consideration; and I may say at once that an unconditional compulsion might become too cruel to be carried out. We must not forget that the sufferers from a disease up to the present incurable have every claim to be pitied and cheered. What we can do, however, without any restriction is to spread the knowledge and the fear of this scourge and its infectiousness amongst the people of the parts of the globe wherever it does occur. For Iceland we can gladly say we may hope to see some success from the exertions we have made. The inhabitants are scattered about the coast line in some 4,000 houses. On our return home last year a popular treatise on leprosy, written by Dr. Ehlers and translated into Icelandic, was sent to every household on the island, where it is sure to be read and its illustrations carefully studied during the long winter evenings.

The suggestion of instituting a special hospital in Iceland where lepers could find an asylum was not entertained last year by the local Parliament for want of funds, as far as I understood, and the proceeds of various lectures which we gave for the purpose were only very small when compared with the outlay for even the most primitive asylum. But this year, an Icelandic priest having collected a large sum of money on the Continent, principally in France, I learned to my great satisfaction that it has been decided to erect a leper hospital with sixty beds in Reykjavik.

OBSERVATIONS UPON THE RELATION BETWEEN LEUKÆMIA AND PSEUDO-LEUKÆMIA.

By C. F. MARTIN, B.A., and G. H. MATHEWSON,

M.D., Lecturer on Pathology,
McGill University: Assistant Phy-
sician to the Royal Victoria
Hospital, Montreal.

B.A., M.D.

[From the Medical Clinic of the Royal Victoria Hospital, Montreal.]

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 diagnosed 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, apart from other clinical observations, it is absolutely impossible to make a satisfactory diagnosis. We have time and again observed in patients who were apparently suffering only from grave chlorosis, an enumeration of blood cells corresponding to that usually found in 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 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 specimen, 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, of 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, Askanazy¹ 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 localised, 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 unimpeachable or to convince other authorities on this subject.

Nor can one distinguish between the forms of multiple glandular enlargements or the varieties of splenic tumours, 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 recognised 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 of 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 recognised 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 observation, 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, characterised often by the presence of irregular fever, early enlargement of glands, and onset of hæmorrhages and a rapidly progressive lethal termination. Such is Ebstein's³ 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 at 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. Eichhorst⁴ 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 observe 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 slight 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 Ebstein³ 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 accordingly 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 upon 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 the 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 on 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 that 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, a much enlarged spleen, 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 Hodgkin's 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 others 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 overabundant 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 white cells concerning mainly the lymphocytes, the same class of cells which are increased in lymphatic leukæmia; indeed, it not infrequently happens, 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 the Hodgkin's disease has ended and where the lymphatic leukæmia began. It is upon the occasional occurrence of such events that Penzoldt¹⁵ and Palma⁶ 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 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 element 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 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 of 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. Gulland¹⁷ 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 characteristically 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 leucocyte 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.

(To be continued.)