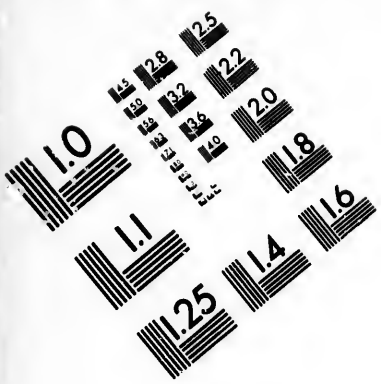

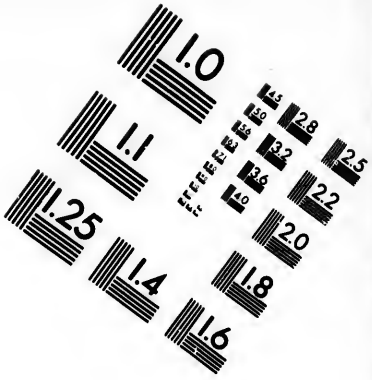

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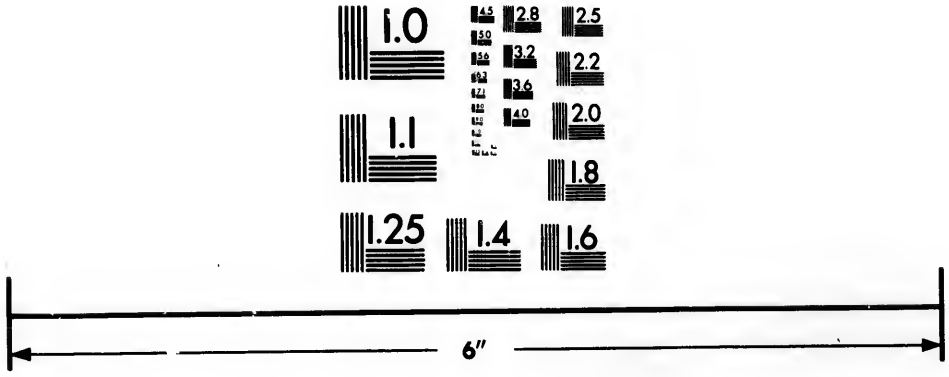

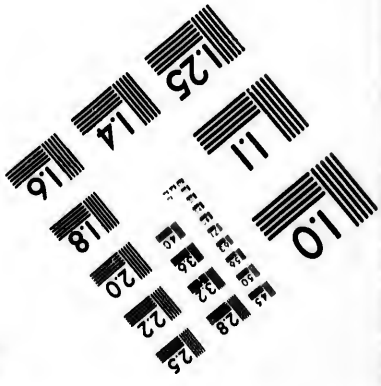

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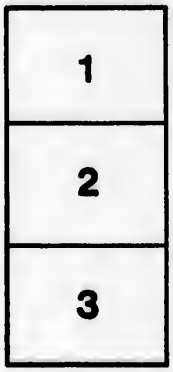

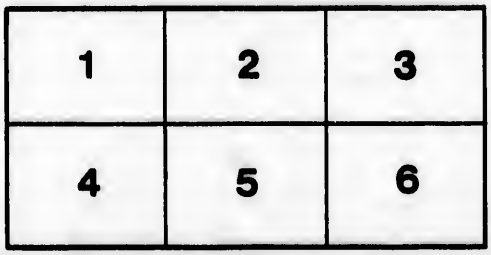

12

OBSERVATIONS UPON THE RELATION BETWEEN LEUKÆMIA AND PSEUDO-LEUKÆMIA.*

BY

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There are few chapters in the domain of clinical medicine which have excited the interest of modern observers more than the diagnostic value of a blood examination. That it is an undoubted aid in the diagnosis of many diseases cannot but be acknowledged by all who have had any experience with these methods. But although they have been so extensively employed within recent years, there can be no question that hitherto the results have not fulfilled our expectations. In the light of the most recent observations it may be said with more than probability that there is no disease known other than those due to parasites which, *per se*, can be diagnosticated by an examination of the blood. Although a certain general law may apply to the conditions of the blood found in the various forms of anæmia, for example, such a law nevertheless is far from being absolute. Many of the secondary anæmias not infrequently show a blood condition which is indistinguishable from that of the progressive pernicious anæmia; and the same may be said of not a few instances where tuberculosis and malignant disease have afforded similar observations. During the past year, also, in a patient suffering from anorexia

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nervosa, the blood examination revealed 900,000 red cells, about 20 per cent. of hæmoglobin, nucleated red cells of various sizes, and otherwise a condition which, from the stained specimens, showed all the characteristic features of the blood of pernicious anæmia.

From the work, too, that has been published in the last few years the diagnosis of such a disease even as leukæmia cannot be established from a mere examination of the blood constituents. As has been shown by a number of recent observers, sarcomatous growths may undoubtedly induce a cellular ratio in the blood which is indistinguishable from that present in a typical true leukæmia. And hence, from our present knowledge, it would seem practically impossible to diagnosticate definitely a leukæmic condition, apart from the numerous concomitant symptoms, objective and subjective.

Having ourselves met in the past few years with not a few cases where an absolute diagnosis of leukæmia or of pseudo-leukæmia was rendered extremely difficult, it has seemed to us worth while to note this fact, and to mention briefly some instances which show how closely related these two conditions really are. That the relation between the two is in itself nothing new we are quite aware, but inasmuch as the matter has only been referred to in connection with isolated cases, and inasmuch, too, as the subject has apparently received far less attention than it deserves, we have taken upon ourselves to emphasise it the more.

Previous to careful and systematic examination of the blood the French writers, under the term "adénie," or "diathèse lymphogène," grouped together all those diseases which appeared to involve mainly multiple lymphatic glandular structures; hence they included leukæmia and pseudo-leukæmia under the same head. And it was not until some years later that an examination of the blood revealed occasional differences which permitted of a subdivision into various forms of lymphogenous diathesis and of a separation of the two diseases above mentioned. Since that time it has been the practice of physicians to describe under different headings these two closely allied diseases, and yet within the past few years case after case has been recorded to show that such a separation is scarcely justifiable.

If we compare, for example, the morbid anatomy of the two affections, we observe to all intents and purposes identical conditions; we may get in both the same lymphoid overgrowths in the

organs and in the tissues, not only where lymphoid elements previously existed, but elsewhere as well, and, above all, in the bone marrow. Within the last year, however, Askanazy (1) writing in *Virchow's Archiv*, and following the views of Neumann, (2) who regarded leukæmia as a disease primarily of the bone marrow, has asserted that the morbid anatomy of the two diseases has one great distinctive feature; that in leukæmia the marrow throughout is diffusely affected, while in pseudo-leukæmia the changes are always localized, manifesting perhaps multiple lymphomata, but never a diffuse lymphoid or pyoid condition. From the number of cases on record, however, proving the contrary the distinction would scarcely seem justifiable; while Askanazy's explanation of the absence of bone marrow changes in some cases of true leukæmia are scarcely forcible enough to render the theory unimpregnable or to convince other authorities on this subject.

Nor can one distinguish between the forms of multiple glandular enlargements or the varieties of splenic tumors, for the macroscopic and microscopic lesions are throughout interchangeable; in both one may have a like tendency to infiltration of cells; and, in both the true and the so-called false disease metastases may occur in almost any part of the body. Recent observations have in this respect borne out the older theories of those who recognized between the two conditions no distinctive morbid anatomy.

There is no more satisfactory proof necessary to bear out the theory of this close relationship than is obtained in a casual perusal of the literature of the past decade, dealing with some cases of leukæmia, for it sufficiently illustrates the many difficulties one meets with in endeavouring to differentiate between cases of true leukæmia and Hodgkin's disease. Almost every year within that period one or more cases are recorded, showing with what hesitation the observer is inclined to make any absolute distinction. If distinction there be, it is universally recognized to be a clinical consideration only, for from the morbid anatomy alone we can obtain no satisfactory differentiation other than the presence of increased leucocytes within the blood vessels. Even this, from the point of view of pathological diagnosis, is not free from objection, inasmuch as we may be at a loss to decide whether or not such a condition has been a terminal process, as so commonly occurs. The leucocytosis itself is a purely clinical observa-

tion, and it is mainly upon this feature that any question of differential diagnosis rests.

Concerning the clinical picture of the two maladies, we find in each an identical classification into types; in both a chronic form is described and in both a more acute, characterized often by the presence of irregular fever, early enlargement of glands, early onset of hæmorrhages and a rapidly progressive lethal termination. Such is Ebstein's (3) case of acute Hodgkin's disease, in which, except for the condition of the blood, all the essential features of the case were identical with those of an acute leukæmia. Such, too, appears to be the reason why authors occasionally speak of a lymphatic Hodgkin's disease where a lymphocytic leucocytosis occurs of too moderate a degree to warrant the application of the term leukæmia.

In the more chronic forms of these two diseases there is often a different mode of onset of the lymphoid enlargements, inasmuch as in Hodgkin's disease it is the glands, while in leukæmia it is the spleen that is first affected. Yet such a distinction is far from being absolute. Cases of Hodgkin's disease have been observed in which the spleen alone has been affected, while other lymphoid structures remained quite normal, and we have seen one such case in the hospital here in which, from general physical conditions as well as from examination of the blood, it was impossible to make any other diagnosis than that of a splenic form of Hodgkin's disease.

Whether or not we are justified in considering the two diseases as distinct from any other clinical conditions apart from the blood examination we are unable to say. Eichhorst (4) suggests that an essential difference between the two diseases may be observed in the urine; that in leukæmia there is an excess of uric acid, while in Hodgkin's disease he has never been able to discover any such condition. Considering, however, the frequency with which diseased blood conditions are attended with superabundance of uric acid in the urine, it would seem that an altered metabolism which induces the leucocytosis might likewise explain the presence of excessive uric acid in the urine, and that the condition may be associated in some way with the altered blood condition. That such a process does indeed occur has been proved experimentally by Kühnau (5) who has shown that an excessive leucocytosis is invariably associated with an increased production of uric acid. In this case, then, such a

differentiation as suggested by Eichhorst would have quite as little satisfactory foundation as has the basis of differentiation by means of an examination of the blood.

It may very reasonably be questioned whether such a variable symptom as the incidence of leucocytosis should *per se* form a basis for the classification or whether from our present knowledge we are not laying too much stress upon this one condition.

It may be stated, in the first place, that in leukæmia the leucocytosis is notoriously inconstant; that during the course of the disease the white cells may for a long time maintain a normal ratio to the red, though all the other classical signs of the disease be present—a stage which is commonly known as the *aleukæmic* period of the malady; such a circumstance is indeed common enough, and has been placed on record already by a number of observers. Mosler (6), Seelig (7), Troje (8), and several more have made notes of cases illustrating this point. For a longer or shorter time each of these observers had occasion to see patients manifesting the usual symptoms of Hodgkin's disease. In each instance, however, the condition of the blood became altered, presenting later on a leucocytosis corresponding to that found in leukæmia, and some have regarded such as examples illustrating the sequence of one malady upon another, distinctly separated therefrom. At the same time, in each instance the author questions his right to maintain so absolute a distinction, in view of the renewed observations that are being made, and which would seem to prove not only that the leucocytosis of leukæmia is notoriously inconstant, but that in all probability there is but a single influence at work producing this differentiation of the two maladies. Troje has suggested that some inhibitory mechanism regulates the distribution of leucocytes through the circulation; that where leucocytosis occurs in the blood the regulating apparatus is inefficient, and hence we observe young developing forms free in the circulation. The further theory is suggested that to a certain extent the vessel walls may inhibit or stimulate the exudation of leucocytes by their greater or less porosity, thus explaining the occurrence of metastases.

Such cases as these above described, no matter how they are explained, would certainly indicate a marked variability in the leucocytosis which, too, would appear from the records to depend in no way upon treatment. Cases which have occurred in the Royal

Victoria Hospital have shown both in the acute and in the chronic form not only wide variation in the cellular ratio of the blood corpuscles, but in many instances the condition of the blood has been such as to render absolute differential diagnosis impossible. Meeting then, as we do, so many stages of leucocytosis in the multiple lymphomata varying from a normal ratio up to an excess of the white over the red cells, it may be questioned whether those cases recorded by Ebstein (3) and others, where leukæmia has followed upon Hodgkin's disease, are really to be looked upon as instances of one disease complicating another, or whether we are not rather observing the same disease in its different forms.

It by no means infrequently happens that in cases of multiple lymphomata the number of white cells borders so closely on the ratio found in leukæmia that we are in doubt as to the presence of a true leukæmia or of an ordinary leucocytosis. Nor is this all; one may find in other diseases a leucocytosis quite as marked numerically as seen in leukæmia. Such a condition has recently been described by Palma (9). In his case there were multiple glandular swellings throughout the body, while the blood condition was normal, and finally the diagnosis of Hodgkin's disease was established. A month later, however, the blood showed all the characteristics of true leukæmia, and shortly after the patient died, showing at the necropsy a primary round-celled sarcoma of the thymus gland with metastases in the various organs, with multiple hæmorrhages and a bilateral suppurative nephritis. Such a case is in itself sufficient to show how impossible it is from the blood alone to make a satisfactory distinction between a number of these diseases which induce leucocytosis. Similar instances, too, have come within our experience at the Royal Victoria Hospital, where patients have entered with symptoms pointing to true leukæmia, and with a blood-count likewise assuring one of such a condition; and yet at the necropsy primary sarcoma of the pelvic organs was found, with numerous metastases, somewhat resembling the case described by Palma. One of these patients entered the hospital with general *malaise*, enlargement of the spleen and some fever. Within a few days after admission purpuric spots developed on the body, while hæmorrhages were manifest from the gums, from the stomach and the intestines. There was a marked leucocytosis of about 1 to 100, the leucocytes being chiefly of large mononuclear

variety. Within a week after admission the patient died, having developed nodules in the skin, high fever, progressive asthenia, repeated hæmorrhages, and showing shortly before death a still more marked mononuclear leucocytosis. A diagnosis of leukæmia was made, though the necropsy revealed a primary sarcoma of the cervix uteri.

In another patient the condition was somewhat similar. She was admitted because of hæmorrhages from the stomach and purpuric spots upon the trunk and limbs. The course of the disease was progressively severe up to her death, two weeks after admission. The examination of the blood had revealed a ratio of white cells to red of 1 to 21, the leucocytes being chiefly of the lymphatic variety. From our experience of the other case just mentioned, and from a few similar instances recorded by Fagge (10), the diagnosis of sarcomatosis was made and verified at the necropsy, the primary lesion existing in the ovaries. It would have been natural under the ordinary conditions to have made the diagnosis of leukæmia were it possible to regard the blood examinations as a reliable means of diagnosis in all cases. Some instances recorded by Fagge are practically identical with the two just described, and while the author has already published them as instances of sarcomatosis, Ebstein, in his classical work on leukæmia, considers Fagge to be in error as having confused sarcomatosis and true leukæmia. Our own cases, however, not only aid in bearing out the diagnosis made by Fagge, but would seem to further emphasise the great confusion to which we are liable on attempting to distinguish any of the various lymphomatous diseases by an examination of the blood alone.

We have observed, too, an instance bearing a similar instructive lesson in the wards of the General Hospital some years ago—a case which has since been put upon record by Professors Adami and Finley (11). The patient referred to was a girl, aged 11, who was admitted to the hospital on account of a violent hæmatemesis. An examination revealed great anæmia and a ratio of the white cells to the red which bordered on the line between leukæmia and leucocytosis. The spleen was very much enlarged. After a few days' sojourn in the hospital the patient died, presenting the typical morbid anatomical changes of leukæmia or of Hodgkins' disease, the diagnosis in such a case being absolutely impossible. Nor are the multiple lymphomata the only diseases which may be followed by this so-called

leukæmic condition of the blood. Litten (12), Gottlieb (13), and have recorded cases of pernicious anæmia which have manifested in the course of that malady a blood state typical of true leukæmia.

We must therefore conclude that an enormous increase of white cells is certainly not in itself diagnostic of leukæmia, nor is there any special class of diseases to which an over-abundant leucocytosis is confined, inasmuch as the most varied kinds of disease may, under peculiar conditions, manifest extreme leucocytosis. Such, for example, are some cases of pneumonia, malignant disease, and the terminal stage of many affections; so far as numbers are concerned, under a great variety of conditions, the blood examination may be indistinguishable from that of leukæmia.

It is, however, usually held that in leukæmia a special type of leucocyte is increased—namely, the mononuclear in contradistinction to the secondary leucocytosis from other causes and accompanying other affections which is chiefly of the polynuclear variety; and for the different forms of leukæmia there is in each case a different kind of leucocyte which is thought to be characteristic—for the myelogenous form, the myelocyte; for the splenic form, the hyaline cells; for that type in which the lymph glands are most affected, the lymphocytes.

While it must be granted that such preponderance of one form frequently obtains, it must be acknowledged that the condition is not absolutely diagnostic of true leukæmia. Above all, it is generally accepted that in Hodgkin's disease we may at times get a marked leucocytosis, the increase of the white cells concerning mainly the lymphocytes, the same class of cells which are increased in lymphatic leukæmia; indeed it not infrequently occurs, as stated by Professor Osler (14, that the lymphocytosis of Hodgkin's disease may become gradually so marked as to be quite indistinguishable from that found in lymphatic leukæmia. Such instances are described as cases of Hodgkin's disease which have run into lymphatic leukæmia, and yet the process may be so gradual as to render it impossible to decide where Hodgkin's disease has ended and where the lymphatic leukæmia began. It is upon the occasional occurrence of such events that Penzoldt (15) and Palma (9) believed that there exists a lymphatic Hodgkin's disease different from the ordinary variety of Hodgkin's disease, and which may be a prelude to true leukæmia.

In one disease, then, we we already find the possible development of a great increase of the leucocytes characteristic of one form of leukæmia. The same, too, has been found in the mononuclear increase referred to already in several cases of sarcoma, a leucocytosis which both numerically as well as morphologically bore all the characters found in true leukæmia; nor can we believe that in a host of other affections where leucocytosis occurs that any absolute rule may be laid down as regards the type of the leucocytosis. While it may perhaps be generally accepted that in carcinoma the leucocytosis is mainly polynuclear, yet we have seen not a few cases where a distinct and indeed sometimes enormous increase of the large mononuclear elements was obvious. Further, one of the resident physicians of the Royal Victoria Hospital, Dr. R. B. Shaw, who has been engaged of late in a study of the leucocytes found in secondary anæmias, has observed a most irregular variation in the type of the leucocytes, whether relatively or absolutely increased, that the mononuclear may sometimes not only equal in numbers the polynuclear leucocytes, but not infrequently there is a distinct preponderance of either the lymphocytes or the large hyaline forms.

While, however, it may be agreed that so far as the lymphocytes and the large hyaline forms are concerned there is nothing in the examination of the blood which enables us to absolutely differentiate between Hodgkin's disease and true leukæmia, yet in the myelogenous form there is perhaps less difficulty, inasmuch as one finds there a type of leucocyte which probably does not occur normally in the blood. This myelocyte, as it is called, while increased in this form of leukæmia to a marked extent, is nevertheless absent in other varieties of that disease; and it seems but justifiable, from this fact alone, to exclude this cell as an essential feature in the diagnosis of all leukæmias. At all events it does not occur in the lymphatic form, nor is it always to be found in the splenic variety; on the other hand, too, it is now known to occur in conditions other than leukæmic, though, so far as we know, never to the same extent.

The eosinophile cells, as is well known, offer no feature of absolute diagnostic importance; not only do they seem to be increased in emphysema, pemphigus, scarlatina, etc., but every now and again an examination of patients in whom the blood condition is presumed to be normal there may occur a most marked increase in eosinophilous

cells. We have examined slides from the blood of a patient in the practice of Dr. Hamilton, of Montreal, where slight anæmia had been suspected, and were surprised to find that whereas the red cells appeared almost normal, there was a distinct eosinophilous leucocytosis, probably 50 per cent. of the white cells showing eosinophile granules. One of us while recently in Baltimore, had an opportunity of seeing a patient in Dr. Osler's wards who suffered from trichiniasis, and in whose blood there were 60 per cent. of eosinophilous cells.

In an interesting work upon the blood formation, Dr. Saxer, (16) of Marburg, has recently urged that red and white cells proceed originally from what he calls primary wandering cells; that from these cells the various forms of leucocytes may arise, and that so far as origin is concerned they are all the same. The differentiation comes late in the development, and the various forms represent merely the different stages of growth. He has shown that one variety—namely, the myelocyte—is capable of developing in the mature organism into the red blood cell. The significance of this is apparently of no small importance as affording an explanation of the frequent occurrence of myelocytes in the blood of leukæmic patients. Some defect in the development of the leucocytes has occurred, and they have probably, he thinks, not performed their important functions.

The work is chiefly of interest as showing that all leucocytes are members of one series, the one developing from the other, as could readily be proved from a study of the subject on the basis of embryology.

Another work of importance in this regard is that of Dr. G. L. Gulland (17) on the granular leucocytes, in which he has been able to show from a study of the various forms of cells, and of their staining reactions, that we are after all quite unprepared as yet to make any arbitrary classification of the white cells of the blood from the results of our staining methods alone. He considers that the shape of the nucleus has no relation to the presence or absence of granules; that all varieties of leucocytes are merely stages of development; that, further, while they may be divided for convenience into hyaline, acidophile, and basophile, yet all forms are derivatives of lymphocytes. It is further impossible to say from the kind of cell in excess in the blood as to what organ is affected. To say that a nucleus is character-

istically trilobed, as do Kanthack and Hardy, seems to him unjustifiable, the shape of the nucleus never being a characteristic feature.

If, then, we are to take cognisance of this work of Dr. Gulland's, we are obliged to confess that we are still far from attaining to a satisfactory basis of diagnosis through means of our staining reactions, by which we endeavour to differentiate the various types of leucocytes and to base thereon a definite standard of classification in disease. But these views of Saxer and Gulland cannot as yet be accepted in their entirety, for both of these authors appear blind to the fact that leucocytes or wandering cells can, under certain conditions, originate from fixed connective tissue, muscle, and endothelial cells, as has been amply proved by Ranvier, Metchnikoff, and Joseph Griffiths. We certainly cannot state that all leucocytes and all forms of leucocytes have a similar origin. Recognising, too, as we are compelled, that the results obtained from the various stains differ greatly according as there are slight variations in their constituent elements, the question of microchemical reactions remains still, to a certain extent, an unsatisfactory problem.

Of all the forms of leukæmia, that which is most akin to Hodgkin's disease is, of course, the lymphatic form, and as exemplifying the difficulties of differentation, the following case is appended, having come to our notice during the past year. The clinical history of our case is briefly as follows, and we are indebted for our abstract from the notes to Dr. Robertson, the resident physician of the hospital:

A French-Canadian, aged 18 years, entered Professor James Stewart's wards, November 24th, 1895, complaining of cough and headache, "lumps" over his body, and painful swelling of the left arm. He had been ill for only five weeks, excepting for a temporary swelling of the lip, contracted shortly before and resulting, he supposed, from using a borrowed flageolet. This had resulted in painful intermittent swellings of the lips for a few days previously, but had quite subsided a day or two before his general illness. The earliest manifestations of disease were glandular enlargements beneath the chin and the angle of the jaw, which in two or three days had so progressed as to involve also the glands beneath the auricle, and those in the posterior triangles of the neck. Before the end of the first week another lump was seen on

the forehead, small in size and beneath the skin. Likewise the glands in the groin became involved, and there was pain over the region of the anterior crural nerves of both sides. There was otherwise no distress at the time, but early in the second week of his illness there had ensued great pallor with weakness and dyspnœa, and the patient's symptoms became alarming. He was confined to bed but slept poorly, suffering for the most part from orthopnœa. Epistaxis commenced about the same time and has frequently since recurred. Deafness seemed to have occurred simultaneously, while, on the night before admission, painful swelling of the left arm ensued. Dr. Vipond, who kindly asked one of us to see the case with him, permitted his removal to the hospital, where he was admitted the following morning.

His personal history is of interest mainly in that when aged 4 years he suffered from some disease whereby his eyesight was almost permanently lost, leaving his vision up to the present day greatly impaired. The history of this illness is unsatisfactory. His habits were good, his occupation light, and he had otherwise been well up to his present illness. There was no venereal history.

The family history manifested no evidence of tuberculosis nor other hereditary taint.

Condition on Admission.—The patient is a young man, markedly anæmic, unable to lie down on account of cough and dyspnœa. He is somewhat deaf and apathetic, but intelligence seems good; he is rather somnolent, though on account of the dyspnœa he does not sleep well; he has headache, pain in the left elbow and arm. Temperature, 101 1-5°; pulse, 136; respirations, 31.

Lymphatic System.—The lymphatic glands all over the body, so far as can be determined, are enlarged and firm. They are all more or less movable, quite painless, and not tender. There is no evidence of suppuration nor even of acute inflammation or involvement of the skin. This applies to the glands beneath the jaw, in the triangles of the neck, in both axillæ and the inguinal regions, the epitrochlear glands, the occipital glands, and those behind the episternal notch; there is distinct dulness over the manubrium sterni, evidently from involvement of the retrosternal glands.

Locomotor System.—The muscles are fairly well developed; the left arm from wrist to shoulder is much swollen and œdematous.

There is universal anasarca, and the skin generally has a rather oily look. There are numerous purpuric spots about the right elbow, and a few upon the back. On the forehead there is a subcutaneous nodule 2 inches in diameter, which is slightly tender and moderately firm. There is slight tenderness on percussion over the long bones and the sternum.

Circulatory System.—The pulse is rapid, fairly full and regular. The apex of the heart beats in the fifth space in the nipple line, to which point the left transverse dulness extends; vertically the dulness begins at the third space above. There is a fairly loud systolic murmur at the apex, transmitted into the axilla and to the back. There is no accentuation of either basal second sound.

Respiratory System.—There is dyspnœa with rapid shallow respirations, frequent cough, and some slight mucoid expectoration occasionally tinged with blood. An examination of the chest reveals a few dry *rales*, but otherwise no abnormality beyond the dulness over the sternum previously mentioned.

Digestive System.—The lips are dry, the tongue very pale and thinly coated. The teeth are very irregular and covered with sordes. Both tonsils are distinctly swollen, very pale, and on the right side there are a few submucous hæmorrhages. The appetite is fair and the bowels regular. The abdomen is not distended nor tender. The liver dulness extends in the right mammillary line from the fifth space downward 2½ inches. The organ is not palpable. Splenic dulness extends from the eighth to the eleventh space, but the viscus cannot be felt. There is no ascites.

Genito-Urinary System.—There is no priapism. The testicles appear normal. The urine is straw-coloured, clear, with a creamy, yellowish-white sediment and a few grains of uric acid. The urine is acid, specific gravity 1020, free from albumen and sugar; microscopically a large abundance of urates and uric acid crystals. No casts can be detected.

The Blood.—There is a tendency to hæmorrhage both from the nose and in the expectoration. The blood which flows from the finger on puncture is very pale, and the bleeding is stopped with great difficulty; the red cells 1,310,000, white cells 24,000, hæmoglobin 21 per cent. Stained slides show a very marked lymphocytosis, with an abundance of transitional forms. There is likewise a large number of

polynuclear neutrophiles, many of which show undoubted evidence of mitosis. There is some irregularity in the size and shape of the red cells, and many of them are nucleated, in some cases their nuclei showing a breaking up into two, three, or more parts.

The Nervous System.—Apparently normal; special senses. Eyes: So far as can be ascertained the patient seems quite blind to any test; the pupils are widely dilated; there is a constant, rather coarse lateral nystagmus. Dr. Buller, on examination of the fundus, reported a double retinitis pigmentosa of unusual type, the pigment not showing the usual stellate arrangement following the vessels. The discs show indistinct borders, somewhat red, and with a few recent changes due to the present disease, and probably a few hæmorrhages.

Diary of Case.—The treatment adopted consisted in the first place of hypodermic injections of liquor sodii arsenitis, 5 minims daily, progressively increasing the doses by 1 minim every alternate day. Restricted diet was further advised, and some alcoholic stimulants recommended; apart from this the various symptoms were treated as they arose. A few days after admission severe and prolonged epistaxis ensued, necessitating plugging of the posterior nares, which after some time controlled the bleeding. Another examination of the blood, made a few days later, showed 580,000 red cells, 60,000 white, mainly lymphocytes; hæmoglobin 15 per cent. On December 2nd, a little more than one week after admission, the patient appeared much better, and a more accurate examination of the blood revealed the following results: On a large number of slides 1,500 leucocytes were noted, and the percentages of the different varieties were found to be as follows: Lymphocytes, 76 per cent.; polynuclear neutrophiles 19.5 per cent.; large mononuclears, 1.8 per cent.; transitional forms, 2.3 per cent.; eosinophiles, 0.35 per cent. Considerable difficulty was experienced in making an accurate estimate, inasmuch as very many small, dark, round bodies presented, resembling both in size and staining reactions the nuclei of red cells, free in the circulation; and, on the other hand, while the majority of lymphocytes would show a small zone of protoplasm around their nucleus, in others, again, the nucleus itself was less deeply stained than that of the red cells, and there was yet no evidence of a cell body. All such which were in any way dubious as being either lymphocytes or escaped nuclei were not taken into consideration in the estimate.

Many nucleated red cells were seen, mostly normoblasts, with a few megaloblasts. There was a marked poikilocytosis. The general blood count gave the following result: Red cells, 1,595,000; white cells, 17,300; that is to say, a ratio of 1 white to 94 red cells. For several days subsequently there was marked general improvement, and the blood count showed 2,030,000 red cells, 34,000 leucocytes, hæmoglobin 42 per cent. On December 20th the patient, who had for the previous couple of days seemed weaker, manifested some new symptoms. Two rapidly-growing subcutaneous nodules appeared on the forehead, one of them being distinctly tender, and bleeding from the nose again ensued, necessitating plugging.

For the next three days the patient became distinctly worse; severe epistaxis continued, which was barely controlled with the greatest efforts. The dulness over the sternum increased in size and intensity, larger nodules could be felt in the region of the retroperitoneal glands about the abdominal aorta, and in general the patient's whole condition was that of one moribund. Cultures from the blood were taken, but remained sterile. Examination of the blood on this, the last day of his life, showed a very much more marked leucocytosis, the lymphocytes being almost in excess of the red blood cells. Throughout the whole course of his stay in the hospital the temperature had assumed an irregular intermittent type. The patient died on December 23rd, less than nine weeks from the onset of his illness.

The case, then, as observed, is of interest in more than one particular: in the first place as illustrating the difficulties of diagnosis between leukæmia and Hodgkin's disease. With a leucocytosis, which varies from a proportion of 1 to 75 up to 1 to 120, or even more, it will seem scarcely justifiable to make an absolute diagnosis of lymphatic leukæmia, particularly when we know that occasionally the blood in Hodgkin's disease may assume exactly that condition, the leucocytosis being of the lymphocytic variety. Myelocytes were not present. The presence of numerous nucleated red cells will to many suggest the diagnosis of leukæmia, although such a condition might occur in the most varied forms of disease which produce hæmolysis. Among other points that may be of interest in connection with this case is the mode of onset, which corresponds with that described by Hinterberger (18) and others as showing the essential nature of such

processes. In collecting together a large number of cases note has been taken of the many instances of acute lymphomatous affections where the onset has followed upon some affection of the alimentary tract, such as stomatitis or ulcerative enteritis or similar conditions, all leading to the suspicion that the disease has arisen through the entrance of some toxic or infective agent by way of the alimentary canal. As will be seen from the history of our present case, the symptoms followed directly upon an acute and painful affection of the lips and gums.

Whether or not, then, finally, we are justified in recognizing in leucocytosis any special type of disease, our knowledge does not at present permit us to decide; but when we consider the difficulty with which author after author endeavours to satisfactorily classify and separate these different affections, it may not for the present seem unreasonable to still maintain under one group all these various forms —the leukæmias in their various manifestations, acute and chronic, lymphatic, splenic, and myelogenous, the similar varieties of Hodgkin's disease, and all such like affections characterized by a hyperplasia of the lymph glandular structures where no primary focus of disease can be found to account for such a condition.

It merely remains for us to record our indebtedness to Professor James Stewart, in whose clinic the patients were observed, and by whose kind permission the material was placed at our disposal.

Since presenting the above paper before the Canada Medical Association, one of us (C. F. M.) had the opportunity of observing and treating a patient in whom the symptoms were so suggestive of the intimate relationship between leukæmia and pseudoleukæmia, that it seemed to us well worthy of mention in this article. A full report of the case has recently been published in the *Montreal Medical Journal* by Drs. Robins and Argue, resident physicians of the Royal Victoria Hospital.

The patient was a young Canadian, aged 19, and was sent to the Royal Victoria Hospital on August 6th by Dr. A. E. Vipond. For two weeks previously he had been suffering periodically from epistaxis, high irregular fever, progressive asthenia and pallor. There was general glandular enlargement, and his blood condition remained

normal, so far as the leucocytes were concerned; in other words, the symptoms pointed definitely to acute Hodgkin's disease.

The blood examination on his admission revealed 3,166,000 red cells, 8,000 white, and 42 per cent. of hæmoglobin. For the first two weeks after his sojourn in the hospital his general condition improved, the leucocytes were not markedly increased at any time, nor were there any other notable changes. Suddenly, however, on the fifteenth day after entry, there was a marked change, with increased fever, recurrent hæmorrhages from the nose, and the blood examination within two days showed over 60,000 white cells to the c.mm. This leucocytosis persisted for a week, his condition otherwise getting progressively and rapidly worse. Life was prolonged but for one week more, and during that period the leucocytes again diminished in number, returning in about two days to normal, and on the day previous to death an estimate showed merely 14,000 to the c.mm. It was observed, too, that the uric acid increase in the urine was coincident with the subsiding leucocytosis.

In the illness then, which lasted in all about six weeks, there was a period where undoubtedly all the typical signs of acute leukæmia were present, while on other occasions the examination revealed the usual classical symptoms of acute Hodgkin's disease. Nor is this merely a sequence of a leukæmia upon that of Hodgkin's disease, inasmuch as later the symptomatology had returned again to that of the original malady.

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