Secondary or Symptomatic Leukæmia.

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The division of anæmias into primary and secondary has long been practised and accepted. That a similar division of leukæmias may conveniently be made, it is the object of this paper to demonstrate. So far as the writer has been able to ascertain, no paper has been written from this point of view, although certain French authors have come very near to it (Dominici [13], Emile Weil [59]). As a consequence, much of the material to be presented in favour of this thesis has been derived from a perusal of reports of cases which were written from some other point of view, and from which particulars of value for the writer's purpose are frequently omitted in the most aggravating manner. The evidence should, therefore, be rather judged as a whole than criticized case by case.

What is ordinarily called leukæmia the writer would call primary leukæmia, and this may be regarded as a disease of which the chief clinical and pathological features reflect the response of the blood-forming organs to a stimulus of which the nature is unknown. It is convenient to suppose that this stimulus is produced by the excessive destruction of leucocytes within the body, just as after a sublethal dose of benzene the red cells are destroyed in the body, and their products give rise to a characteristically extensive and irregular reaction of those blood-forming organs which are concerned in the formation of red cells.

In leukæmia, then, and in response, as we more or less plausibly suppose — the point cannot be argued here — to excessive leucocyte destruction, the blood-forming organs show a great and irregular exaggeration of white cell formation. Nor is this confined to the marrow, glands and spleen—i.e., the normal blood-forming organs of the adult. The liver also takes a share, and after death we find in Glisson's capsule a by no means inconsiderable amount of tissue, which is morphologically (and presumably functionally) identical with that of the marrow or glands, as the case may be. In this condition of the liver we have one of the surest criteria of the presence of leukæmia. Further search will reveal similar growths in other organs, and in organs, moreover, which are not associated with blood formation even in fœtal life. In all these situations we must assume the presence of

primitive cells, which are capable of forming blood cells under the influence of a sufficiently powerful stimulus. This assumption is supported by many facts which cannot be detailed here.

Now, for primary leukæmia we hypothecate the most powerful of all stimuli—viz., an excess of the products of leucocyte destruction, and consequently the resulting changes are better marked than in any other condition. Almost invariably, for example, there is so great a proliferation of white cells that the blood shows from five to fifty times the normal number of white cells. This, however, is not an essential of the disease; we know little or nothing of the mechanism by which the cells of the marrow are shed into the blood-stream, but clinical observation sufficiently attests that this is a very variable factor even in the individual case of leukæmia, and that the blood may in some cases or at some times be practically normal. Hence, although a "leukæmic blood-picture" is good evidence of the changes in the organs detailed above, its absence by no means excludes such changes.

It may be at once stated that in secondary leukæmia the full blood-picture of primary leukæmia is rarely met with, just as in the secondary hæmolytic anæmias—e.g., chronic benzene poisoning—the full, so-called "pernicious," blood-picture of Addisonian anæmia is not often met with.

Histologically, the secondary leukæmias fall naturally into two classes—viz., secondary lymphæmia and secondary myelæmia, these being the usual divisions also of primary leukæmia. The former seems to be especially associated with septic diseases, the latter with cancer.

Clinically—and here it must be admitted that much more information is necessary before anyone can venture to speak with assurance—it seems that we can recognize certain classes of cases more often associated with secondary leukæmia than others. Of course, in all these cases the leukæmia is purely a symptom, it is secondary to obvious or plausibly conjectured causes. Some of these classes can now be discussed, and mention will be made of the reasons for their inclusion and of apparently allied, but not certainly identifiable, cases.

Secondary Leukæmia in Septic Processes.

Cabot [8] has put on record four cases in which there was a blood-picture so similar to that of primary lymphæmia as to cause considerable misgiving to the attending physicians. Yet all these cases made a good recovery, and one at least was known to be well fifteen years later. In the latter case the lymphocytes reached 70 per cent. of all white cells.

It was that of a young physician, who infected his finger at an autopsy, and had thereafter swelling of the glands in the axilla of the same side, and later in the opposite axilla also. In the next case, one of persistent boils, the lymphocytes reached 86 per cent., and it is further noted that they were unlike the ordinary hæmic lymphocyte, in that they showed mitotic figures and other irregularities. One may legitimately attach some importance to this fact when a diagnosis of leukæmia as against lymphocytosis is under consideration. Cabot's other two cases were of a more doubtful type. The blood, indeed, was that of leukæmia, but the clinical signs seems to have been very indefinite, so that the diagnosis of primary leukæmia is not altogether excluded. In both, sore throat and enlargement of the glands were present. Dr. Braxton Hicks, of the Westminster Hospital, informs me that he has seen a similar case, and I remember also a case under the care of Dr. Gossage, in the same institution, which presented a lymphæmic blood-picture and swelling of the glands with a septic condition of the mouth. These cases all made a good recovery, and no autopsy was possible. The diagnosis must, therefore, rest on the blood condition and the fact that the glands were swollen, even those in no direct or indirect communication with any septic focus.

Lindsay Steven [53] reported a case of broncho-pneumonia in a child aged 1 year 10 months, in which the white cells reached 236,000 per cubic millimetre, of which 65 per cent. were mononuclears. They are referred to as lymphocytes, but W. K. Hunter, who examined some of the films, notes that some of them stained abnormally, so that we may assume that they were allied to the abnormal lymphocytes which one expects to meet with in leukæmia. The patient died, but the account of the autopsy is devoted to the condition of the lungs. Cabot also reports two cases of pneumonia in children, aged 1 year 3 months and 6 years respectively. Both seem also to have had pertussis. In the first the white cells reached 185,000, with 64 per cent. of lymphocytes, and in the second 94,000, with 66 per cent. of lymphocytes. A lymphocytosis is, of course, a common feature of pertussis, apart from the pneumonia (Meunier [39], Grulee and Phemister [21], Churchill [11], &c.). It may also be noted that high white cell counts, but with the polymorphs in excess, have often been met with in ordinary lobar pneumonia. Emerson [15] reports 105,000 white cells in a man aged 25, Cabot [10] 100,000 per cubic millimetre, Laehr [34] 115,000, and other authors similar figures. In none of the cases here quoted as secondary lymphæmia has there been an autopsy, nor has secondary lymphæmia any bad prognostic significance.

In secondary myelæmia associated with septic processes the data are more satisfactory. Austrian [2] reports a case of broncho-pneumonia with mastoiditis in a child aged 4, which proved fatal. The white cells reached 192,000, and the percentage of myelocytes was from 10 to 14 per cent. This is not a high percentage, but a little arithmetic shows that the total number of myelocytes per cubic millimetre was over 23,000. There was also a varying percentage of cells which could not be classified under any of the ordinary headings, and these were perhaps myeloblasts. The autopsy showed "marked hyperplasia" of the marrow, although there were "still some areas of fat remaining." The "large neutrophile myelocyte" was the predominant cell. The Malpighian bodies in the spleen were grey and "tremendously enlarged." The parenchyma of the liver was infiltrated with "mononuclear cells and occasional myelocytes." The bronchial and mediastinal glands were much enlarged. On these facts, especially the liver changes, the presence of a process to which the name leukæmia may properly be given seems established. Austrian, however, remarks categorically: "Leukæmia is definitely excluded by the history, by the physical findings, and by the necropsy." One may assume that he means that primary leukæmia is so excluded. This does not mean that he would necessarily exclude secondary leukæmia. This is the most complete case that I am able to bring forward in this class. Morawitz [40] records a case in which the patient was aged 16, and suffered from "a feverish malady of the heart without sequelæ." The white cell count was always low, but the myelocytes reached 15 per cent., and of these 1·5 per cent. were eosinophile myelocytes. Recovery was complete. Hirschfeld and Kothe [26] report a case of gangrenous appendicitis complicated by hæmorrhage from a duodenal ulcer in a boy, aged 10. The white cells reached 190,000 and the myelocytes 7 per cent. The highest total count of myelocytes recorded by him in this case is over 11,000 per cubic millimetre. The report is very short.

Fractures and Secondary Leukæmia.

The second class of cases, and one to which one draws attention with some diffidence, comprises those in which a fracture has been accompanied by peculiar blood changes. The classical case is that of Simon [51], in which an adult negro sustained a fracture of the ankle by having the leg crushed. On admission to hospital the blood showed merely a polymorph leucocytosis, but a week later the following changes

were noted—viz., the wound was septic, the spleen was enlarged, and the blood showed 50,000 white cells, with 15 per cent. of neutrophile myelocytes, 1·2 per cent. of eosinophile myelocytes, and 17·5 per cent. of mast cell leucocytes. A week later, the leg having been amputated in the meantime, the blood was almost normal, and three months later was quite normal. Simon appears to have been at some pains to search the literature for similar findings, but with little result. He says, however: "Hastings writes me that in two cases he has seen myelæmia with myelocytes between 3 and 7 per cent., the one being a severe crush of the thigh and femur, and the other one of the forearm, with no break in the skin and no evidence of infection." Wiczkowski [61] records the case of a man, aged 24, who also sustained a crush of the ankle, and in whom the inguinal glands on the side of the crush were enlarged ten days later. Soon all the glands and the spleen were enlarged, and the white cells reached 590,000 per cubic millimetre. The patient died, but no autopsy was permitted. The case is reported because the author claims to have infected animals from an emulsion of a recently excised gland, and the ætiology and exact nature of the leukæmia are not discussed. It is a peculiar coincidence that Hirschfeld and Kothe [26] also report a case in which there was a fracture of the leg and a leucocytosis of 108,000, but no differential count is given. The patient was a girl, aged 16. Wonderful theories have been built up on less remarkable coincidences, but one cannot help feeling that sepsis was probably the important factor in these three cases, and in any case there is not sufficient evidence to incriminate the fractures *per se*. Simon's case was certainly septic, and so also was that of Hirschfeld and Kothe, while in Wiczkowski's case the foot was swollen, and although sepsis is not specifically mentioned the whole report is very short and incomplete.

Cancer and Secondary Leukæmia.

This paper is the outcome of an original intention to collect from the literature cases of myelo-phthisic anæmia. This term has been used to cover all cases in which the marrow was physically encroached upon by new growth, &c., and in which anæmia resulted. So soon, however, as one came to consider cases of cancer with metastases in the bones, it was apparent that the nature of the encroaching growth was of far more importance than the area of marrow which it was able to displace. It was also noted that there might be many cancer metastases or other

growths in the marrow and yet no anæmia. Further examination of those cases in which blood changes did occur showed that there was a very distinct parallel with myelæmia. This was obviously not primary myelæmia, and was therefore thought of under the provisional title of secondary myelæmia. This soon brought to mind cases such as those already noted, and the conception of secondary leukæmia took shape.

It must also be noted that primary leukæmia itself is regarded by some as a cancer and as having particular affinities with round-celled sarcoma. Some authors have even included cases of primary leukæmia in papers on cases of cancer with bone metastases, but all cases to which a suspicion of such a mistake—as the writer holds it—attaches have been excluded from the list of some thirty cases of cancer with bone metastases here considered. In some of these the evidence of secondary myelæmia is overwhelming, and two or three of these will alone be considered in any detail. It may be stated that they include only cases in which mention is made of the blood condition.

The first case has not yet been published. It is that of a woman, aged 47, who was under the care of Dr. Hutchison at the London Hospital. She was also seen by Dr. Parkes Weber. The pathological report will be published by Dr. Turnbull shortly. I am extremely indebted to these gentlemen for the kindness with which they have permitted me access to the records of the case, and especially to Dr. Turnbull, who has shown me all the sections and specimens connected with it. The patient died from cancer of the breast and during life was very anæmic. The white cells were 22,000 per cubic millimetre, and the myelocytes 8·5 per cent. It is of interest that a blood count of this kind, which might be paralleled from the records of all kinds of widely differing diseases, was nevertheless associated with extremely extensive myeloid changes in all the organs. At autopsy the marrow was found to be almost entirely replaced by cancerous infiltration, and the same was true of the spleen, the liver, many of the glands, and the affected breast. The other breast was free from cancer, but nevertheless showed considerable areas of tissue which was composed of cells such as are met with in the marrow. Such tissue was also found about the cancer growths in other organs. It contained not only neutrophile and eosinophile myelocytes, but also foci of red cell formation, in the centre of which were seen primitive nucleated red cells, and at the periphery those more fully formed. The red cells in the blood also showed the changes which one meets with in primary myelæmia. Nevertheless, there were still some fatty areas in the marrow itself.

The case of Kurpjuweit [32] was very similar. The patient was a woman, aged 34. The primary disease was in the stomach. The liver, spleen and some of the glands showed myeloid transformation. The blood showed 11 per cent. of myelocytes, but the total number of white cells was not increased.

In the case of Kast [31], a man with carcinoma of the penis of eighteen months' duration, the spleen was myeloid and contained Charcot-Leyden crystals, the marrow contained the same crystals. The liver does not seem to have been examined microscopically, but it is noted in connexion with the glands that those which did not contain cancer were myeloid. The white cell count was rather remarkable, the numbers reaching 120,000 per cubic millimetre, but the myelocytes were only 1 per cent. These three cases are typical examples of secondary myelæmia.

It may be noted that Shoemaker [50] records a high count in a case of cancer of the stomach, the white cells reaching 125,000 per cubic millimetre, but gives no differential count, nor does he seem to have examined the bones after death. Austrian [2] quotes von Limbeck as recording a case of multiple cancer with 120,000 white cells per cubic millimetre, but I cannot find the account which seems to be referred to in von Limbeck's book. Cabot [9] records a case of cancer of the peritoneum in which the kidney and spleen were affected, and in which the white cells reached 152,000, but with these exceptions one has not been able to find any very high counts in cancer.

Mercury Poisoning and Secondary Leukæmia.

There are two cases of interest in this connexion, and they are brought forward here because of the simple nature of the presumed cause of the leukæmia. They are very incomplete. Moulinier [41] reports the case of a man who took an unknown but considerable quantity of bichloride of mercury. He died fifteen days later, and at autopsy the spleen was found to show " complete myeloid and erythroblastic transformation." There were no blood counts or further microscopical examination, but the writer mentions that there were many nucleated red cells in the sinuses of the spleen—if one may so interpret his phrase, " des lacs sanguins sans parois propres."

Beck [4], in another case of mercury poisoning, records that the spleen was enlarged and of soft consistence with opaque follicles. The blood showed myelocytes. Such cases might well form the inspiration of some useful research work.

Other Cases of Secondary Leukæmia.

Emile Weil [59] investigated cases of variola before suppuration had set in and found remarkable changes in the blood which were of short duration, being soon displaced by the usual polynuclear leucocytosis. He remarks apropos of the blood-picture: "En même temps co-existe toute la série des formes leucocytaires qu'on peut voir dans la leucémie myélogène." He also finds nucleated red cells but rarely, except in the hæmorrhagic form. He claims that he is the first to describe this "syndrome." Courmont and Montagard [12] covered the same ground and agreed with his "leukæmic" finding.

Labbé and Delille [33] record a case of hereditary syphilis in a child, aged 1 month, with enlarged spleen. The white cell count was increased and the mononuclears were altogether 85 per cent. Of these, 50 per cent. were large mononuclears. In the discussion which followed his communication several speakers emphasized the fact that this "anémie pseudo-leucémique" was only a symptom and not a disease and might be met with in syphilis, rickets, tuberculosis, and intestinal infections. Dominici [13] carried out some experiments on dogs with the idea of producing myeloid changes, and seems to have been very successful in experimental tuberculosis, typhoid, sepsis, and potash poisoning. He remarks that the hæmopoietic organs react as a whole to these poisons but does not bring the changes into comparison with those of primary leukæmia.

Dr. Turnbull informs me that he has always taught that the splenic anæmia of infancy described by von Jaksch was a myeloid leukæmia, and very kindly showed me slides from several cases which certainly seem very strongly to support that contention.

As already explained, it was the original intention of this paper to deal with cases of cancer with bone metastases as examples of myelophthisic anæmia. For this purpose a considerable number of cases had been collected from the literature before it appeared better to consider them from a different point of view—viz., as examples of secondary leukæmia. The accompanying table gives the results of blood examinations in thirty-six cases of cancer in which marrow metastases were found post mortem. Only a certain number of these can be cited as examples of secondary leukæmia, and some did not even show anæmia of any kind; but on the whole, one cannot help remarking that this is a very extraordinary series of blood counts and one not to be paralleled from the records of cancer without such metastases, or of any other

disease. The examination of the spleen, marrow, &c., in this series of cases is not always recorded, but when this is the case frequently gives valuable evidence of some degree of that process to which the writer would give the name secondary leukæmia. Three cases (those of Turnbull, Kurpjuweit [32] and Kast [31]) have already been referred to.

In three of these cases the red cell count was below one million, the lowest being 681,000 per cubic millimetre (Frese [19], Kurpjuweit [32]). Some of these low counts have depended in part at least on the presence of hæmorrhage during life (Houston [27], Harrington and Teacher [23], Turnbull, &c.), but in this lowest of all there is no mention of hæmorrhages except those in the retina. As in his other case Frese mentions that hæmorrhages were profuse during life there is no reason to suppose that he would not have done the same in this also had it been the fact. It may be noted that retinal hæmorrhages are mentioned in four cases out of the thirty-six. There are fifteen cases in which the red cells touched under two million per cubic millimetre—i.e., half of the cases in which the red cell count is recorded. This would not be the case in cancer without metastases. In Price-Jones's [45] thirty unselected cases only two showed counts below 2,000,000 per cubic millimetre. In many of the cases here detailed the blood-picture associated with Addisonian anæmia was very closely simulated, there being a colour index above unity in no fewer than seventeen cases, megaloblasts in at least thirteen cases, and poikilocytosis in most of those in which the point is referred to.

The blood-picture, so far as the red cells are concerned, seems to the writer to conform to one of three types, viz.:—

(*a*) Severe anæmia with relatively few nucleated red cells but many poikilocytes, abnormalities of staining, &c.—i.e., the so-called "pernicious" type. To this belong Cases 3, 4, 10, 12, 13 and 28 in particular (fig. 1). Probably the case of Epstein, not in this table, belongs here, as does that of Ehrlich, Case 35, in which no exact numbers are given.

(*b*) A type in which the large numbers of nucleated red cells seem to be the most remarkable feature. In this respect the blood condition approaches that seen in primary myelæmia and is uncommon in any other condition. Thus Wolfer found 29,000 nucleated red cells per cubic millimetre and the writer has met with 16,000. In my own case only about 2 per cent. were megaloblasts, and there was only one count of the six made which showed so many nucleated cells. In the other counts, however, the numbers were still from 3,000 to 5,000. Cases 5,

6 and 14 show counts of over 1,000, and Case 16 over 4,000 nucleated red cells per cubic millimetre (fig. 2). Several authors mention the presence of nucleated red cells without further specification.

(*c*) A type in which the blood is practically normal, or the red cell count even abnormally high. Price-Jones [45] records 6,390,000 red cells, with 95 per cent. of hæmaglobin, but even here there were some nucleated red cells. In two cases the writer has seen over 5,000,000, but in neither were there any nucleated red cells at that time. It must, of course, be admitted that many causes productive of a secondary polycythæmia may be in operation in cancer cases.

Since the mere recital of figures is a somewhat unsatisfactory method of conveying a graphic picture of the blood condition, the writer has devised a method, of which illustrations are given. This aims at giving in a diagram some idea of what one might expect to see in any one field under the microscope. The three types mentioned are thus set forth:—

The exact method of making a diagram is as follows: For every 100,000 red cells per cubic millimetre one is depicted in the diagram. For every 100 nucleated red cells one is depicted. If poikilocytosis is noted as "present," one-tenth of the cells in the diagram are represented as poikilocytes, if as "marked" or "many" then one-third, if as "extreme," "very marked," &c., then two-thirds. Megalocytes are represented on the same principle, and if desired polychromatophilia can also be indicated. If more than one nucleated red cell is to be shown (as in Case 14 for example), these are depicted as megaloblasts or normoblasts, according to the relative numbers of the two varieties in the original films.

It is naturally from a consideration of the white cells that we shall expect to derive indications of the presence of secondary leukæmia, but as has already been pointed out, the presence of only a few myelocytes in the blood is no proof that there is not a most extensive myeloid change in the organs (vide Turnbull's case). Of thirty cases in which the differential blood count is referred to, no fewer than twenty-four showed myelocytes. The highest percentages were 31·3 per cent. in a case of the writer's, 17 per cent. in a case of Kurpjuweit [32], and 18·7 per cent. in a case of Frese [19]. In two of these eosinophile myelocytes were present, while the other (Frese [19]) showed nc less than 11·7 per cent. of myeloblasts. Altogether seven cases showed above 10 per cent. of myelocytes. At least six cases showed myeloblasts. It is occasionally stated that cancer of bone gives rise to

eosinophilia, but this series shows no eosinophile count above 4·8 per cent. The total number of white cells is very variable, in twelve cases it was below 10,000—i.e., there was no leucocytosis. The highest number of white cells was 120,000 per cubic millimetre in the case of Kast [31] already referred to. Generally speaking, the total numbers of the white cells are not high—on the whole they agree very well with the counts in Price-Jones's [45] thirty cases.

Other evidences of secondary leukæmia are to be found in the organs, but the reports have very frequently proved useless as regards details, hence the material available for this purpose is small.

The marrow has differed very widely—sometimes it is almost absent from its usual sites, its place being taken by tumour masses or fibrous tissue. Where smaller masses of tumour have been noted lying amongst the cell-forming marrow, some reaction of the latter is often obvious. It was, however, absent in the case of Parmentier and Chairol [43], judging from the illustration they give, and was very slight in one of the writer's cases. This reaction may take various forms; most frequently the growth is surrounded by hæmorrhage, less often the marrow formation seems to have been inhibited in the neighbourhood of growths. In others, and perhaps the majority of the cases, the marrow shows the changes one would expect from the condition of the blood, but it is not clear that the presence of cancer determines any particular change in its immediate neighbourhood. In Turnbull's case, however, there was evidence in various parts of the body that the cancer growth had influenced the surrounding tissues in the direction of causing them to develop myeloid cells.

The spleen is mentioned in seventeen cases, and in twelve of these it was enlarged. Parmentier and Chabrol [43] are inclined to make splenomegaly one of the chief diagnostic points of the presence of bone metastases in cancer. It may be noted that sundry investigators—e.g., Price-Jones [44], Medigreceanu [38], &c., working on the transmission of cancer to mice, have noted that the spleen is usually enlarged to a considerable extent. The normal mouse spleen is a myeloid organ, so that the enlargement is of some interest in connexion with the myeloid spleens, which are associated with some of the cases here recorded. Of seven cases in which the spleen seems to have been examined microscopically six showed definite myeloid changes. It is true, of course, that the number of cases is small, but, on the other hand, the proportion is large, as was also the myeloid change extensive.

The liver has been less carefully examined than the spleen.

Houston [27] found "an indefinite iron reaction;" Turnbull found it extensively myeloid, Parmentier and Chabrol [43] seem to have found it enlarged, but merely state that it was fatty and had no growth. Kurpjuweit [32] found myeloid reaction, &c. One can only state that there is no evidence of much value except that of myeloid changes in two cases. The liver was more often the site of extensive growth than not.

The glands have been noted as enlarged in most cases, but microscopical examination has not been frequently reported. Turnbull found some myeloid glands, as did Kurpjuweit [32] and Kast [31], but all other notes deal only with the presence or absence of growth. Nevertheless, the presence of myeloid changes in the lymph glands of as many as three cases is a very noteworthy feature.

Other tissues are only noted as the site of myeloid growth in Turnbull's case. Such cases would be comparable to the "nodular" [56] variety of primary leukæmia—i.e., the clinical variety in which growths are found in the skin, &c. (i.e., in places where normally lymphoid tissue is not found). Again, this finding, although standing alone at present, is very strong evidence in favour of the identification of the process which it exemplified with primary leukæmia.

A few other signs or symptoms met with in leukæmia have been met with. Thus, in Parkes Weber's case the appearance of the retina from the description seems to have been very similar to that of leukæmic retinitis. Boggs and Guthrie [6] found in their case the Bence-Jones body in the urine, and this they have also found in three cases of leukæmia. It has also been found by other authors in leukæmia (Weinberger [60]). Several authors in this series, however, specifically exclude Bence-Jones proteinuria. In Kast's [31] case Charcot-Leyden crystals were noted in the spleen and marrow. These are isolated, but interesting, findings.

Details of cases are to be found in the appended tables and in the original papers referred to. It has been possible to include some cases in the tables of which mention has not been made in the paper—this is not to be understood to imply that they are necessarily of comparatively small importance, the fact being that the writer has continued to search the literature as occasion offered since this paper took its present shape, and has found it impracticable to incorporate all the new material except in the form of tables.

Conclusions.

What conclusions can be legitimately drawn from the material here presented, material which, so far as the writer has been able to ascertain, has never been previously collected with the idea of sustaining such a thesis as is implied in the title to this paper—viz., the existence of a secondary leukæmia comparable to secondary anæmia, in that both own (in many, but not necessarily all cases) some obvious ætiological factor, and are defined with sufficient clearness to prevent their confusion with what have long been designated primary anæmias, and with what one may now call, without fear of misunderstanding, the primary leukæmias?

It is obviously not for the writer to judge whether his thesis is sustained, or rather one should say his theory, for a thesis is an arguable hypothesis existing apparently for the purpose of being argued about, but a theory is an arguable hypothesis existing for the purpose of use as a substructure to as yet unattained information. The proof resides in the cases which have been referred to; they are here presented in a very much abbreviated, and to that extent biased, manner, but the full reports are open to any interested person. It has not, however, appeared to the writer that there is anything in any of these reports to invalidate the suggestions he makes, with the sole exception of the remark made by the Austrian on his case, which remark has been quoted in full. Apart, however, from the facts adduced, there are theoretical reasons which should lead one to expect a secondary leukæmic process to occur.

Leukæmia may be considered as strictly comparable to Addisonian, so-called "pernicious," anæmia. The latter, undoubtedly, represents the reaction of the blood-forming tissues to destruction within the body of red blood cells. Its blood-picture (poikilocytosis in an extreme form, high colour index, nucleated red cells, &c.) has frequently been produced by poisons which are known to have as one of their properties the destruction of red cells, and this destruction is, moreover, obvious in the blood-stream before the "pernicious" blood-picture develops. Of recent years the progress of Addisonian anæmia, or at least of allied anæmias with a similar blood-picture, has been materially modified by the removal of the spleen—an organ which the researches of Hunter [29], Banti [3], Gilbert and Chabrol [20], and others has shown to be essential to the full development of hæmolysis after the administration of an admitted blood poison. There is then a type of blood-picture

which is usually associated with extreme precedent hæmolysis in the body. In Addisonian anæmia it is commonly supposed that the hæmolytic agent is bacterial, but proof is wanting in any generally accepted form.

The writer *provisionally* accepts the hypothesis that the primary leukæmias are strictly comparable to Addisonian anæmia—that they are probably the reaction of the blood-forming organs to excessive destruction of white cells within the body and in all probability of bacterial origin.

Now as a hæmolytic type of anæmia may be found but rarely, and in most cases to a much less extent, in other processes than that to which the name of Addisonian anæmia was given by William Hunter, so also leukæmias, similarly rare and undeveloped, are to be met with. These are the cases with which this paper deals. It will be noted that in both cases there is an increased and not a diminished activity of the hæmopoietic organs.

There is, on the other hand, a type of anæmia in which the marrow activity is diminished—the not infrequently described cases of acute aplastic anæmia with a fatty marrow are examples of this. They are paralleled in the white cell series by the leucopenia with which they are accompanied, and probably also by that of the leucopenia in many other diseases. These are all leucopenias in which the marrow cells are diminished: there seems to be no exact parallel in reduction of the lymphoctye series.

A further type of anæmia is that which follows blood loss—i.e., external hæmorrhage. This would seem to be paralleled by the leucocytosis which accompanies it. The reaction to blood loss is, in either case, an increase in the activity of the marrow, and not a decrease, as the term "anæmia" might allow one to suppose. It is of interest that chronic and repeated blood loss "exhausts" the marrow, and with it the leucocytosis which gives way to a leucopenia.

Inflammatory leucocytosis the writer would suppose to be comparable to secondary polycythæmia — both probably depending on a biochemical process of which we know nothing. Both are capable of being invoked by comparatively simple bodies—e.g., phosphorus, carbon monoxide. The fact that secondary polycythæmia is a comparatively unimportant clinical feature and leucocytosis the opposite need not invalidate the suggestion that they are similar reactions in their essential nature.

The extreme polycythæmia of erythræmia is perhaps comparable to

myelomatosis or Kahler's disease in the white cell series. Ribbert's [46] case of erythroblastoma needs verification, but if established would destroy this parallel. It may be mentioned that, although the abnormal cells of myelomatosis do not gain access to the blood-stream as such, the enormous output of the Bence-Jones body in the urine suggests very strongly that the degree of proliferation differs in its manifestation and not in its extent from that seen amongst the red cells in erythræmia.

The above suggestions are not presented with the weight of evidence or length of discussion which they deserve, but the writer certainly feels that a comparison of the reactions of the red and white cell tissues (and perhaps of other tissues also) to different agents affords evidence in favour of the existence of a secondary leukæmia—evidence of a purely theoretical nature.

Taking the facts and the theory together, the writer makes the following suggestions, in which, so far as he can discover, he has not been anticipated by any other writer, although certain authors—e.g., Erb [18], Ziegler and Jochmann [63], Eppenstein [16], Huber [28], Strauch [54], Turck [55], Dominici [13], Weil [59], &c.—seem to have approached but not comprehended his point of view, viz. :—

(1) That leukæmia may properly be divided into primary (or idiopathic) and secondary or symptomatic.

(2) That secondary leukæmia may be either lymphatic or myeloid in structure and is seldom if ever as pronounced in its histological features as the primary form.

(3) That secondary leukæmia is comparable to secondary hæmolytic anæmia—i.e., to the form of anæmia which follows blood destruction in the body. It exists, as this does, but rarely in extreme forms and quite commonly in lesser degrees.

(4) The study of cases of cancer with bone metastases shows that the two are by no means infrequently found in conjunction in this disease.

(5) That the division of leukæmias into primary (or idiopathic) and secondary or symptomatic is a necessary expedient at the present time, although subsequent research may be expected to show that all leukæmias are dependent on ascertainable causes and are in that sense secondary.

Appendix.

Previously unpublished cases of cancer with bone metastases :—

Case I.—Dr. Parkes Weber has kindly given me permission to make use of and to publish this case. K. M., aged 32. No previous illness, one child alive and well. Present illness of five months' duration and commenced with weakness and vomiting after food. Five weeks ago had pain radiating to the back and right shoulder. Three weeks ago noticed jaundice. No diarrhœa. On admission to hospital was anæmic and of a bright yellow colour. The spleen and liver appeared enlarged, but were not distinctly felt. No pain or tenderness anywhere. Slight ascites. Pulse 116. Apical systolic bruit. Lungs, *nil.* No enlarged glands. Gums bleed easily. Urine: Specific gravity, 1023, marked Gmelin's reaction. No special indican. Trace of albumin. Four days later jaundice seemed less bright. Some diarrhœa. Temperature has been raised to about 100° F. on several occasions. The optic nerves were not affected. The right retina showed two whitish, slightly raised plaques which were bordered by red hæmorrhage. There were four or five other plaques with no hæmorrhage and partly covering the retinal vessels. Vessels normal. Left retina similar to right but no hæmorrhage. On the next day œdema of the bases of lungs and of the legs was noted. Patient died three days later. The fæces were acholic throughout her stay in hospital.

Autopsy (Dr. Parkes Weber): Brain not examined. Heart, 9 oz., nothing special. A little bile-stained fluid in left pleura. Lungs negative except old quiescent tuberculosis at right apex. Liver, 94 oz., full of umbilicated new growths. Complete obstruction of bile-ducts about hilum. Stomach dilated. Pylorus surrounded by new growth, but mucous membrane little, if at all, affected. Spleen weighed 7 oz. and was soft and of a creamy red colour. Both suprarenals seemed to be occupied with some whitish new growth, but the kidneys presented no naked-eye abnormality. Many retroperitoneal and other intra-abdominal glands showed invasion by new growth. Left humerus sawn through longitudinally to show the bone-marrow of the shaft, which was practically replaced by innumerable small nodules of new growth separated from each other by red marrow—i.e., red metaplasia.

Histology: Pylorus shows typical carcinoma. No hepatic cirrhosis nor myeloid transformation. Much new growth. Some of the vessels were filled with cancer thrombi and some apparently with organizing blood-clot. Spleen (two pieces cut) showed no myeloid transformation nor infiltration nor nucleated red cells. Ovaries and other tissues showed malignant growth. Marrow from humerus showed carcinoma metastases and red marrow free from fat cells; this was from the shaft of the bone. Blood from the heart showed a good many nucleated red cells.

Case II.—Under the care of Mr. Tubby at the Westminster Hospital. I am indebted to him for permission to publish it. The first three blood

examinations are reported by the kindness of Dr. Hebb and were made by the clinical clerk in his laboratory. The latter three examinations are by the writer. Unfortunately the clinical notes of the case are lost and no autopsy was possible. F. S., aged 39. Breast amputated and glands in axilla removed for spheroidal-celled carcinoma. Readmitted to hospital some months later. She appeared anæmic and slightly yellowish, but to the best of the writer's recollection had no other marked signs. The diagnosis of bone metastases was suggested, but not, I believe, on account of the blood changes. Certainly the blood examinations made at this time were not filed amongst other cases under cancer, but under myelæmia. Nothing is known of the further history of the patient.

Case III.—E. H., aged 51, under the care of Dr. Court in the Chesterfield Hospital, to whom I am indebted for permission to publish it. Autopsy and blood examination by writer. For somewhat less than two months the patient had suffered from "rheumatism"—i.e., pain in the bones and back. This did not yield to any of the usual remedies, and it was soon apparent that the diagnosis was less satisfactory than usual. Admitted to hospital with no other signs except the pain in the bones, which was extremely severe before death. Nervous system normal, no enlargement of glands, spleen, or liver, thoracic viscera apparently normal. A few days before death he was troubled with vomiting for the first time, the vomited matter containing nothing abnormal. He had also mental symptoms, being confused, and not appearing to appreciate the nature of his surroundings. Before death he was in a condition similar to that of Addison's disease, except that there was no pigmentation. The pulse was small, frequent, and of low tension, and there was persistent vomiting, restlessness, and mental symptoms.

Autopsy: Skull not examined. Large growth pressing on pancreas, but not involving it or the stomach and appearing to arise in the abdominal or retroperitoneal glands. The semilunar ganglia were not found, being involved in the new growth, but the adrenals were normal. Metastases in liver, lungs, and a few glands about the pancreas. Also in all the vertebræ, ribs and sternum. Lower end of femora and upper of tibia showed only fatty marrow, with the slightest trace of red marrow in one femur. The metastases were in many cases surrounded by areas of hæmorrhage.

History: The primary growth is a spindle-celled sarcoma. The liver contains secondary growths but no myeloid infiltration or other alteration. The marrow shows the presence of metastases in part surrounded by hæmorrhage, but not otherwise affecting the marrow tissue proper. There is little or no fibrosis. There is possibly a slight excess of nucleated red cells and of small giant cells, but this may be a local variation as only one piece of marrow was affected.

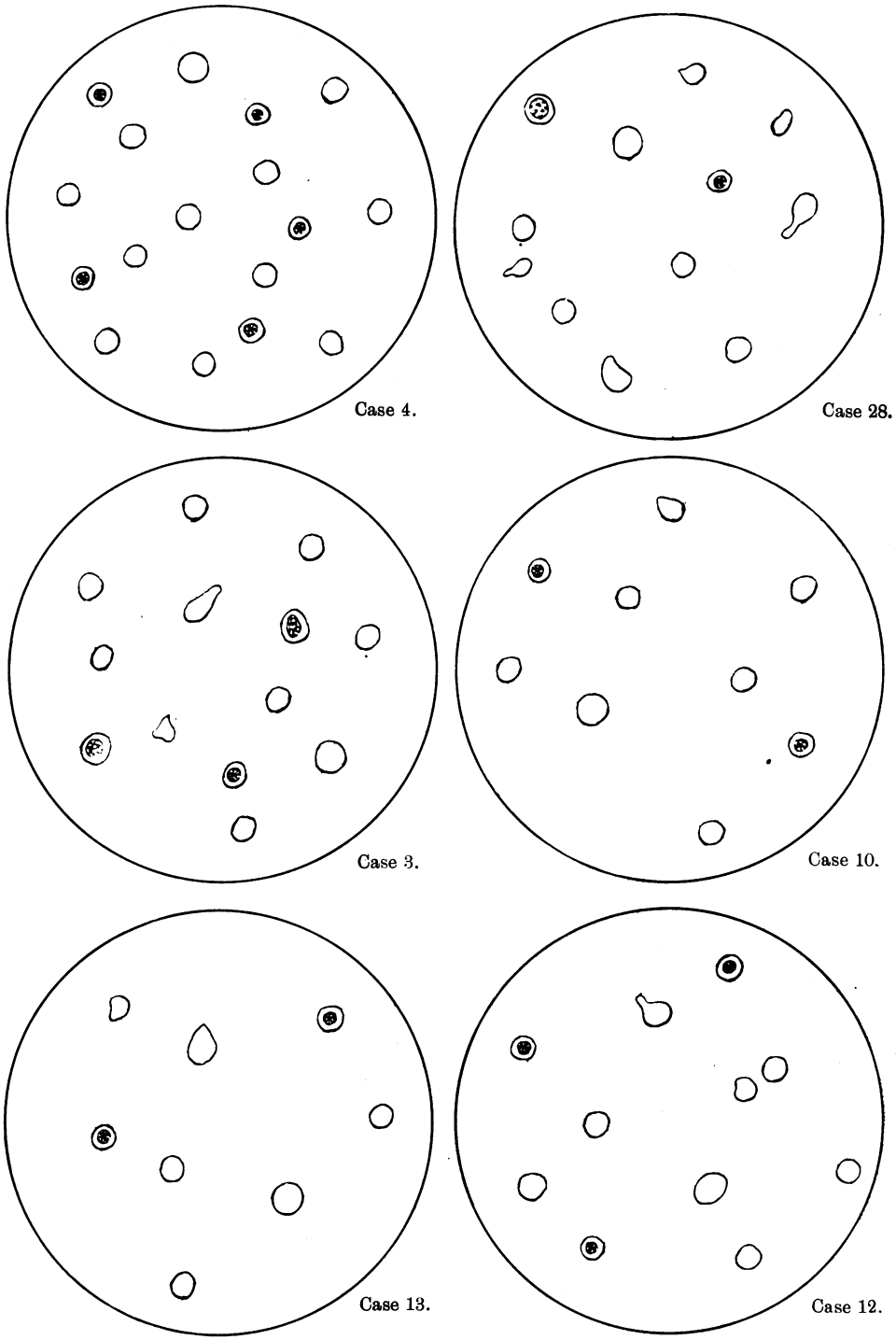

FIG. 1.

Cancer with bone metastases. Diagrams of blood examinations in cases showing severe anæmia.

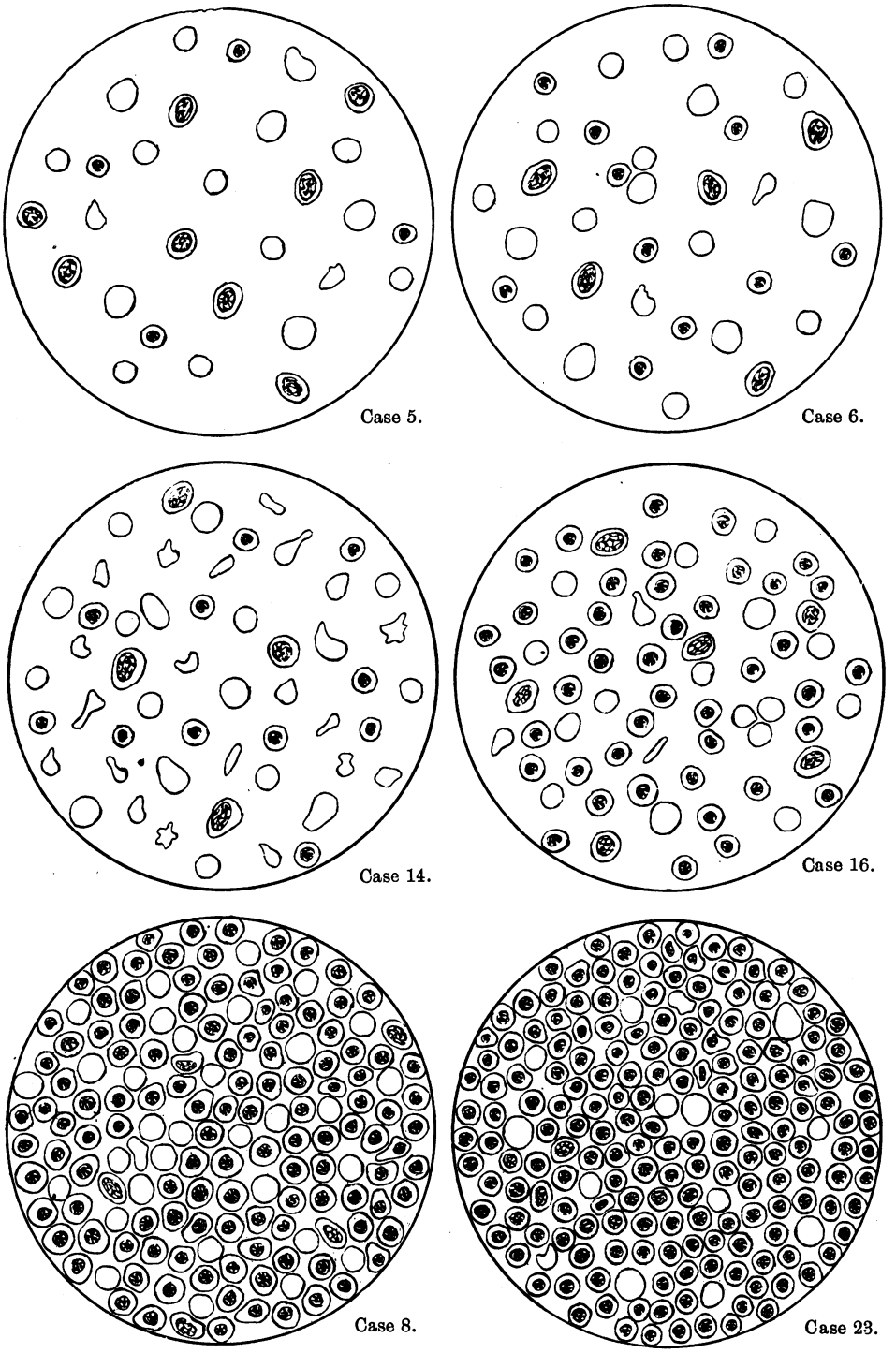

FIG. 2.

Cancer with bone metastases. Diagrams of blood examinations in cases showing excess of nucleated red cells.

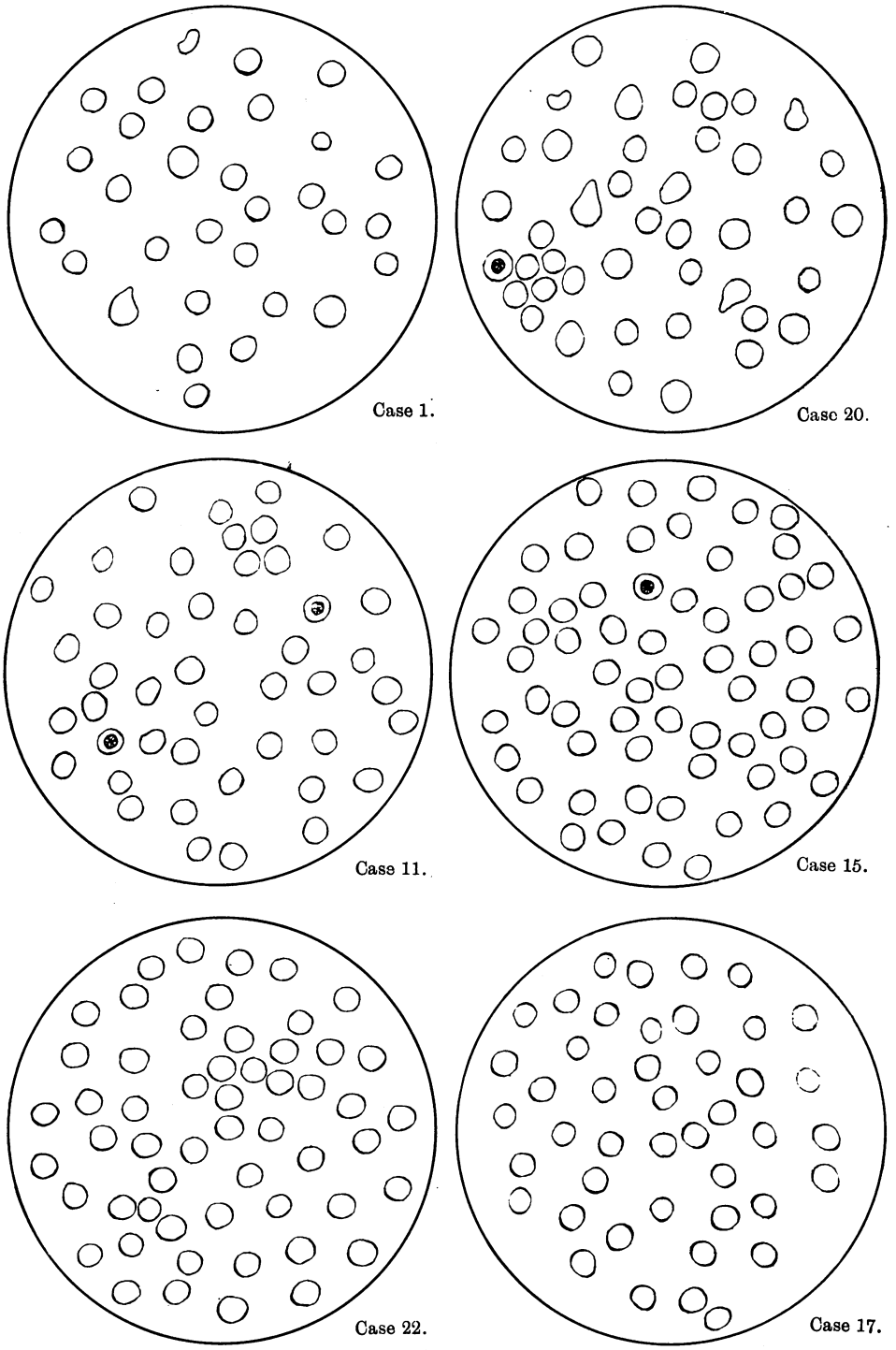

FIG. 3.

Cancer with bone metastases. Diagrams of blood examinations in cases showing little or no anæmia.

TABLE OF BLOOD EXAMINATIONS IN CASES

Case	Author	Age	Day of observation	Red cells per cubic millimetre	Nucleated red cells per cubic millimetre	Normoblasts to megaloblasts	Colour index	Megalocytes	Poikilocytes	Polychromasia
1	Hawley [24]	55	1	3,172,000	One seen	—	1·2	A few	A few	None
2	Harrington and Kennedy [22]	52	1	2,751,000	One seen	—	1·12	Many	Moderate	Slight
			6	2,325,000	Two seen	0:2	1·304	—	—	—
			10	3,000,000	—	—	1·03	Fewer	—	—
			14	2,610,000	—	—	1·307	—	—	—
			18	2,525,000	—	—	1·12	—	—	—
3	Houston [27]	42	1	2,300.000	603	16:29	1·06	Many	Many	Present
			22	1,600,000	480	27:13	1·03	Many	Many	Present
			59	1,070,000	88	6:2	1·38	Many	Many	Present
			289	1,000.000	270	8:10	1·28	Many	Many	Present
4	Parkes Weber	32	1	1,056,000	204	100:0	—	—	Moderate	None
			6	1,248,000	446	—	1·25	Few	None	Marked
5	Harrington and Teacher [23]	64	1	1,600,000	924	4:29	1·09	Many	Moderate	Marked
			9	1,900,000	1,056	1:5	1·1	Many	Few	Marked
			17	1,800,000	1,120	5:9	0·9	Many	Few	Marked
			22	—	Present	10:23	—	Many	Few	Marked
6	Parmentier and Chabrol [43]	45	1	1,940,000	1,540	2:1	1·57	Many	Present	Present
7	Epstein [17]	—	1	—	Many	—	—	—	—	—
8	Wolfer [62]	37	1	1,550,000	25,900	—	0·483	Many	Present	—
9	Kurpjuweit [32]	51	1	3,250,000	Present	—	0·801	—	Few	Slight
			15	3,200,000	Present	17:7	0·781	—	Few	Slight
10	Kurpjuweit [32]	34	1	1,825,000	91	—	0·694	None	None	None
			10	718,000	177	10:1	1·42	Some	None	None
11	Kurpjuweit [32]	42	1	4,320,000	147	100:0	0·697	—	—	—
12	Frese [19]	26	1	2,400,000	None	—	0·937	None	None	None
			36	800,000	Many	100:0	0·812	—	—	—
13	Frese [19]	28	1	900,000	Moderate	100:0	1·16	Many	Moderate	Present
			13	681,000	Moderate	—	0·915	—	—	—
14	Price-Jones [45]	58	1	4,420,000	—	—	—	A few	A few	—
			6	3,760,000	—	—	—	Many	A few	—
			20	4,040,000	—	—	—	Many	A few	—
			38	4,450,000	180	100:0	—	Many	Many	—
			49	3,800,000	1,482	13:6	—	Many	Extreme	—
15	Price-Jones [45]	63	1	4,270,000	36	100:0	1·07	—	—	—
			8	4,490,000	—	—	1·08	—	—	—
			15	4,870,000	—	—	0·98	—	—	—
			29	6,390,000	72	100:0	0·75	—	—	—
16	Schleip [49]	33	1	--	--	—	—	—	—	—
			17	2,944,000	—	—	0·689	—	Present	—
			42	2,328,000	Few	100:0	0·869	—	—	Frequent
			48	1,984,000	Present	2:1	1·05	—	—	—
			49	—	4,860	14:3	—	Present	—	Marked

* These figures include

OF CANCER WITH BONE METASTASES.

Hæmoglobin per cent.	White cells per cubic millimetre	Polymorphonuclears	Eosinophiles	Mast cells	Transitionals	Small mononuclears	Large mononuclears	Neutrophile myelocytes	Eosinophile myelocytes	Myeloblasts	Complicating hæmorrhages
75	7,300	63·0	None	—	—	27·0	10·0	None	—	—	No
62	2,500	56·4	1·6	None	14·0	19·6	4·8	1·2	—	2·4	No
60	3,750	68·5	1·0	1·5	12·0	10·5	4·0	0·5	—	2·0	—
62	6,770	64·8	0·8	None	9·2	19·2	2·4	2·8	—	0·8	—
68	4,000	78·6	0·2	0·2	7·6	6·6	3·0	1·6	—	2·2	—
56	10,000	91·0	None	None	4·8	1·2	1·8	1·0	—	0·2	—
49	6,700	54·0	0·6	—	0·8	36·2	8·4	—	—	—	Yes
33	6,000	56·4	—	—	3·0	38·3	2·2	—	—	—	—
27·6	5,500	67·2	—	—	0·4	30·4	2·0	—	—	—	—
25·6	7,500	53·4	0·8	—	0·8	43·4	0·4	1·2	—	—	—
—	10,200	78·0	1·5	—	—	11·0	8·0	1·5	—	—	Slight
30	18,600	63·2	None	0·2	1·4	14·4	9·4	11·4	—	—	—
35	14,000	63·0	0·7	—	18·8*	16·7	—	0·8	—	Present	Yes
42	8,000	52·2	0·6	0·2	28·2*	13·8	—	5·0	—	Present	—
35	8,000	59·0	0·1	—	25·5*	13·5	—	1·25	—	Present	—
—	—	54·6	0·8	—	21·4*	17·2	—	6·0	—	Present	—
60	3,500	60·0	4·0	—	—	21·0	6·0	8·0	—	0·6	No
19	1:25 to 1:40	—	Two seen	—	—	—	—	Many	—	—	—
15	20,000	66·0	—	—	2·5	22·0	5·5	4·0	—	—	—
53	22,700	62 5	2·0	—	12·0	23·5		Many	—	—	No
50	26,600	29·5	1·5	—	11·5	46·5		16·0	1·0	—	—
25	9,100	48·4	1·0	Present	8·2	19·2	12·2	11·0	—	—	Yes
20	6,700	42·5	1·2	1·0	10·5	21·7	15·3	8·7	—	—	—
60	19,700	86·1	0·7	—	—	6·2	3·0	4·0	—	—	Slight
45	8,740	—	—	—	—	—	—	—	—	—	Yes
13	20,000	Increased	Normal	—	—	—	—	None	—	—	—
21	9,220	64·5	1·0	0·5	11·0	15·0	—	8·0	—	—	No
12	10,150	—	—	—	—	—	—	—	—	—	—
—	12,830	70·6	1·5	0·5	4·1	23 2		—	—	—	—
—	10,500	70·2	1·1	0·5	5·3	22·7		—	—	—	—
—	12,000	73·1	4·8	0·4	6·8	15·2		—	—	—	—
—	9,000	70·0	1·9	0·5	13·1	14·3		—	—	—	—
—	19,100	85·0	0·2	None	4·1	10·5		—	—	—	—
90	9,000	60·0	1·0	0 6	7·2	30·6		—	—	—	—
95	12,600	67·0	0·3	0·3	7·7	24·5		—	—	—	—
95	9,000	61·5	0·2	0·2	8·5	29·5		—	—	—	—
95	12,500	69·0	0·5	1·3	3·5	25·1		—	—	—	—
—	7,200	—	—	—	—	—	—	—	—	—	—
40	8,000	—	—	—	—	—	—	—	—	—	—
40	12,600	—	—	—	—	—	—	—	—	—	—
40	16,400	82·0	1·2	—	2·9	8·2	—	0·8	—	4·9	—
—	18,000	58·8	—	—	1·7	20·6	—	7·0	—	11·7	—

large mononuclears.

TABLE OF BLOOD EXAMINATIONS IN CASES

Case	Author	Age	Day of observation	Red cells per cubic millimetre	Nucleated red cells per cubic millimetre	Normoblasts to megaloblasts	Colour index	Megalocytes	Poikilocytes	Poly-chromasia
17	Schleip [49]	34	1	4,452,000	None	—	1·17	—	—	Present
18	Naegeli [42]	45	1	2,168,000	315	51:12	1·06	Many	Present	—
19	Ward	—	1	4,760,000	486	7:2	0·68	—	Slight	Moderate
20	Ward [58]	44	1	4,920,000	90	94:6	0·51	Many	Moderate	Marked
21	Ward [58]	41	1	4,725,000	None	—	1·2	None	None	None
			58	4,350,000	None	—	0·942	None	None	None
			300	5,290,000	None	—	0·619	Few	Few	Frequent
			660	4,780,000	23	94:6	0·694	Many	Many	Frequent
22	Ward	51	1	5,615,000	None	—	0·758	None	None	None
23	Ward [57]	39	1	3,850,000	A few	—	0·7	—	None	—
			15	3,460,000	5,520	—	0·695	—	—	—
			20	3,930,000	3,216	—	0·57	—	—	—
			41	3,360,000	3,565	30:1	0·865	—	—	Slight
			48	3,380,000	16,000	—	0·882	—	—	—
			55	4,270,000	4,333	49:1	0·718	—	—	—
24	Arneth [1]	25	1	1,072,000	Present	—	—	Present	Present	Present
25	Kast [31]	56	1	3,500,000	—	—	—	—	—	—
			3	3,150,000	—	—	0·873	—	—	—
			6	3,020,000	Few	—	—	A few	Few	Slight
26	Turnbull	47	1	2,150,000	Many	—	1·04	Present	Present	Present
27	Luzzatto [37]	—	—	Severe anæmia	—	—	—	—	—	—
28	Braun [7]	64	—	1,500,000	Present	—	1·0	Present	Present	Present
			—	1,200,000	Present	—	1·45	Present	Present	Present
			—	1,002,000	Present	—	1·5	Present	Present	Present
29	Hirschfeld [25]	63	1	1,000,000	Present	—	1·0	Present	—	—
30	Hirschfeld [25]	53	*a*	1,800,000	—	—	1·11	—	—	—
			b	1,500,000	Present	—	1·0	—	—	—
31	Rotky [47]	—	—	—	—	—	—	—	—	—
32	Sailer and Taylor [48]	—	—	1,110,000	Present	—	0·9	—	—	—
33	Bloch [5]	41	?	3,000,000	Few	100:0	0·83	—	—	—
			1	—	—	—	—	—	—	—
			20	1,700,000	—	—	0·70	Present	—	—
34	Israel and Leyden [30]	30	1	Moderate anæmia	Present	—	—	—	—	—
35	Ehrlich [14]	25	1	Severe anæmia	—	—	—	—	Present	—
36	Boggs and Guthrie [6]	37	1	4,000,000	—	—	0·925	—	—	—

OF CANCER WITH BONE METASTASES—(*continued*).

Hæmoglobin per cent.	White cells per cubic millimetre	Polymorpho-nuclears	Eosinophiles	Mast cells	Transitionals	Small mono-nuclears	Large mono-nuclears	Neutrophile myelocytes	Eosinophile myelocytes	Myeloblasts	Complicating hæmorrhages
105	7,600	58·6	0·8	1·6	3·9	35·1	—	0·7	—	—	—
46	6,000	66·0	None	—	3·2	19·0	—	6·0	—	2·0	—
65	10,800	50·7	0·6	None	10·2	31·2	4·8	2·4	—	—	No
50	9,000	68·9	0·8	0·5	2·9	23·3	2·7	0·9	—	—	No
115	3,700	51·0	0·4	1·8	2·2	42·2	2·4	None	—	—	No
82	7,500	53·2	2·4	1·2	0·8	41·2	1·2	None	—	—	—
65	6,700	50·0	4·2	0·6	7·6	34·0	3·2	0·4	—	—	—
66	5,800	49·0	0·8	None	7·6	41·0	0·8	0·8	—	—	—
85	8,560	68·0	0·2	—	8·6	21·4	1·8	None	—	—	No
56	20,300	60·0	3·0	—	1·0	23·0	13·0	—	—	—	No
			55				45				
48	23,000								—	—	—
45	13,000	50·0	1·0	—	—	24·0	25·0	—	—	—	—
58	28,333	51·2	1·0	0·2	5·0	8·8	2·0	30·9	0·4	—	—
60	31,875	47·6	0·8	1·6	3·2	9·6	1·2	31·0	—	—	—
60	21,250	44·2	0·8	—	14·4	11·6	5·4	23·6	—	—	—
—	23,400	75·0	—	—	—	—	—	7·0	—	—	—
—	110,000	—	—	—	—	—	—	—	—	—	—
55	114,000	—	—	—	—	—	—	—	—	—	—
—	120,000	96·17	0·42	Few	—	2·16	0·16	1·09	—	—	—
45	22,000	59·0	1·0	0·5	—	31·0	—	8·5	Present	Present	Yes
—	—	—	—	—	—	—	—	Present	—	—	—
30	8,400	—	—	—	—	—	—	—	—	—	—
35	9,600	—	—	—	—	—	—	—	—	—	—
30	10,700	—	—	—	—	—	—	—	—	—	—
20	30,000	78·8	0·5	—	—	4·6	4·6	11·0	—	—	—
40	15,000	—	—	—	—	—	—	—	—	—	—
30	20,000	+	—	—	—	—	—	Many	—	—	—
—	16,000	—	—	—	—	—	—	—	—	—	—
20	45,000	—	1·5	—	—		46·0	9·0	—	—	—
50	6,000	56·7	0·1	—	1·4	30·5	4·9	6·4	—	—	—
—	—	65·0	0·1	None	0·1	23·7	2·4	8·7	—	—	—
23	—	69·0	—	—	3·0	12·0	4·0	12·0	—	—	—
—	1:50	—	—	—	—	—	—	Many	—	—	—
—	—	Few	—	—	—	—	—	Many	—	—	—
74	9,200	—	—	—	—	—	—	—	—	—	—

CASES OF CANCER WITH BONE

Author	Case	Age	Sex	Primary site	Nature of growth	Fractures	Bone pains
Frese [19]	2	28	F.	Stomach	Carcinoma	No	Yes
Kurpjuweit [32]	2	34	F.	Stomach	Epithelioma	No	Yes
Frese [19]	1	26	M.	Stomach	Carcinoma	No	Yes
Hirschfeld [25]	1	63	F.	Breast	Carcinoma	—	—
Houston [27]	1	42	F.	Breast	Scirrhus	No	No
Braun [7]	1	64	M.	Prostate	Carcinoma	—	Yes
Arneth [1]	1	25	M.	Stomach	Scirrhus	—	—
Sailer and Taylor [48] ...	1	—	—	Stomach	Carcinoma	—	—
Parkes Weber	1	32	F.	Stomach	Carcinoma	No	No
Hirschfeld [25]	2	53	F.	Breast	Carcinoma	—	—
Wolfer [62]	1	37	M.	Stomach	Carcinoma	—	—
Bloch [5]	1	41	—	—	Sarcoma	—	Yes
Harrington and Teacher [23]	1	64	F.	Stomach	Scirrhus	—	Yes
Parmentier and Chabrol [43]	1	45	M.	Stomach	Scirrhus	No	No
Schleip [49]	1	33	M.	Stomach	Epithelioma	—	Yes
Naegeli [42]	1	45	M.	? Stomach	Carcinoma	No	Yes
Turnbull	1	47	F.	Breast	Scirrhus	No	—
Harrington and Kennedy [22]	1	52	M.	Stomach	Scirrhus	No	Yes
Kast [31]	1	56	M.	Penis	Carcinoma	Yes	Yes
Hawley [24]	1	55	F.	Breast	Carcinoma	Yes	Yes
Kurpjuweit [32]	1	51	F.	Bile-ducts	Carcinoma	Yes	Yes
Ward [57]	5	39	F.	Breast	Carcinoma	No	—
Price-Jones [44]	1	58	F.	Breast	Carcinoma	No	—
Price-Jones [44]	2	63	F.	Breast	Carcinoma	No	No
Kurpjuweit [32]	3	42	M.	Stomach	Carcinoma	No	—
Ward [58]	3	41	F.	Breast	Carcinoma	Yes	Yes
Schleip [49]	2	34	M.	Appendix	Colloid cancer	—	Yes
Ward	4	—	F.	Breast	Epithelioma	No	Yes
Ward [58]	2	44	F.	Breast	Carcinoma	No	Yes
Ward	5	51	M.	Glands	Sarcoma	No	Yes
Boggs and Guthrie [6] ...	1	37	F.	Breast	Epithelioma	No	Yes

METASTASES, CLINICAL FINDINGS, &c.

Splenomegaly	Spleen myeloid	Hæmorrhages	Metastases	Lowest red cell count	Highest percentage of myelocytes
Yes	Yes	Retinal	Lungs, liver, pleura, glands, sternum, vertebræ, ribs, femur	681,000	8·0
Yes	Yes	Melæna, purpura	Liver, pancreas, glands, vertebræ (ribs free)	718,000	11·0
No	—	Retinal, epistaxis, gums	Lungs, brain, glands, ribs, vertebræ, skull, pelvis	800,000	None
Yes	—	—	Glands, liver, ribs, femur, skull	1,000,000	11·0
—	—	Retinal, purpura, epistaxis, hæmoptysis	Skin, omentum, liver, spleen, tibia	1,000,000	1·2
—	—	—	Sternum, femur, tibia	1,002,000	—
—	—	—	Lung, liver, spleen, glands, sternum, vertebræ	1,072,000	7·0
—	—	—	—	1,110,000	9·0
No	No	Retinal gums	Liver, suprarenals, glands, humerus	1,056,000	11·4
Yes	—	—	Adrenals, liver, clavicle, skull, femur, ribs	1,500,000	Many
—	—	—	Lungs, liver, pancreas, femur, vertebræ	1,550,000	4·0
Yes	—	—	Kidney, suprarenal, ribs, vertebræ, femur	1,700,000	12·0
Yes	—	Frequent melæna	Pleura, liver, diaphragm, œsophagus, kidneys, pancreas, ribs, femur, humerus, vertebræ	1,600,000	5·0
Yes	Yes	None	Femur, glands	1,940,000	8·6
No	—	—	Vertebræ, ribs, pelvis, skull	1,984,000	18·7
No	—	Purpura, epistaxis	Liver, vertebræ, sternum	2,168,000	8·0
Yes	Yes	Purpura, gums, vaginal	Glands, liver, spleen, ovary, femur, vertebræ, sternum, ribs	2,150,000	8·5
?	?	None	Two glands, sternum, ribs, femora (vertebræ free and tibiæ)	2,325,000	3·8
Yes	Yes	None	Liver, pleura, heart, glands, kidneys, ribs, sternum, vertebræ	3,020,000	1·09
—	—	—	Breast, femora, vertebræ, fibulæ, &c.	3,172,000	None
Yes	Yes	None	Glands, ovaries, thyroid, pleura, kidneys, adrenal, skull, ribs, vertebræ, sacrum, sternum	3,200,000	17·0
—	—	—	—	3,360,000	31·3
—	—	—	Glands, breast, pleura, vertebræ	3,760,000	None
—	—	—	Glands, breast, mesentery, peritoneum, liver, vertebræ	4,270,000	None
—	—	Hæmatemesis	Liver, glands, vertebræ	4,320,000	4·0
Yes	—	None	Glands, femur, ribs	4,350,000	0·8
Yes	—	—	Glands, mesentery, vertebræ, sternum	4,452,000	0·7
—	—	None	Glands, sternum, ribs	4,760,000	2·4
—	—	None	Vertebræ	4,920,000	0·9
No	—	None	Liver, lungs, pancreas, glands, vertebræ, ribs, sternum	5,615,000	None
—	—	—	Skull, ribs, femora, ilia, tibia	4,000,000	None

CASES OF SECONDARY LEUKÆMIA AND

No.	Author	Age	Result	Autopsy	Primary disease	Glands		Liver		Spleen	
						Enlarged	Myeloid	Enlarged	Myeloid	Enlarged	Myeloid
1	Cabot	20	R.	No	Sore throat	+	—	—	—	—	—
2	Wiczkowski	24	D.	No	Crushed foot—probably septic	+	—	+	—	+	—
3	Hirschfeld and Kothe	16	—	No	Compound fracture of leg—sepsis	+	—	—	—	—	—
4	Lindsay Steven	2	D.	Yes	Broncho-pneumonia	—	—	—	—	—	—
5	Cabot	6	R.	No	Pertussis, pneumonia	—	—	—	—	—	—
6	Lenoble	$\frac{3}{12}$	D.	Yes	Multiple abscesses	+	+	—	—	+	+
7	Lenoble	$\frac{2}{12}$	D.	No	Infective jaundice	—	—	+	—	0	—
8	Lenoble	3	D.	—	Von Jaksch anæmia	—	—	—	—	+	—
9	Cabot	—	R.	No	Septic finger	+	—	—	—	—	—
10	Labbé and Delille	$\frac{1}{12}$	—	—	Congenital syphilis	—	—	—	—	+	—
11	Turnbull	47	D.	Yes	Cancer	+	+	+	+	+	+
12	Cabot	20	R.	No	Persistent boils	+	—	—	—	—	—
13	Cabot	37	R.	No	Adenopathy (? nature)	+	—	—	—	—	—
14	Hirschfeld and Kothe	10	D.	—	Gangrenous appendicitis	—	—	—	—	—	—
15	Morawitz	16	R.	No	"Feverish heart malady"	—	—	—	—	—	—
16	Simon	—	R.	No	Fractured ankle—sepsis	—	—	—	—	+	—
17	Austrian	4	D.	Yes	Broncho-pneumonia and mastoiditis	+	—	+	+	+	—
18	Cabot	$1\frac{3}{12}$	—	—	Pertussis, pneumonia	...	...	...	...	...	...
19	Kast	56	D.	Yes	Cancer	+	+	+	—	+	+
20	Kurpjuweit	34	D.	Yes	Cancer	+	+	+	+	+	+
21	Parmentier and Chabrol	45	D.	Yes	Cancer	+	—	—	—	+	+
22	Kurpjuweit	51	D.	Yes	Cancer	+	—	+	—	+	+
23	Frese	28	D.	Yes	Cancer	+	—	+	—	+	+
24	Naegeli	45	D.	Yes	Cancer	—	—	+	—	0	—
25	Ward	39	—	No	Cancer	+	—	—	—	—	—

* Includes large

OTHERS REFERRED TO IN PRECEDING PAGES.

Red cells per cubic millimetre	Nucleated red cells per cubic millimetre	Hæmoglobin	White cells per cubic millimetre	Polymorpho-nuclears	Eosinophiles	Mast cells	Transitionals	Small mononuclears	Large mononuclears	Neutrophile myelocytes	Eosinophile myelocytes	Myeloblasts
—	—	—	9,000	28·0	1·0	—	—	71·0		—	—	—
5,600,000	—	—	3,600	36·0	—	2·0	—	62·0		—	—	—
—	—	—	27,000	—	—	—	—	—	—	—	—	—
—	—	—	590,000	—	—	—	—	—	—	—	—	—
—	—	—	87,000	—	—	—	—	—	—	—	—	—
—	—	—	108,000	—	—	—	—	—	—	—	—	—
4,800,000	—	90	236,000	—	—	—	—	—	—	—	—	—
—	—	60	227,000	33·6	0·5	—	—	50·2	15·2	—	—	+
—	—	—	72,000	—	—	—	—	—	—	—	—	—
—	—	—	94,600	30·0	—	—	—	66·0	—	—	—	—
3,749,000	—	70	31,000	40·3	5·0	0·5	0·7	49·0	4·3	0	0	0
—	Present	—	—	50·8	0·6	0·5	5·0	25·0	3 5	14·5	0·1	0·1
—	Present	—	—	51·0	1·7	0·6	—	6·3	34·4	6·0	—	—
—	—	—	20,000	—	—	—	—	70·0		—	—	—
1,984,000	300	—	Increased	8·0	7·0	—	—	32·0	50·0	3·0	—	—
2,150,000	Many	45	22,000	59·0	1·0	0·5	—	31·0	—	8·5	+	+
5,180,000	—	—	3,400	18·0	—	—	—	82·0		—	—	+
—	—	—	16,400	14·0	—	—	—	86 0		—	—	—
—	—	—	15,000	14·0	—	—	—	86·0		—	—	—
—	—	—	30,500	25·0	—	—	—	8·0	67·0	—	—	—
—	—	—	14,500	51·0	1·6	—	—	41·0	8·3	—	—	—
—	—	—	8,200	56·0	2·0	—	—	38·0	4·0	—	—	—
1,000,000	—	—	190,000	80·6	—	—	—	—	12·0	7·3	—	—
881,000	294	25	9,800	74·0	0·5	0·5	1·5*	19·0	—	4·5	—	—
1,300,000	210	35	4,000	65·0	0	0·5	5·0*	14·5	—	13·5	1·5	—
1,952,000	—	40	5,400	49·0	1·0	0	2·6*	41·2	—	6·2	—	—
3,200,000	—	60	9,800	62·0	3·4	0·6	9·0*	25·0	—	0	0	0
4,400,000	—	90	4,500	63·0	1·0	0	5·0*	31·0	—	0	0	0
—	—	—	—	83·0	—	—	—	—	—	—	—	—
—	4,000	—	50,000	56·2	6·2	17·5	—	3·0	2·5	15·0	1·2	—
—	Few	—	—	—	—	4·0	—	—	—	Few	—	—
—	—	—	—	59·0	4·0	1·0	—	30·0	10·0	0	—	—
4,860,000	—	87	130,000	—	—	—	—	—	—	—	—	—
—	1 464	—	183,000	52·0	4·0	—	3·0	24·0	0·6	12·0	—	4·4
—	1,512	—	126,000	56·0	3·0	—	2·0	21·0	1·6	14 0	—	2·4
—	3,456	—	192,000	54·0	3·0	—	2·0	22·0	4·0	12·0	—	3·0
—	—	—	103,000	35·0	0·5	—	—	64·5	—	—	—	—
3,150,000	—	55	114,000	—	—	—	—	—	—	—	—	—
3,020,000	Few	—	120,000	96·1	0·4	Few	—	2·1	0·1	1·1	—	—
1,825,000	91	25	9,100	48·4	1·0	—	8·2	19·2	12·2	11·0	—	—
718,000	177	20	6,700	42·5	1·2	1·0	10·5	21·7	15·3	8·7	—	-
1,940,000	1,540	60	3,500	60·0	4·0	—	—	21·0	6·0	8·0	—	0·6
3,200 000	Present	50	26,600	29·5	1·5	—	11·5	46·5		16·0	1·0	—
681,000	Present	12	10,150	64 5	1·0	0·5	11·0	15·0	—	8·0	—	—
2.168,000	315	46	6.000	66·0	0	—	3·25	19·0	—	6·0	—	2·0
3 360,000	3,565	58	28.333	51·2	1·0	0·2	5·0	8·8	2·0	30·9	0·4	+
3,380.000	16,000	60	31,875	47·6	0·8	1·6	3·2	9·6	1·2	31·0	—	+
4,270,000	4,333	60	21,250	44·2	0·8	—	14·4	11·6	5·4	23·6	—	—

mononuclears.

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DISCUSSION.

Dr. F. PARKES WEBER said that the bringing of all these cases together was very important for purposes of comparison and classification. He differed from Dr. Gordon Ward in regard to terminology. An absolute or relative increase in the white blood cells or in a particular kind of white blood cells, when the cause of the increase was recognized, should, Dr. Weber believed, be termed an absolute or relative *leucocytosis*, whether it were a general leucocytosis, a polymorphonuclear leucocytosis, a myelocytosis, or a lymphocytosis, and whether in nature it were reactive towards an infection or due to mechanical or toxic disturbance of the blood-forming organs. Other cases of absolute or relative increase in the white blood cells could be classed as leukæmias, whether myeloid—i.e., medullary (including myelocytic and myeloblastic) or lymphatic (including lymphocytic and lymphoblastic). Formerly a moderate increase of white cells was called a leucocytosis and a large increase was called a leukæmia or leucocythæmia. That plan was very misleading, but now Dr. Gordon Ward was grouping together under the term "secondary leukæmia" a great number of cases which he (Dr. Weber) believed should be included as examples of leucocytosis, myelocytosis, or lymphocytosis, because the cause of the increase of the white cells was known. The term "leukæmia" should, he believed, be reserved for those cases in which the cause of the absolute or relative increase in the white cells remained unknown—that is to say, the term "leukæmia" should be used only for those cases of increase of white cells which in the present state of knowledge were "primary." To speak of "secondary leukæmias" was, he thought, *a contradiction in terms*, and made the existing confusion in the nomenclature "worse confounded." He considered by analogy that an excess in the red blood cells, when the reason was known, should be called an "erythrocytosis," but when the increase was of unknown cause, that is to say (according to the present state of knowledge) "primary," it should be called an erythræmia. A case could not be classed as one of leukæmia merely because a myeloid transformation was discovered in the spleen or elsewhere. Such myeloid transformation might be reactive in nature and might be experimentally produced. Compare the experimental work of Von Domarus, R. Herz, A. Werzberg, F. Albrecht, &c. See also Moulinier's paper on "Complete Myeloid Tranformation of the Spleen in Subacute Poisoning by Perchloride of Mercury."[1] A condition of osteosclerosis occurred in some cases of myeloid leukæmia and a condition of bone-softening (from absorption of bone salts) in others, but he (Dr. Weber) did not believe there were any cases in which it could be reasonably supposed that a leukæmia had developed as a result of osteo-sclerosis. He was glad to find that Dr. Ward had not included such cases as examples of "secondary leukæmias."

[1] *Arch. de Med. Navale*, Par., 1903, lxxx, p. 347.

In a case of myeloid leukæmia (spleno-medullary leucocythæmia) accompanied by acute Ménière's symptoms, which he (Dr. Weber) described in 1900,[1] the new bone formation in the bones examined (bones of the ear) was evidently a result of (or part of) the leukæmic disease. In a case of myeloid leukæmia reported by Dr. F. W. Mott at the same meeting[2] the necropsy showed a condition of softening and rarefaction of the petrous bone, probably likewise in some way a result of the leukæmic disease (the softening probably being a more direct effect, and the new bone formation a more chronic and "reactive" process). He did not think that there was sufficient reason for applying the term "leukæmia" to so-called splenic anæmia (pseudo-leukæmia) of infants. If the exciting cause of what one now called leukæmias (what Dr. Ward termed "primary leukæmias") ultimately became known, there should be no leukæmias left in medical terminology, for to speak of "secondary leukæmias" was (as already stated) to introduce a "contradiction in terms"; all leukæmias could then be grouped amongst the leucocytoses.

Dr. GORDON WARD, in reply, apologized to Dr. Parkes Weber for having withdrawn certain cases from his paper since he showed him a draft. If he understood his criticisms aright, they were directed to disputing the whole basis of the theory of secondary leukæmia. He would reserve the term "leukæmia" for what he had called "primary leukæmia," and all other conditions he would refer to as leucocytosis, myelocytosis, &c., according to the predominant cell in the blood. To his mind, the condition of the blood itself as discovered in one or two examinations of that in some cutaneous area was as often as not a very misleading factor in the diagnosis of blood diseases so-called. He had therefore endeavoured to focus attention on the change in the organs, although he admitted that in this paper he, to a large extent, had to depend on cases which were very partially examined and in which these changes were sometimes more a matter of inference than of ascertained fact. He most certainly believed that we could distinguish at least two kinds of hæmopoietic reaction to sepsis — i.e., the ordinary polymorph leucocytosis which was not accompanied by changes in the spleen, glands, or liver, and the "secondary leukæmia" in such cases as those of Austrian, in which there were changes in the organs and in which the blood approximated to that of primary leukæmia. Both of these conditions could of course be produced experimentally; that this should be the case was no argument against their essential difference. The conception of secondary leukæmia harmonized and reduced naturally to one group a great number of anomalous cases, of which the cases of cancer with which he had dealt were good examples. It had long been desirable that these cases should be harmonized, for they had hitherto merely existed as exceptions which had seemed to invalidate otherwise acceptable rules. Secondary leukæmia, of course, was hardly ever a very marked

[1] *Med.-Chir. Trans.*, Lond., 1900, lxxxiii, p. 185.

[2] *Med.-Chir. Trans.*, 1900, lxxxiii, p. 209.

condition as seen in the blood-stream, and in this respect resembled secondary anæmia. This was an aspect of the question which might properly be emphasized, for the term "leukæmia" had most unfortunately come to denote in the minds of many people not a disease involving many organs, which it was, but merely a condition of the blood-stream. It could not be too strongly emphasized that there were hardly any true blood diseases—i.e., diseases of the circulating blood cells. There were, in fact, only two classes; in the first we found coal gas poisoning and the two varieties of enterogenous cyanosis, and in the second malaria and similar parasitic diseases. In none of these were the blood-forming organs affected except in a manner secondary to the affection of the blood cells in the circulation. In other diseases the determining cause acted primarily on the blood-forming organs, and what we saw in the blood-stream was only a more or less accurate reflex. It appeared to him that the cases of Cabot—which he called infective lymphocytosis—and the cases of Austrian and Turnbull were not examples of a process which was usefully described in terms of the blood findings. They were allied to each other as lymphæmia and myelæmia were allied to each other and histologically also they were leukæmias. He believed that the leukæmic reaction was by no means confined to the primary leukæmias, and these cases, to quote typical examples, if they were to be rationally classified at all, seemed to be necessarily included as examples of a process to which the name "secondary leukæmia" was alone applicable.