CLINICAL PATHOLOGY IN GENERAL PRACTICE

POLYCYTHAEMIA, LEUKAEMIA, AND CYTOPENIA

BY

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In most branches of medicine the excellent advice to "define one's terms" is neglected, but in haematology the necessity is inescapable, more particularly because the meaning of a term cannot always be derived from a study of its etymology. "Polycythaemia" is an example of this difficulty; it might well be expected to indicate an increase in number of all the cells in the blood, but by accepted usage its meaning is restricted to an increase above normal in the number of erythrocytes per cubic millimetre. It is qualified sometimes by the adjective "rubra," an illicit union of Greek and Latin, which, if distasteful to the classicist, gives it greater precision.

By derivation the word "leukaemia" means white blood, and this was exactly what Virchow intended to indicate when he devised it in 1845. The morbid anatomists have since shown us that its basis is an unexplained and uncontrolled proliferation of primitive leucocytes throughout the haemopoietic organs; leukaemia in the sense of white blood is an inconstant epiphenomenon, but the term is too well established to be replaced by one more logical.

"Cytopenia" means a reduction below the normal in the number of cells per cubic millimetre of blood: it is used in a non-specific sense and is applicable to erythrocytes, leucocytes, or platelets. Sometimes it is qualified by the prefix "pan," when it indicates a simultaneous reduction in all three of these elements.

POLYCYTHAEMIA

The significance of an erythrocyte count cannot be appreciated without knowledge of the limits of normal. Discombe, in an earlier article in this series,* has given the normal ranges as follows: erythrocytes 4,300,000–6,400,000 per c.mm.; haemoglobin 12–17 g. per 100 ml. (100% Haldane=14.8 g. per 100 ml.); and the packed red cell volume 42–48%. Polycythaemia rubra, therefore, may be defined as a state in which the erythrocyte count exceeds 6,400,000 per c.mm. This increase is almost invariably accompanied by a parallel increase in the packed cell volume and usually by a rise in the haemoglobin level.

Relative Polycythaemia

An increase in the erythrocyte count does not necessarily indicate an increase in the total number of circulating erythrocytes. It may be due to a reduction in the plasma volume and is then to be observed when dehydration occurs from a reduced intake of fluid, diarrhoea, vomiting, or profuse sweating; or when there is a sudden effusion of plasma into damaged tissues as in the shock of thermal burns and the crush syndrome. In all these conditions the increase in the erythrocyte count is transient and the cause evident; diagnosis is not in doubt, but blood examination often affords a useful index of the degree of blood concentration and thus of the reduction in plasma volume. This type of disturbance is sometimes described as "relative polycythaemia."

One variety demands special mention because it is often confused with polycythaemia vera. It is commonly seen

in middle-aged males in whom anxiety symptoms are salient; hypertension is present in at least half the patients and splenomegaly never occurs. The erythrocyte count is moderately raised, seldom exceeding 7,000,000 per c.mm.; the leucocyte count is below 10,000 per c.mm., and no immature forms are seen. Recent observations on the blood volume of such patients by J. H. Lawrence and his colleagues* have shown that the plasma volume is reduced and the total erythrocyte mass is not increased. The recognition of this disorder is important because treatment aimed at reducing the total erythrocyte volume is likely to be harmful. The condition is probably that described by Gaisbock in 1922 as polycythaemia hypertonica, although an attempt has been made to rename it, in the fashionable idiom, "stress erythrocytosis."

Secondary Polycythaemia

Polycythaemia, often termed secondary, occurs in anoxic states whatever their cause. The most striking examples are met with in cyanotic congenital heart disease in which the erythrocyte count may exceed 9,000,000 per c.mm. with a parallel elevation in the haemoglobin level. It is rare, but has occasionally been noted, in acquired (rheumatic) heart disease. In lesser degree it is common in pulmonary disease, particularly emphysema and fibrosis of the lung; it is a feature of diffuse atheroma of the pulmonary vessels. Its occurrence at high altitudes is well known, and it is seen when anoxia is due to decrease of the oxygen-carrying capacity of the blood in sulphaemoglobinemia or methaemoglobinemia. In Cushing's syndrome and occasionally with cerebral tumour its occurrence is well attested but ill understood. In all these varieties of secondary polycythaemia there is an increase in the total erythrocyte mass, but the plasma volume is usually somewhat reduced; splenomegaly does not occur, unless for some unrelated reason, and the leucocyte and platelet counts are normal.

Polycythaemia Rubra Vera

Polycythaemia rubra vera is a disorder of the haemopoietic tissues characterized by a marked and persistent increase in the total erythrocyte count. It is, however, a disease in which all the elements of the bone marrow proliferate, and leucocytosis with thrombocytosis is the rule. The clinical features are a cyanosis, plum-coloured in winter and brick-red in summer, with splenomegaly. The erythrocyte count may be as high as 12,000,000 per c.mm., and in about 10% of patients normoblasts are observed. The haemoglobin reading may exceed 20 g. per 100 ml. The packed cell volume (haematocrit) is constantly above 50% and may reach 75%. Three-quarters of the patients have a leucocyte count above 10,000 per c.mm. Blood volume studies have shown the total mass of circulating erythrocytes to be increased, sometimes to three times normal; the plasma volume is normal or somewhat reduced.

Diagnosis requires a persistently raised erythrocyte count without other cause for its elevation; in the absence of blood volume estimations a diagnosis of polycythaemia vera should not be entertained when the figure is below 7,000,000 per c.mm. It is made likely by an increase in

*Lawrence, J. H., Berlin, N. I., and Huff, R. L., *Medicine*, 1953, 32, 323.

the leucocyte count, due to an excess of myeloid cells, particularly when immature forms are present, by a raised platelet count, and by splenomegaly.

LEUKAEMIA

The cellular proliferation of leukaemia "breeds true," and thus three cytological types—myeloid, lymphatic, and monocytic—can be recognized. The process may be acute or chronic; however, only three well-defined clinical varieties exist because the acute forms, in the main, differ only cytologically and chronic monocytic leukaemia is of extreme rarity. These clinical forms are acute leukaemia, chronic myeloid leukaemia, and chronic lymphatic leukaemia.

The proliferative process affects the blood in three ways. First, the proliferated cells may overflow into the circulation, causing alterations in the peripheral leucocyte count which may be qualitative or both quantitative and qualitative; when the total leucocyte count is not increased the unfortunate epithet "aleukaemic" is applied. Secondly, by a process of crowding out or by differentiation of primitive cells to the leukaemic type, the other elements in the bone marrow are reduced in number, and anaemia, thrombocytopenia, and leucopenia ensue. Thirdly, secondary effects, probably related to splenomegaly, may occur; of these the haemolytic anaemia, which sometimes complicates chronic lymphatic leukaemia, is the most important.

Acute Leukaemia

The patient with acute leukaemia usually comes under observation because of anaemia or a haemorrhagic state. The degree of anaemia is variable, but often intense, haemoglobin levels of 3–5 g. per 100 ml. being common; the erythrocytes are commonly of normal size and well filled with haemoglobin; thus the mean corpuscular volume (M.C.V.) and mean corpuscular haemoglobin concentration (M.C.H.C.) are normal. Occasionally some macrocytosis is noted but the M.C.V. seldom exceeds $110 \mu^3$. In most instances regenerative phenomena, such as reticulocytosis, polychromasia, and normoblastosis are lacking. In the more acute varieties the platelet count is reduced when the patient is first seen; in all it falls progressively as the disease advances. Haemorrhagic phenomena, a prolonged bleeding time, diminished clot retraction, and a positive tourniquet test usually accompany its reduction.

The leucocyte count varies. It is probably true to say that normal or low figures are more common than high, particularly in the myeloid form. There may be a profound leucopenia of 500 cells per c.mm. or less or an extreme leucocytosis of 250,000 per c.mm. or more. The predominant cell varies with the type of leukaemia. In the acute myeloid form it is the myeloblast, and these cells may form 95% of the circulating leucocytes. In the leucopenic cases, however, the proportion of myeloblasts may be as low as 5%. It is noteworthy that the myeloid cells show no regular gradation from the most primitive to the most mature and that a "hiatus leukaemicus" (Naegeli) often separates the myeloblasts from the granulocytes (see Fig. 1). In acute lymphatic leukaemia again the total leucocytes count varies, but it is the rule for lymphoid elements to be present in obvious excess; in some cases these are easily classifiable as lymphoblasts, but frequently less primitive cells predominate. In monocytic leukaemia there is almost always a leucocytosis, although it is seldom above 30,000–40,000 per c.mm. Monoblasts and promonocytes predominate and usually form a high proportion of the total.

In the leucopenic forms, particularly when the proportion of primitive cells is low, firm diagnosis is impossible without examination of the bone marrow. The findings are usually characteristic; the marrow is richly cellular and 80–90% of the cells are primitive myeloid, lymphoid, or monocytic elements. In acute myeloid leukaemia the changes are sometimes less clear-cut, particularly when the

disease is not rapidly progressive; here the proliferation may be mainly at the level of the promyelocyte or less commonly affecting equally promyelocytes and myelocytes.

The diagnosis of acute leukaemia is not usually difficult when the results of blood and bone-marrow examinations are available. Aplastic anaemia may be suggested by the blood count; the leucoerythroblastic anaemia of skeletal carcinomatosis should not cause confusion, for the hiatus leukaemicus is lacking (Fig. 1). Leukaemoid reactions to infection or acute haemolysis seldom give rise to the preponderance of primitive cells seen in acute leukaemia. An exception to this is the myeloblastic response occasionally seen with generalized tuberculosis; it may be impossible on haematological grounds alone to distinguish this from acute myeloid leukaemia.

Chronic Myeloid Leukaemia

In chronic myeloid leukaemia there is seldom any difficulty in diagnosis. By the time the patient seeks advice the changes in the blood are usually fully developed and characteristic. Anaemia of moderate severity is the rule, the haemoglobin level lying most often between 6.5 and 7.5 g. per 100 ml.; the erythrocyte count is reduced in proportion, the anaemia being normocytic and normochromic; occasional normoblasts may be seen. The platelet count is normal or raised, sometimes to figures above 750,000 per c.mm. The striking alteration is, however, in the leucocytes: the total number is increased, most often perhaps to about 250,000 per c.mm., but counts of above 1,000,000 per c.mm. are sometimes seen. These high figures are due entirely to a great excess of myeloid cells; fully segmented neutrophils usually predominate, and if the cells are placed in grades it will be found that the numbers in each diminish with decreasing maturity. This dispersion is shown in Fig. 2, where the maturity of the myeloid cells of blood and bone marrow in a case of chronic myeloid leukaemia is compared.

Deviations from the picture described are rarely seen, except after treatment, when the blood may be indistinguishable from normal. Occasionally, however, chance

FIG. 1.—Histograms showing maturity dispersion of myeloid cells in the blood in aleukaemic myeloid leukaemia (left) and erythroblastic anaemia (right). Note the "hiatus leukaemicus" in the left-hand histogram. (Reproduced by permission of the editor of the *Proceedings of the Royal Society of Medicine*.)

FIG. 2.—Histograms showing maturity dispersion of myeloid cells in marrow and blood in a case of chronic myeloid leukaemia. (Reproduced by permission of the editor of the *Quarterly Journal of Medicine*.)

directs that the blood count shall be made before the characteristic changes have developed, and in such instances a persistent and unexplained neutrophil leucocytosis is discovered; when such patients are followed the typical haematological features of the disease are found gradually to appear. It is unlikely that a true leucopenic, or aleukaemic, chronic myeloid leukaemia ever occurs. Such a label has often been attached in the past to patients now recognized as suffering from myelosclerosis in whom the blood changes are those of leuco-erythroblastic anaemia.

In many typical cases of chronic myeloid leukaemia increase in the eosinophil and basophil granulocytes is to be noted; rarely eosinophils, and much more rarely basophils, predominate; these varieties are spoken of as chronic eosinophilic or basophilic leukaemia. More common is a form in which the features of polycythaemia rubra vera and chronic myeloid leukaemia both exist; in such cases neither the erythrocyte nor the leucocyte counts usually reach the high levels which occur in typical examples of either disease. This disorder has been given the name "chronic erythromyelosis."

Chronic Lymphatic Leukaemia

In chronic lymphatic leukaemia the only constant feature of the blood count is a relative, and usually also an absolute, increase in lymphocytes. In the early stages the total leucocyte count is often below 20,000 per c.mm., with lymphocytes making up perhaps 60–80% of the total. As the disease progresses the total leucocyte count rises and may reach figures in excess of 300,000 per c.mm.; with this increase there is a parallel rise in the number of lymphocytes, which may surpass 99%. The type of cell varies: in the more chronic form it is the small lymphocyte; in others a larger cell with more abundant cytoplasm and an indented nucleus—"the lymphosarcoma cell" of some authors—may occur. In all a characteristic feature is the uniformity of cell type. Lymphocytes are more fragile than other leucocytes and often fragment when films are made, to leave numerous "basket cells," "smear cells," or "Gumprecht's shadows." This is particularly true of the less mature varieties.

In the earlier stages of many cases of chronic lymphatic leukaemia anaemia is absent and the platelet count unaffected. After months or years lymphoid infiltration of the bone marrow makes its appearance and there is a progressive fall in erythrocyte and platelet counts. Terminally, profound anaemia and thrombocytopenia are common.

In a proportion of patients with this disease a symptomatic haemolytic anaemia supervenes, imposing upon the haematological features of chronic lymphatic leukaemia those of excessive blood destruction. A rise in the serum bilirubin, urobilinuria, a sudden aggravation of anaemia with reticulocytosis, and a positive Coombs test mark this complication.

Bone-marrow puncture biopsy is of limited value in diagnosis because lymphoid infiltration of the marrow is seldom intense in the early stages, when extreme peripheral lymphocytosis is lacking and anaemia slight.

CYTOPENIA

Cytopenia has already been defined as a non-specific term indicating a reduction in some or all of the types of cell of the circulating blood. In the present discussion it is used in the restricted sense of leucopenia or reduction in the number of leucocytes per cubic millimetre; erythrocytopenia and thrombocytopenia are considered only when associated with it.

The lower limit of the leucocyte count in health is about 3,100 per c.mm. (Discombe), although it is rare to meet figures below 3,600 per c.mm. Leucopenia may therefore be said to exist when the count falls below 3,000 per c.mm. It will be appreciated that this figure refers to the sum total of the leucocytes, a term which embraces all five varieties of normal white blood cell. In the present con-

nexion the neutrophils are of outstanding importance, because leucopenia is virtually synonymous with neutropenia. Lymphopenia occurs rarely and in practical haematology is most frequently the result of radiotherapy. The lower limit of the normal neutrophil count may be taken as 2,500 per c.mm. and of the lymphocyte count as 1,000 per c.mm. When leucopenia is profound the neutrophils are most affected, but all other varieties of leucocyte are also greatly diminished in number.

Ex hypothesi neutropenia or any other cytopenia might be brought about by defective formation of the cells in question, by their excessive destruction, or by some impediment to their emigration from the bone marrow. Little practical help is gained by attempting to compress the causes of neutropenia into these categories, because in many instances the operative mechanism is not understood. The following classification does little more than group together the neutropenias by the disorders with which they are associated.

Infections

There are certain infections in which leucopenia is commonly stated to be a characteristic or even a diagnostic feature. These are the enteric group of fevers, brucellosis, virus infections such as influenza and sandfly fever, and the typhus fevers. Application of the criteria proposed by Discombe shows that these infections are marked rather by absence of leucocytosis than by leucopenia. It is relatively uncommon for the leucocyte count to fall below 3,000 per c.mm. in any of them. In the differential count neutropenia with "shift to the left" is the main feature, usually with an absence of eosinophils.

Leucopenia is the rule in malaria and kala-azar; in the latter it may be extreme and associated with necrotic angina or other secondary infection. In both these disorders it is possible that the neutropenia is "splenic" in the sense considered below.

Infections of overwhelming severity, particularly some examples of septicaemia and generalized miliary tuberculosis, may be accompanied by neutropenia. It is difficult to distinguish infections, the severity of which is enhanced by pre-existing neutropenia, from those intense enough to paralyse leucopoiesis.

Bone-marrow Failure

When the haemopoietic functions of the bone marrow are destroyed by physical or chemical agents, pancytopenia results. There is a normocytic normochromic anaemia without evidence of blood regeneration; the leucocyte count falls, perhaps to a few hundreds per c.mm., with disappearance of granular cells; the platelet count is similarly reduced. Such damage may result from exposure to radioactive substances or may be caused by a rapidly increasing number of drugs and other chemical products. The same picture is sometimes seen without apparent extrinsic cause, when it is termed "idiopathic aplastic anaemia."

It is more common for damage to the bone marrow, whether physical or chemical in nature, to be less overwhelming and to affect predominantly one cytological series, often the leucocytes. This sequence is well seen with therapeutic irradiation and after such drugs as the nitrogen mustards and triethylene melamine. There is an initial slow fall in lymphocytes which is followed by a sudden and precipitous drop in the neutrophil count when large doses are used.

Cytopenia is a sequel of bone-marrow failure due to other causes. Leucopenia is the rule with the functional disturbance of leucopoiesis which accompanies the erythroblastic hyperplasia both of pernicious and of hypochromic anaemia. It is common when the bone marrow is invaded or replaced by abnormal cellular proliferations as in leukaemia, myelomatosis, carcinomatosis, and myelosclerosis. The blood changes in leukaemia have already been considered. In the three last disorders pancytopenia with-

out qualitative changes may occur; in carcinomatosis, but especially in myelosclerosis, a leuco-erythroblastic anaemia is common. This is marked by a normochromic normocytic anaemia with a moderate reticulocytosis and normoblastosis; the leucocytes are commonly reduced in numbers, but the differential count shows a "shift to the left" of the granular cells from a high percentage of segmented neutrophils to an occasional myeloblast with a regular reduction in the proportions of the intermediate classes as their maturity diminishes (see Fig. 1); there is thrombocytopenia. Leuco-erythroblastic anaemia is considerably less common in myelomatosis; in this disease the leucopenia is often more striking than the anaemia or the thrombocytopenia, but occasionally the blood is flooded with the proliferating cells to cause a "plasma-cell leukaemia."

Associated with Splenomegaly

Leucopenia, often with thrombocytopenia, marks many diseases in which there is massive splenomegaly. Examples in which this association is common are congestive splenomegaly (Banti's syndrome), Felty's syndrome, and Gaucher's disease. It is occasionally observed in Hodgkin's disease, Boeck's sarcoidosis, and various forms of reticulosis and reticulosarcoma causing outstanding enlargement of the spleen. This symptom-complex is sometimes termed secondary splenic neutropenia; a primary variety has been recorded in which the excised spleen shows only non-specific reactive hyperplasia.

Although splenectomy is usually followed by restoration of the blood count to normal, the exact connexion between the spleen and the leucopenia is uncertain. Examination of the bone marrow shows hyperplasia of the myeloid series, and thus distinguishes these cases from those in which leucopenia is due to aplasia. It has been suggested that the spleen exerts some inhibitory influence upon discharge of leucocytes from the bone marrow.

Immuno-neutropenia

This ungainly term describes a variety of neutropenia apparently due to antineutrophil substances of the immune-body type. Moeschlin and Wagner established this mechanism as operative in agranulocytosis due to amidopyrine*; the leucocyte antibody acts in the presence of antigen as an agglutinin, and destruction of agglutinated neutrophils is thought to proceed in the lungs. In agranulocytosis of this type the leucocyte count falls precipitously within an hour or two of taking the causative drug; figures of 200-300 per c.mm. with absence of granular cells are not rare. Bone-marrow changes vary with the duration and the intensity of the leucopenia; when short and mild most of the myeloid series, except the mature granulocytes, are well represented; with increasing severity and duration there is progressive disappearance of this series, starting with the most mature elements and finally leaving the bone marrow depleted. These changes, formerly attributed to maturation-arrest, are now thought to be due to active depletion of the bone marrow by the intense peripheral destruction of granulocytes.

The importance of this cause of neutropenia is not yet known. It may well be responsible in acute diffuse lupus erythematosus in which pancytopenia is the rule; it has been recorded in primary atypical pneumonia. It seems probable that it explains the common agranulocytosis of explosive onset seen not only after amidopyrine but with sulphonamide, thiouracil, troxidone, tripeleminamine, and many other drugs.

Cyclical or Periodic Neutropenia

This is a rare disorder, often starting in infancy, in which periods of extreme neutropenia alternate with periods in which the leucocyte count is within normal limits. There is no anaemia or thrombocytopenia, and bone-marrow

examination shows normal granulopoiesis. The leucocyte count will often show a pure neutropenia, sometimes with an absolute increase in lymphocytes and eosinophils. During the neutropenic phases infective phenomena are common. The cause is unknown and the course extends over many years; in some instances spontaneous recovery occurs.

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PAEDIATRICS AND CHILD HEALTH IN FRANCE

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In France, children's diseases occur against a background which is in most respects similar to that in this country, but there are certain differences of climate, race, and distribution of population, while social and economic factors are of even greater importance. The area of France is more than twice that of Great Britain, but the population is only 42 millions, of whom a considerably smaller proportion live in towns and suburbs; so the problems of rural medicine are important. Nevertheless, the highest infant mortality rates occur in the industrial and densely populated regions of the Nord and the Pas-de-Calais. Until 1941 the population had been declining, as a result of the low birth rate, for nearly a century, but this tendency has now been reversed by the generous maternity benefits and family allowances under social security, and in 1951 the birth rate was 19.4 and the natural increase in population 6.1 per 1,000. There is, in addition, a certain amount of immigration, and at present about two million foreigners are in the country, of whom the Algerians (400,000) form the largest group.

Wages are low, and the cost of living is higher than in this country, but wage-earners with children are greatly helped by the "allocations familiales," which often exceed the father's wages. There is a fixed payment for a child born within two years of marriage, a monthly allowance which reaches its maximum for the second and third children, and an additional payment if the father is the only wage-earner in the family. Examples of the family allowances are:

No. of Children	Mother Working	Mother at Home
1	—	1,725 fr. per month
2	4,385 fr. per month	11,285 " " "
3	11,000 " " "	19,625 " " "
4	17,610 " " "	26,235 " " "

**Acta haematol., Basel, 1952, 8, 29.*