even before the onset of the epistaxis.

6. Although the case became critical from the time the nasal haemorrhage set in, still the patient did not appear to

die from loss of blood, but rather from an acute septicaemia, with high temperature and a steadily-increasing pulse. The epistaxis could always be controlled by plugging.

7. The presence of a purpuric eruption on the body, as virtually the only sign for several weeks.

8. As is usual in the acute lymphatic cases, the white cells are almost exclusively large lymphocytes.

We thus see that acute leukaemia is generally of the lymphatic type, occurs in young subjects, is generally fatal in from two to four months, and is uninfluenced by treatment.

NOTES ON THE MICROSCOPICAL EXAMINATION OF BONE MARROW.

(METHOD AND CLASSIFICATION.)¹

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THE interest attaching to the red bone marrow as a probable factor in the causation of the so-called blood diseases, and as an agent controlling the course of many other diseases not specially regarded as blood diseases, has created a demand for a more thorough knowledge of the sources and causes of variation of the different blood cells, and for a more systematic examination and study of the cytology of the red bone marrow.

The subject is complicated by several technical difficulties arising from the readiness with which the marrow cells undergo *post-mortem* changes; from the unsatisfactory results obtained by the smear preparation and sections now generally employed, whereby the true appearance of the cells is most liable to be destroyed or masked by artifacts; and also from the absence of a suitable scheme for classifying the varieties of cells. The method of preparing and the system of classification to be described in the following notes, and which have been adopted in the examination of a very large number of specimens of bone marrow obtained from various sources, including besides those taken at human *post-mortem* examinations, those prepared from freshly killed dogs, cats, kittens, rats, rabbits, guinea-pigs, mice, chickens, pigeons, frogs, etc., in both adult and fetal states, have been found, in great measure, to overcome these difficulties and to establish the study of the bone marrow on a basis comparable with that of the cytology of the blood.

METHOD.

Marrow is obtained as soon as possible after death, from a rib or vertebra, by squeezing it out of the bone by means of strong forceps or scissors; in the animals above mentioned it was obtained from the femur. It is conveniently collected on a platinum loop, and transferred at once to a watch-glass containing the dissociating reagent. There results a more or less complete emulsion, and the cellular elements of the marrow are dissociated.

To obtain this result repeated trials were made with a number of different solutions, including distilled water, salt solution, various strengths of alcohol, formalin, Eau de Javelle, solutions of urea, etc., but owing either to their insufficient dissociating action or to the production of chemical changes that interfered with the subsequent fixing and staining of the cells, these were all discarded in favour of a 10 per cent. solution of neutral glycerine.

This dissociating reagent is prepared by diluting glycerine with ammonia-free distilled water to form a 10 per cent. solution, and titrating this against decinormal sodium hydrate, using phenolphthalein as an indicator. The initial reaction of this solution varies from +0.1 to +0.5 (Eyre's scale). This reagent has a specific gravity of 1.029 at 15.7° C.

A loopful of 10 per cent. glycerine is then placed on a clean cover slip, and to this a loopful of the marrow emulsion is added and very gently spread over the surface of the slip. The film thus prepared is allowed to dry in the air, without heating, until a uniform ground-glass appearance is produced; this usually results within five minutes, unless the film is too thick. The film is then fixed and stained with a combined eosin and methylene-blue solution (Jenner's blood stain), for two and a half minutes, washed with ammonia-free distilled water, dried thoroughly and mounted in xylol balsam. It is in fact treated exactly as a blood film.

On microscopical examination the various cells should be seen well separated from each other, so that they can be individually studied and classified. A field showing eight to

ten cells is to be aimed for: experience soon enables one to judge on this point. Care must be taken to avoid making the emulsion too concentrated or the films too thick, lest the cells are crowded together and the object of the film be defeated.

CLASSIFICATION.

Red bone marrow consists of connective tissue, fat, blood vessels, lymphatics, nerves, and particular cell elements characterized by a peculiar transitional nature and a tendency to produce atypical forms. This atypical transitional constitution is the great obstacle to the satisfactory classification of the marrow cells, since it is frequently very difficult to decide into what class the various intermediate cell forms should be placed.

In film preparations the cells to be classified are the myelocytes or marrow cells proper, and those cells that belong to the blood. There are two chief divisions into red cells and white cells.

Red Cells.

The red cells comprise (a) the non-nucleated red cells of the blood, (b) the nucleated red cells of the marrow. The varieties of these cells will not be discussed in these notes, but it may be mentioned that the nucleated red cells in normal marrows number about 10 to every 100 of the white cells, though this proportion is often considerably increased in diseased conditions.

White Cells.

The white cells are classed into two divisions, the non-granular and the granular.

The non-granular group comprises:

- (a) Giant or mother cells.
- (b) Lymphoid or primitive cells.

The granular group comprises:

- (c) Coarse oxyphile cells.
- (d) Fine oxyphile or neutrophile cells.
- (e) Amphiphile cells.
- (f) Coarse basophile cells.
- (g) Fine basophile cells.
- (h) Polymorphonuclear leucocytes.

Without entering upon the question of the functional and developmental nature of these cells it is desirable to shortly describe the appearances relied upon for purposes of recognition:

(a) *The giant or mother cells* have the appearance of zoogloic masses with rounded, irregular, bulging margins. They vary in diameter from 20 to 50 μ . The protoplasm appears to be indistinctly granular and stains faintly neutrophile. In the depth of the cell are three to five or more nuclear bodies about 4 μ in diameter, staining faintly basophile, and containing one or two small deeper staining nucleolar-like bodies. These cells constitute about 1 per cent. of all the white cells.

(b) *The lymphoid or primitive cells* exhibit many varieties of transitional forms. Commonly they closely resemble the above-mentioned nuclear bodies of the giant cells, being round, homogeneous masses about the size of a red-blood cell, staining faintly basophile, showing no distinction of nucleus and surrounding cell substance, and containing one or two nucleolar-like bodies that stain more deeply basophile. Transitional forms extend in several directions. On the one hand, they present all grades of cells, from those showing a scarcely perceptible rim of differentiated cell substance to the fully developed cell with deep-stained margin of hyaline protoplasm, indistinguishable from the lymphocyte found in the blood. On the other hand, this early differentiating rim of cell substance takes a faintly oxyphile stain, and all grades can be observed between this and cells that are not to be distinguished from the nucleated red cells. A third series shows oxyphile granules in the fine rim of early differentiated cell substance and all the subsequent grades from this to the fully-developed granular cell. This lymphoid or primitive cell is the most important of the white cells, and constitutes about 50 to 60 per cent. of all the myelocytes. An examination of marrow taken from a new-born infant shows over 70 per cent. of these cells, and in fetal marrow the proportion is very much greater.

(c) *The coarse oxyphile granular cells* have pale basophile staining nuclei resembling the primitive cell, surrounded by a varying amount of reticular cell substance in the meshes of which are coarse oxyphile staining granules. Apart from variations in size of the nucleus and in the number of the granules, these cells are the most constant and typical cells found in the marrow. They constitute about 5 per cent. of all the white cells. Clinically they are known as eosinophile myelocytes. It may be noted that these cells appear very