

# RES MEDICA

Journal of the Royal Medical Society



## The Nature of Leukaemia

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### Abstract

The classification of leukaemia as a pathological process has proved difficult, as it exhibits features of more than one of the main disease types. It is most widely recognised as a neoplastic disease, but it does not behave entirely in this way; the remitting and relapsing course of the chronic leukaemias is not at all typical of the malignant diseases. In some respects, leukaemia resembles a profound metabolic disturbance, while its presentation and course in the acute form are similar to those of a fulminating infection. This last comparison is rather difficult since severe local infection and even septicaemia are sometimes found in association with the acute types of leukaemia. Although a viral agent has been established as causative in avian leukaemias, no micro-organism has yet been shown to be associated with the human forms of the disease. The uncontrolled proliferation of primitive cells of the leucopoietic system and the capacity of these cells to infiltrate various tissues with an eventual fatal termination is in keeping with a neoplastic process and may represent an extreme form, in company with such conditions as diffuse myelomatosis. However, local deposits of leukaemic tissue such as chloroma are not as common as the local type of myeloma.

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ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, May 1961, 2(4): 11-13

doi: [10.2218/resmedica.v2i4.359](https://doi.org/10.2218/resmedica.v2i4.359)

# THE NATURE OF LEUKÆMIA

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Based on a dissertation read before the Royal  
Medical Society on Friday, 18th November, 1960.

The classification of leukaemia as a pathological process has proved difficult, as it exhibits features of more than one of the main disease types. It is most widely recognised as a neoplastic disease, but it does not behave entirely in this way; the remitting and relapsing course of the chronic leukaemias is not at all typical of the malignant diseases. In some respects, leukaemia resembles a profound metabolic disturbance, while its presentation and course in the acute form are similar to those of a fulminating infection. This last comparison is rather difficult since severe local infection and even septicaemia are sometimes found in association with the acute types of leukaemia. Although a viral agent has been established as causative in avian leukaemias, no micro-organism has yet been shown to be associated with the human forms of the disease. The uncontrolled proliferation of primitive cells of the leucopoietic system and the capacity of these cells to infiltrate various tissues with an eventual fatal termination is in keeping with a neoplastic process and may represent an extreme form, in company with such conditions as diffuse myelomatosis. However, local deposits of leukaemic tissue such as chloroma are not as common as the local type of myeloma.

What more specific evidence exists to indicate that leukaemia is a neoplasia? Cytological study of malignant cells shows them to have certain general characteristics which include a high proportion of nuclear material in the cell, numerous mitotic figures and abnormalities of the nucleus, the presence of giant cell forms, and basophilism of the cytoplasm. In other words, these cells show rapid and disordered growth and division, and are immature. These criteria of malignancy are all fulfilled by the immature cells of the human leukaemias. Although mouse leukaemias are in some respects different from the human disease, certain basic similarities exist, and in the mouse the disease appears to be a neoplasm, responding to therapeutic measures which are effective against neoplastic tissue in general. It has been suggested that the initial disorder is not located in the leucocytes but rather in some mechanism which governs the proliferative activity of the white cell precursors. The question of the stimulus of leucocyte proliferation is a very interesting one. The leucopoietic tissues can respond to the invasion of the body by micro-organisms by a great proliferation which is promptly suppressed when the infection has been overcome. This "shutting off" of the response is critical and it has been proposed that leukaemia may result as a self-regulating growth after a period during which there is a reversible state of excessive proliferation of the cells under the stimulus of some humoral mechanism. Certainly, leukaemia in its acute form often follows a systemic infection after a variable period. On the other hand, some workers believe that the tendency to the development of the disease may remain latent for a long time and the initiation may depend on some disturbance of the normal physiological response to infection.

Leukaemia is a disease of leucopoietic tissue rather than a disorder of the peripheral blood. The peripheral blood represents a dynamic "pool" reflecting production, release from the marrow, extra-vascular migration and destruction of the leucocytes, and in health, therefore, may be a fairly good index of creation of the cells and their disposal. In leukaemia there is frequently a disturbance of this pool and consequently it may not reflect the production-destruction processes very well. This<sup>b</sup> is often seen in cases of acute leukaemia, where marrow aspirates show an abnormal accumulation of immature white cells which is not reflected in the peripheral blood at that time (Aleukaemic leukaemia), although eventually the abnormal process in the marrow will reveal itself in the peripheral blood. Leukaemias, which virtually always reveal themselves ultimately as a disturbance of the circulating white cells, either in numbers or in morphology, have been variously proposed as disorders of these processes of maturation, release, migration, and destruction, in addition to the obvious one of proliferation.

One of the most interesting theories is that leukaemia represents an arrest of maturation of white cells at an early stage in their development with consequent accumulation of these immature cells and with an accompanying proliferation of the precursors. This would result from a metabolic defect of the leukaemic cell either genetically determined or in response to some extrinsic factor such as a humoral agent or a virus.

In 1925, Minot and Isaacs showed that a transfusion of white cells in man resulted in a rapid disappearance of these cells from the circulation of the recipient and this led to the suggestion that leukaemia might be a disturbance of elimination rather than of production. Bierman and co-workers showed that transfused leucocyte elimination which is rapid in the healthy person is defective in leukaemias. It has been estimated that only about 1% of the body's living leucocytes are circulating and that the degree of saturation of the pool of non-circulating leucocytes may determine clearance rates. A high degree of saturation of this pool in leukaemia could explain the defective elimination. Certainly, it is hard to see how the extensive proliferative changes seen in the marrow could be secondary to impaired clearance, whereas the reverse could well be true. A fundamental physiological mechanism which is not well understood and which is clearly disturbed in the leukaemias is the process of release of white cells from the marrow.

There are two further interesting phenomena which may be considered in connection with leukaemia. These are the leukaemoid reactions and the relationship of aplastic disorders of the marrow.

The term leukaemoid reaction is used to describe changes in the blood and blood-forming organs bearing a close resemblance to those of leukaemia. The condition is not usually associated with the severe thrombocytopenia frequently observed in the leukaemias and this serves to distinguish the two conditions. The principal disorders associated with the leukaemoid reaction are severe infections, including tuberculosis, and widespread malignant tissue deposits. The explanation which is offered for the phenomenon when seen in infection is one of an exaggerated physiological response to the organismal invasion and in severe infections, such as septicaemia, white cell counts of as much as 100,000 per c.mm. with a proportion of immature types are found. Viral infections and whooping cough produce a high count of circulating lymphocytes, the peripheral blood resembling that found in chronic lymphatic leukaemia. All these reactions subside with the termination of the infection. Tuberculosis differs from the other infections in that it can produce an immense variety of marrow reactions ranging from aplasia to hyperplasia of

any one of the elements with such results as polycythaemia vera or thrombocytosis. Myelofibrosis may be of tuberculous origin and the disease here is essentially similar to the idiopathic type. It must be assumed here from the variety of disorders, that the mechanism is one of reaction to the bacillus, perhaps a hypersensitivity, rather than a general response to infection as described above.

When secondary malignant tumours involve the bone marrow extensively there is often found a severe anaemia and thrombocytopenia with the appearance of immature white and red cells in the peripheral blood. This condition is difficult to diagnose and it must be remembered that true leukaemia is frequently associated with malignant disease elsewhere in the body.

Preceding the development of a frankly leukaemic blood and marrow picture by a variable period, there is sometimes seen an aplastic state of the marrow involving most elements and this swings round to the opposite extreme quite quickly. Again, throughout the course of the established disease, there is a tendency to a swing to the aplastic condition for a short time. The metabolic processes going on at these times can only be imagined and it is possible that some physiological defence mechanism, perhaps an immunological response results in this aplasia with a subsequent emergence of a new line of genetically different cells. This might be part of the remarkable "side-stepping" property of the leukaemic cells evidenced by their similar response to presently available chemotherapeutic agents.

Leukaemia is at present a very challenging problem and development of successful therapy for the disease may well lead the way to treatment of all malignant conditions. Until the nature of the disease and its aetiology and pathogenesis are elucidated, therapy must be purely empirical. Big gaps still remain in our knowledge of the processes of maturation, release, and destruction of white cells. What mechanism underlies the spontaneous remissions so frequently observed in the disease and what governs the transformation of chronic leukaemia to the acute terminal form? Are the leukaemias of childhood the same disease as seen in the adult? What determines the change from a chronic lymphocytosis to chronic lymphatic leukaemia?

The chromosomal anomalies recently demonstrated in the chronic myeloid types and the absence of any consistent abnormality of this kind in the acute leukaemias are discoveries which at present pose more problems than they solve. Leukaemia is a disease of enormous complexity with difficulties on every side; much work remains for medical scientists in every field, in its investigation.