REFRESHER COURSE FOR GENERAL PRACTITIONERS**LEUKAEMIA—I. CLINICAL FEATURES AND DIAGNOSIS**

BY

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In an average general practice a man may well work for twenty or thirty years and never meet with a case of leukaemia of the classical type, such as his student memories would associate with an enormous spleen and a visual picture of the spectacular appearance of a blood film, the last perhaps being one of the few unforgettable relics of a practical haematology class. However, the chance of such an encounter has increased, since there is unfortunately no doubt that this dread and fatal disease is far more common than it was twenty years ago, and this not simply because types other than the classical one have come to be recognized.

In some forms there are neither the gross enlargement of the spleen or glands nor the unequivocal and striking changes in the peripheral blood. Indeed, commonly, there is in fact no "leukaemia" or "white blood" arising from a vast excess of leucocytes. Rather is the total of leucocytes not greatly increased or sometimes quite grossly reduced, giving rise to the paradoxical descriptive title of "aleukaemic leukaemia"—a title which appreciates the fundamental relationship with the classical form with regard to course and prognosis, but emphasizes the absence of the leukaemic blood picture. It is therefore interesting, and even justifiable, to speculate whether indeed the "leukaemia" of the disease is anything more than a symptom, since the disease can run a similar course without such a symptom even presenting. If this be so, then all methods of treatment designed merely to reduce the leucocyte count—namely, to effect haematological improvement—would seem to be no more than symptomatic, as they do not strike at the root of the disease. At the outset it is important to appreciate that the reduction of the leucocyte count of the peripheral blood, though often symptomatically beneficial, does nothing towards controlling the disease process. It is also important to know that similar clinical states and suggestive, even highly suggestive, blood pictures caused by certain infections and other primary conditions may closely imitate leukaemia and give rise to the so-called "leukaemoid" blood picture. In these states the prognosis is not necessarily serious, whereas in leukaemia it is inevitably fatal. It is therefore a fundamental rule never to make a diagnosis of leukaemia until the evidence is so unequivocal that no other alternative is possible.

Types of Leukaemia

From the aspects of diagnosis, prognosis, and treatment the leukaemias are best classified on a simple clinical basis as acute, subacute, or chronic, according to the urgency of symptoms, the degree of toxæmia, the fever, the prostration and exhaustion, all of which are prominent in the acute phases or types, whereas symptoms may be minimal or even quite unnoticed when the disease is chronic. Prognosis and response to treatment are inversely proportional to the degree of acuteness of the process.

On the other hand, from the academical or haematological aspect the disease can be divided into very many types. The precursors of each or all of the leucocytes which are found in normal blood may dominate the blood picture and so give rise to named types such as myeloblastic, myelocytic, lymphoblastic, lymphocytic, monoblastic, and monocytic. Numerous atypical forms also occur—for example, eosinophilic leukaemia—whilst allied diseases such as lymphosarcoma provide categories of their own. From the general aspect the main features of these anomalous types are most easily comprehended by their symptomatology.

Clinical Features

Leukaemia is a disease with protean manifestations. Numerous other diseases may be imitated and symptoms may present in any system or in any part of the body. This is because of the basic pathology whereby the mobile leukaemic cells infiltrate all the tissues of the body and, in some sites, may undergo proliferation. The leukaemic infiltration may be gross, thus accounting for enlargement of organs and pressure symptoms, or moderate, or it may be so minimal in some leukaemic states that pathologists even argue about the diagnosis. A leukaemic patient may therefore present at almost any of the special departments of a large hospital, for example, with neurological lesions, Ménière's syndrome, dermatological manifestations, dental trouble, visual changes, bone and joint symptoms sometimes resembling acute rheumatism, haematuria, purpura, abdominal tumour, glandular enlargement, bronchitis, and, indeed, what you will. It is, however, quite possible to select from this difficult and diverse medley of symptoms certain salient features or suspicious findings which bring the diagnosis within the realm of possibility and which certainly justify an examination of the peripheral blood—itself usually sufficient—if not the unequivocally diagnostic, but more extensive, operation associated with examination of the marrow.

Of general symptoms, those which most commonly present arise from the gradually increasing anaemia, which is such a feature of the disease, or the enlargement of the spleen (perhaps noticed or perhaps giving rise to painful traction) or glands. As to the anaemia: any complaint of increasing lassitude, fatigue, distaste for work, lack of energy, inability to concentrate, and, in advanced cases (those who will not readily admit disability), a shortness of breath are all worthy of a blood examination whether or no the spleen and glands are enlarged. This symptom may be the prelude of the simple chronic type, or it may be the history given when the doctor is called to the acute case—that is, one presenting with sudden purpura, gingivitis, stomatitis, fever, toxæmia, and other distressing symptoms. Any haemorrhagic manifestation, be it purpura, bleeding gums, haematuria, haematemesis, or haemoptysis, is worthy of

investigation by a blood examination, especially if the symptom is accompanied by asthenia or fever, or toxæmia.

Lesser degrees of gingivitis and stomatitis found in the chronic forms of leukaemia are perhaps the signs most worthy of suspicion, but are most frequently disregarded; all too often the patient is referred to a dental surgeon for local treatment. This is especially so when the manifestation is no more than a painful swelling of the gum around one tooth, usually a molar or premolar, suggesting a rather diffuse "gumboil" requiring treatment by tooth extraction. Thereafter, the socket does not heal, the patient gets worse, and is eventually discovered to be a case of leukaemia. This insidious presentation with a localized gingival swelling is most common with the monocytic type of the disease, a type which is not very amenable to the orthodox lines of treatment. The lesson to be learned from this knowledge is that any inflammatory, ulcerative, or necrotic lesion of the mouth, pharynx, or gums is worthy of investigation by a blood examination. The diagnosis may not be leukaemia, but this should be excluded, and in any case the examination may reveal a condition such as agranulocytosis, or a blood response suggestive of some particular infection. Splenic or glandular enlargement may be noticed by the patient, the former on account of increasing girth or because of pain from traction. On the other hand, these classical signs and symptoms may be entirely absent, especially in aleukaemic types of the disease, which, indeed, may be extremely insidious in onset.

In brief, most cases of the chronic types of leukaemia will present complaining of some symptom arising from the accompanying anaemia, and this is usually associated with splenic and glandular enlargement, which may have been noticed by the patient or may be elicited at the clinical examination. Gingivitis, stomatitis, or pharyngitis are also common, whilst Ménière's syndrome does not always need the opinion of an otolaryngologist.

The presentation in the acute disease falls into a class by itself, though often the final compelling features in someone in the full tide of his powers have been preceded for weeks or months by a feeling that all is not well, of increasing weakness, lassitude, fatigue, and depression. But suddenly there appears some haemorrhagic symptom, especially widespread purpura and, often, an offensive necrotic stomatitis and gingivitis, accompanied by high fever and a profound degree of toxæmia, which may kill the victim in as short a time as a week. Purpura, fever, toxæmia, and stomatitis should be sufficient warning that what is being witnessed is probably the final phase of an inevitably fatal disease, the nature of which can be readily established by a competent blood examination.

But the most searing tragedies arise in infancy, childhood, and adolescence, since the onset is often so dramatically sudden and the course unbelievably rapid. Any persistent, unexplained, and intractable anaemia, especially in childhood and adolescence, should lead to a suspicion of leukaemia: Nor should the suspicion be dismissed until one, and sometimes more than one, marrow sample has ruled the diagnosis out of court. In youth the disease may closely imitate acute rheumatism, with fever and toxæmia associated with swollen and painful joints caused by leukaemic infiltration.

At the other end of the scale the clinical picture in the aged may be unbelievably symptomless even with grossly enlarged glands and spleen. This is particularly so with the lymphatic type, which in the sexagenarian or older person may produce neither anaemia nor other prominent symptom, but may occasionally give rise to remarkable dermatological manifestations, such as the appearance known as *homme rouge*, which are, unfortunately, usually associated with intolerable itching. These very chronic types in the elderly and aged often persist for years, with or without treatment, and the subject may well die of some other disease without ever having exhibited any of the unpleasant or progressive or dangerous symptoms of leukaemia itself.

A rapidly growing tumour may be the first thing to be noticed in certain forms of leukaemia, as well as in lymphosarcoma. The latter appears to be an allied disease in which the histology of the affected glands is indistinguishable from leukaemia, though there may be no leukaemic blood changes, at least at the onset. However, most cases of lymphosarcoma eventually develop a leukaemic blood picture in the terminal phases, and this final event seems sometimes to be encouraged by radiotherapy.

Uncommon forms of leukaemia include chloroma, in which the local tumour arises beneath the periosteum of the bones, especially of the skull and thorax, and Mikulicz's syndrome of bilateral enlargement of the salivary and lacrimal glands.

Nature of the Disease

Because leukaemia may appear unexpectedly and suddenly or, in contrast, with great insidiousness at all ages, but most dramatically in the young, and most commonly in those who are in the full tide of their powers, the doctor is liable to be closely questioned about the nature of the disease, why it has arisen, and whether it is infectious or inheritable. Most of these questions are unanswerable.

In the *International Statistical Classification of Diseases* leukaemia is placed among the malignant neoplasms of lymphatic and haemopoietic tissues, and this probably provides the best answer to the laity in the present state of knowledge of the disease, since they can comprehend what is meant by a malignant or cancerous process and can appreciate not only its prognosis but also that little or nothing is known about its cause. There is no evidence whatever of the disease being infectious. The intravenous injection of leukaemic blood in human patients has not carried the disease, and all attempts to transmit it to lower animals by blood or by tissue have failed. As with almost all diseases, there have been rare cases of leukaemia in families, but the evidence for a direct transference of the disease in the human subject is not nearly strong enough to exclude coincidence.

Further evidence against the infectious nature of leukaemia is to be found from studies of the disease in infants and mothers. Thus, a leukaemic mother gives birth to healthy children, and no infant developing leukaemia in the first few months of life has been found to have leukaemic parents.

There is, however, one hazard of life which seems to contribute to the incidence of the disease—namely, overexposure or injudicious exposure, or even exposure intermittently over long periods of time, to x rays or

irradiation, the very means which, in graded and calculated doses, are used in an attempt to control the disease. Leukaemia is many times more common in physicians who practise radiology than in their colleagues.

Prognosis

Leukaemia is inevitably fatal with the methods of treatment so far available. Nor do these methods of treatment appear to prolong life to any material or appreciable extent. Much can be done, however, to improve efficiency and to relieve distressing symptoms, whilst it would be unthinkable to abandon all forms of treatment merely because the disease is incurable. Once the diagnosis is made the most difficult problem is to estimate the duration of life. Certain rough rules can be applied, but even these are not absolute, for they take no account of sudden remissions, or, equally, of sudden exacerbations. Thus, patients with acute, subacute, or chronic types may be expected to live for weeks, months, and years respectively. A case which is acute from the outset, with the exception of children, rarely lives for more than a few weeks and does not usually enjoy a remission, whereas the subacute case is more likely to do so. The average chronic case of myeloid leukaemia lives for two to three years, but it is most unwise to promise this time, since it is not often known exactly how long the disease has been in existence, and the intrusion of an unpredictable exacerbation can upset all estimates. It is as well to bear in mind that once haemorrhagic symptoms have appeared (and a frequent and ominous one is haematuria) the end is not far off. An old person with chronic lymphatic leukaemia may live for ten or more years, with or without treatment, and frequently dies of some other disease.

Pregnancy aggravates the leukaemic process; spontaneous abortion, likely to be followed by a fatal haemorrhage, is common. On the other hand, a leukaemic woman may give birth to a healthy child, and if pregnancy occurs there is no reason to terminate it.

Differential Diagnosis

In differential diagnosis the mind may naturally range over a long list of conditions in which splenic or glandular enlargement is found with or without anaemia, and some of these have a superficial clinical resemblance to leukaemia or a haematological picture which arouses suspicion. Most, if not all, can be confidently disposed of by an efficient marrow examination, for it is in the marrow that the leukaemic process invariably starts, and it is there that the disease has usually existed for months, or longer, before it is clinically revealed. The taking of a sample from the marrow should always be entrusted to an expert haematologist, and should not be undertaken by those who are not experienced. The so-called leukaemoid blood pictures which are associated with frank infections, especially in children, usually present no difficulty, with the possible exception of some virus infections, particularly the glandular fever or infectious mononucleosis group, and, rarely, with certain types of acute tuberculosis. A competent haematologist should have no real difficulty in differentiating the peculiar cells of glandular fever from true leukaemia, even though the Paul-Bunnell reaction is negative, and, if in doubt, a marrow specimen should make the diagnosis clear.

From the clinical aspect the doctor can be comforted by the fact that even the severest forms of glandular fever (including the anginose type with extensive and suggestive oral lesions) are unaccompanied by significant anaemia, or at least not by any anaemia of the severe grade, which is almost invariable with febrile toxic acute leukaemia. Likewise, with Vincent's infection of the gums and pharynx, when gingivitis may, similarly, raise the suspicion of leukaemia. Some of these cases may have peculiar blood changes, but not of a degree which should lead to confusion with leukaemia.

The most interesting, and, at the same time, the most difficult leukaemoid diseases, especially with regard to blood changes, are the conditions which give rise to so-called "leuco-erythroblastic anaemia." This descriptive term does not designate a specific disease. It means no more than an anaemia, which may be quite slight, associated with the presence of nucleated red cells (erythroblasts) and a few primitive leucocytes in the blood. It arises from a disturbance of the marrow due usually to a neoplasm in bone or to a secondary neoplastic deposit such as occurs quite commonly when the primary growth is in the prostate, ovary, breast, or thyroid. The tracking down of the primary cause may be tedious and sometimes quite unsuccessful during life, but a marrow examination should exclude all question of leukaemia. As would be expected, a similar suspicious blood picture arises with the uncommon idiopathic myelosclerotic and osteosclerotic conditions, and in such the spleen is also greatly enlarged, giving both clinical and haematological resemblance to leukaemia. Once again the marrow examination is the clue, but on account of the sclerotic nature of the marrow the sample itself is not easy to obtain without a trephine; this fact in itself is highly suggestive of the diagnosis.

MEDICINE IN THE DOMINIONS

SOME IMPRESSIONS OF A TRAVELLING PROFESSOR

Professor D. M. Dunlop, of Edinburgh, visited Australia, New Zealand, and Singapore as the Sims Commonwealth Travelling Professor for 1951. He has summarized his impressions in a report to the Royal College of Physicians, and we record here briefly some of the points he has made.

Australia

What struck Professor Dunlop in Australia was the excellence of the general practitioners, "probably the best men of their kind in the world." He was impressed by the type of men he met—their self-reliance, wide reading, skill, and enthusiasm. "In remote districts they were indeed doing men's jobs and made me feel very humble." Analysing the causes of this excellence, Professor Dunlop notes that the Australian medical student is drawn from the best type in the country. In Australia medicine is *the* profession to adopt. The young graduate holds his house appointment for at most three months, but it is customary for him to have many such short appointments before beginning practice. This is very good for the future general practitioner, though the short period of his appointment to each charge is less salutary for the hospital patients or for his temporary unit. In Australia, when a man goes into practice he often has to work miles away from specialists, and accordingly has to acquire self-reliance and skill. Professor Dunlop praises the high standard maintained by Australian universities in