

RADIO-ACTIVE PHOSPHORUS

IN

LEUKAEMIA

By

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PREFACE

It is a feature of the radiotherapist's work that he finds himself compelled to delve into many different fields of medicine, in none of which however he would claim to be expert. Thus, in addition to urology, laryngology, gynaecology, and others, the author was drawn into the realm of haematology. As a radiotherapist, his initial concern with leukaemia in 1946 was the treatment of patients with x-rays. It was impossible, however, not to become fascinated by this strange disease leukaemia, a disease which has defied our understanding for more than a century, and against which all our modern therapeutic armamentarium is but groping empiricism.

In addition to a general review of the leukaemic disease and its taxonomic, diagnostic, aetiologic and therapeutic problems, it is the object of this thesis to describe and discuss eight years' experience in treating leukaemic patients with radioactive phosphorus. Sections I and II of this thesis are therefore in the nature of a review, with the object of providing some perspective for what follows. Section III discusses the pharmacological features of radiophosphorus, and Sections IV and V represent original work by the author. Section VI provides summaries of the case histories of the sixty patients treated with radiophosphorus at the Christie Hospital and Holt Radium

Institute in Manchester, England. All of the patients discussed in this work were personally treated and managed by the author, except when they required chemotherapy. At such times treatment was supervised by Dr. Edith Paterson, in the same hospital, and close collaboration was maintained throughout the patients' lives.

In any thesis on leukaemia, if only in the interests of space, the writer is faced with the primary task of selectively excluding vast areas of modern thought and important research. An effort has therefore been made here to confine discussion to human leukaemia, rigorously eschewing animal work, no matter how temptingly germane such work might seem. Furthermore, since the main topic in this thesis is the effect of radiophosphorus on chronic leukaemia, discussion of the acute forms of this disease is deliberately limited.

SECTION I

General Review of Leukaemia

- (i) History and Classification
- (ii) Clinical syndromes.
- (iii) Clinical pathology.
- (iv) Aetiology.

HISTORICAL SURVEY

The Leukaemic Disease.

Recently exhibited in the British Museum (1954) an osteogenic sarcoma has been verified involving a prehistoric dinosaur bone estimated at eighty million years old. It is probable that leukaemia is just as old a disease, indeed as old as life itself, but being essentially a soft-tissue lesion it has left no records of its lethal effects. The history of medicine is punctuated by discoveries that one disease, on closer inspection, did in fact consist of two or more syndromes, or that one disease process could manifest itself in diverse ways. Thus leukaemia seems to have concealed itself amongst the many mysterious "fevers" and "declines" of literature. It was not until the 19th century, when the microscope began to be applied to the field of medicine, that the blood and its abnormalities attracted attention.

According to Cecil and Loeb (1952) the disease "had been previously observed by Barth and others, and the initial examination of leukaemic blood had been made by Donne in 1839". Nevertheless most medical historians give credit for the first full description of the leukaemic syndrome to Hughes Bennett of Edinburgh who in 1845 described a case of "leucocythaemia". Bennett remarked that "unless it could be shown that

inflammation and fever were like processes, we must conclude that the alteration in the blood in this case was independent of inflammation so called". Later in the same year Virchow, Professor of Pathology in Berlin, published a similar case. He suggested that what might have been considered pus cells were in fact white blood cells and he called the disease "Weissers Blut" or leukaemia. By 1870 Neumann and others had studied the bone marrow changes associated with the disease, though it was not until the introduction of differential staining methods by Ehrlich about 1890 that detailed morphological studies became possible, and the various forms of the disease identified.

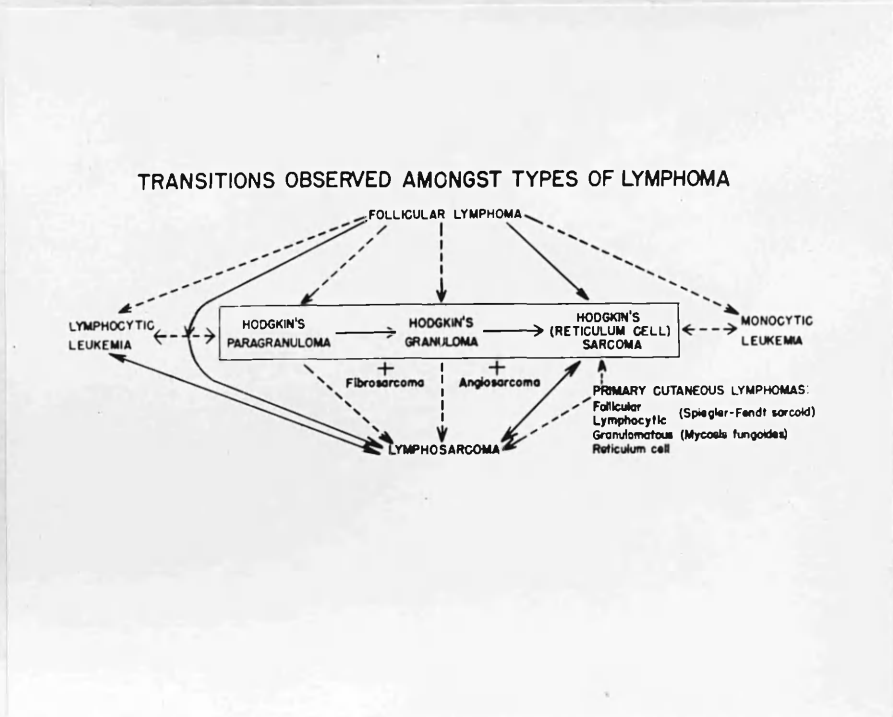
In 1865 Lissauer had found that an acute, febrile, and rapidly fatal disease was in fact leukaemia, and fundamentally similar to the already recognised chronic form of the disease. Thus the existence of an acute and a chronic type of leukaemia became one of the earliest attempts at classification, and by the end of the 19th century, thanks to Ehrlich's stains, myeloid, lymphatic, and monocytic types were clearly recognised, morphologically and clinically.

Based on the pioneer studies of Cohnheim, Metchnikoff, Ribbert, and others, Aschoff (1924) introduced the concept of the reticulo-endothelial system, as a functional entity, and this was considerably extended by the work of Maximow (1930), Pullinger (1932), and Robb-Smith (1938). The latter spoke of

the "progressive hyperplasia of reticular tissue with differentiation to one or more cell types", and he recognised their possible association with the leukaemias - the "haemic reticulososes". The relationship between the frank leukaemias and the various aleukaemic conditions, both myeloid and lymphatic, is still debatable, as also is the link between leukaemia and polycythaemia vera. The "lymphoid reticulosis" described by Israels (1953) may in some cases be the earliest phase of a chronic lymphatic leukaemia, though Willis (1948) has no doubt that lymphatic leukaemia is only the haemic expression of metastatic lymphosarcoma. However, Steinberg and Martin (1946) claim that the cells of lymphosarcoma are immunologically dissimilar to those of lymphatic leukaemia.

In addition to the many atypical leukaemic conditions there are various leukaemoid syndromes - responses to infections, toxins, metastases from malignant lesions, and myelosclerosis - all of which may be confusing. Indeed, Russell, in her "Essay on the Reactions of the Mesenchyme" (1949) observed that "The leukaemias are no doubt a dump heap of conditions, varying from acute haemorrhagic diseases with haemopoietic aplasia, to chronic lymphadenopathies showing some degree of leukaemia which may run a course of years".

Damashek (1951) suggests that all of these typical and atypical leukaemias are perhaps "only different reactions to the



Showing known (——) and probable (-----) transitions between the reticulososes. (Custer, 1952).

Figure 1.

same myelo-stimulatory principle", while Menkin (1947) believes that inflammation and neoplasia (leukocytosis and leukaemia) may yet "come to be regarded as quantitative variations of a single or perhaps several basic physiological disturbances". To Custer (1952) this whole field may be described as the "Borderlands Dim", with many recorded transitions of one lymphoreticular disease into another (Figure 1).

Witts, in his opening address to the 1954 Ciba Foundation Symposium on Leukaemia, observed that "most of us - I know not all of us, but most of us - feel that leukaemia is part of the total problem of cancer". Thus even the malignant nature of leukaemia, about which so much has been written during the past sixty years, calls at least for some philosophic doubt.

Classification of Leukaemia.

The classification of all blood diseases progressed rapidly during the first half of the 20th century, but with increasing knowledge, documentation, and the application of better techniques, the simple was seen to be complex, until at the present time, as Engelbreth-Holm has put it (1954), "the classification of the leukaemias is rather obscure, even more so than ten to twenty years ago". Unfortunately the pioneer workers such as Ehrlich, Naegeli, Sabin, Maximow, and many others, produced not only brilliant researches but confusing

terminologies. The confusion was such that a committee was set up, charged with the Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-forming Organs. This committee published its first report in 1949 but Whitby and Britton (1950) have remarked: "It seems unlikely that this proposed nomenclature will come into general use without further discussion". This is an understatement!

Though there are many attractive (and distracting) theories in the field of leukaemia research, adding daily to the complexity of the subject, what the clinician needs is not the exhaustive documentation of purist taxonomists but a simple working hypothesis to which he may cling in his daily work. The following classification from Whitby and Britton seems adequate:-

1. Myeloid leukaemia. Acute. Chronic.
2. Lymphatic leukaemia. Acute. Chronic.
3. Monocytic leukaemia. Acute. Chronic.
4. Atypical leukaemia and allied diseases.
5. Leukaemoid blood pictures.

These clinical syndromes will be briefly discussed.

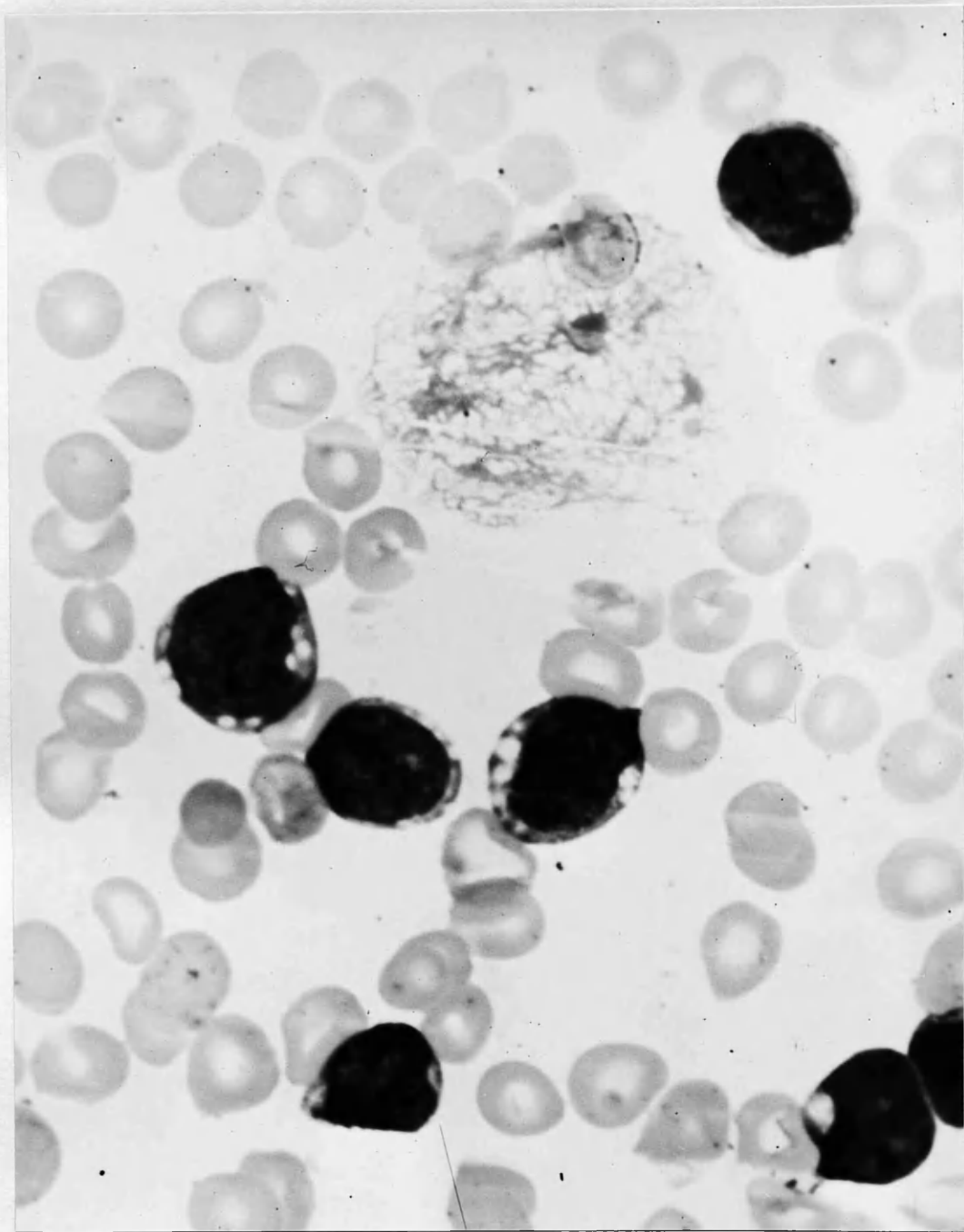
CLINICAL SYNDROMES

Acute Leukaemia

This may occur as a primary manifestation of leukaemia (commonly in children and young adults, but possibly at any age) or it may occur as an acute termination of an established chronic leukaemia. The onset of the primary form is usually sudden, with pyrexia, rigors, sore throat and skeletal pains - a picture easily mistaken for acute rheumatic fever. In children, puffiness of the eyes may suggest acute nephritis, and large mediastinal lymph nodes may give rise to superior vena caval compression with its associated engorgement and distress. The disease is frequently aleukaemic, especially in children, and rapidly progressive anaemia with a generalised haemorrhagic tendency are characteristic. Bleeding may occur from swollen gums, or into the retinae, brain, spinal cord, ear, nose, bowel, kidney or uterus. Clearly such widespread bleeding must produce a great variety of symptoms and signs.

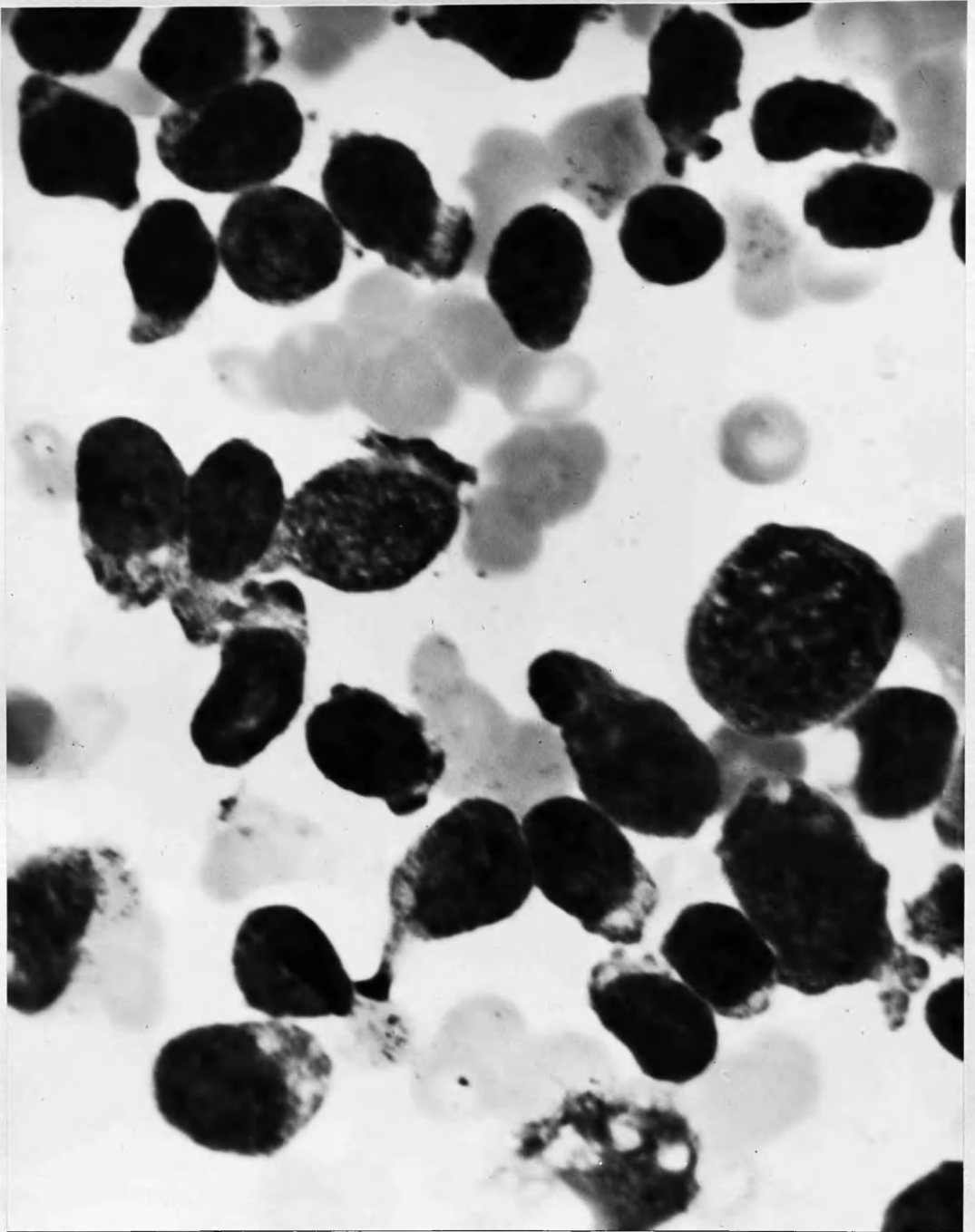
Though spontaneous remissions have often been reported (e.g. Birge et al., 1949), and new methods of treatment may now improve the general condition of the patient for a time, the disease is still inevitably fatal, and usually rapidly - sometimes within a few days of its onset.

Though the commonest type of acute leukaemia in children



Acute Leukaemia - Peripheral Blood Picture

Figure 2 (a)



Acute Leukaemia - Bone Marrow Picture

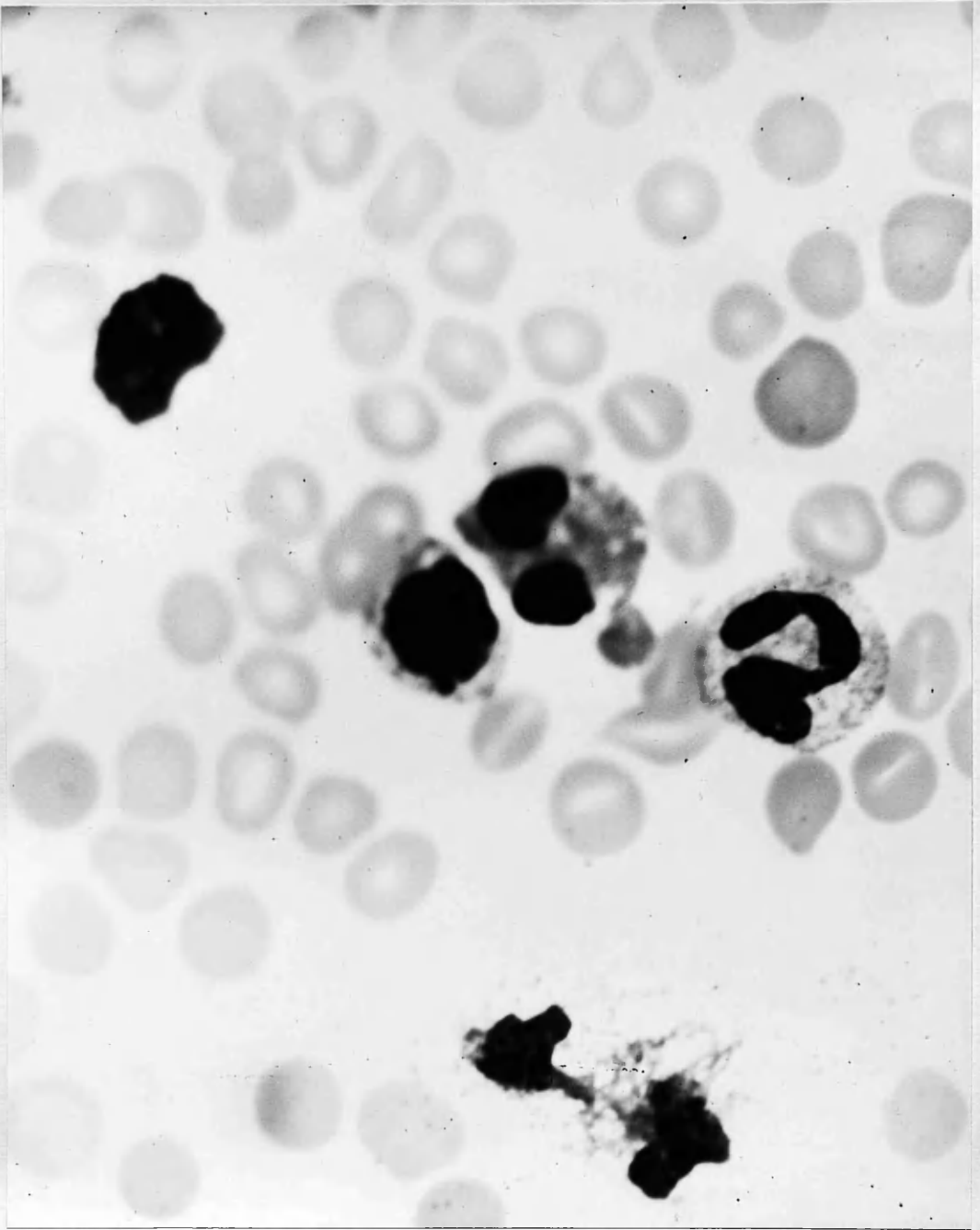
Figure 2 (b)

is lymphoblastic, it is generally agreed that if primary acute lymphoblastic leukaemia occurs at all in adults it must be rare, most diagnosed cases being in fact myeloblastic. Of acute leukaemia Sturgis (1952) claims that "at least five types of the condition have been observed: the myeloblastic, myelomonocytic, lymphosarcoma cell, lymphoblastic, and histio-monocytic". He does, however, concede "that a difference of opinion may arise and in some instances it may be necessary to be content with a diagnosis of an acute leukaemia of undetermined variety or a 'stem cell' leukaemia".

The characteristic change in the blood and bone marrow (Figures 2 a and b) is the presence of a large number of mononuclear cells, either myeloblasts or lymphoblasts, rarely monoblasts. The lack or scarcity of cell-types intermediate between primitive and mature often makes the classification of the type of acute leukaemia difficult.

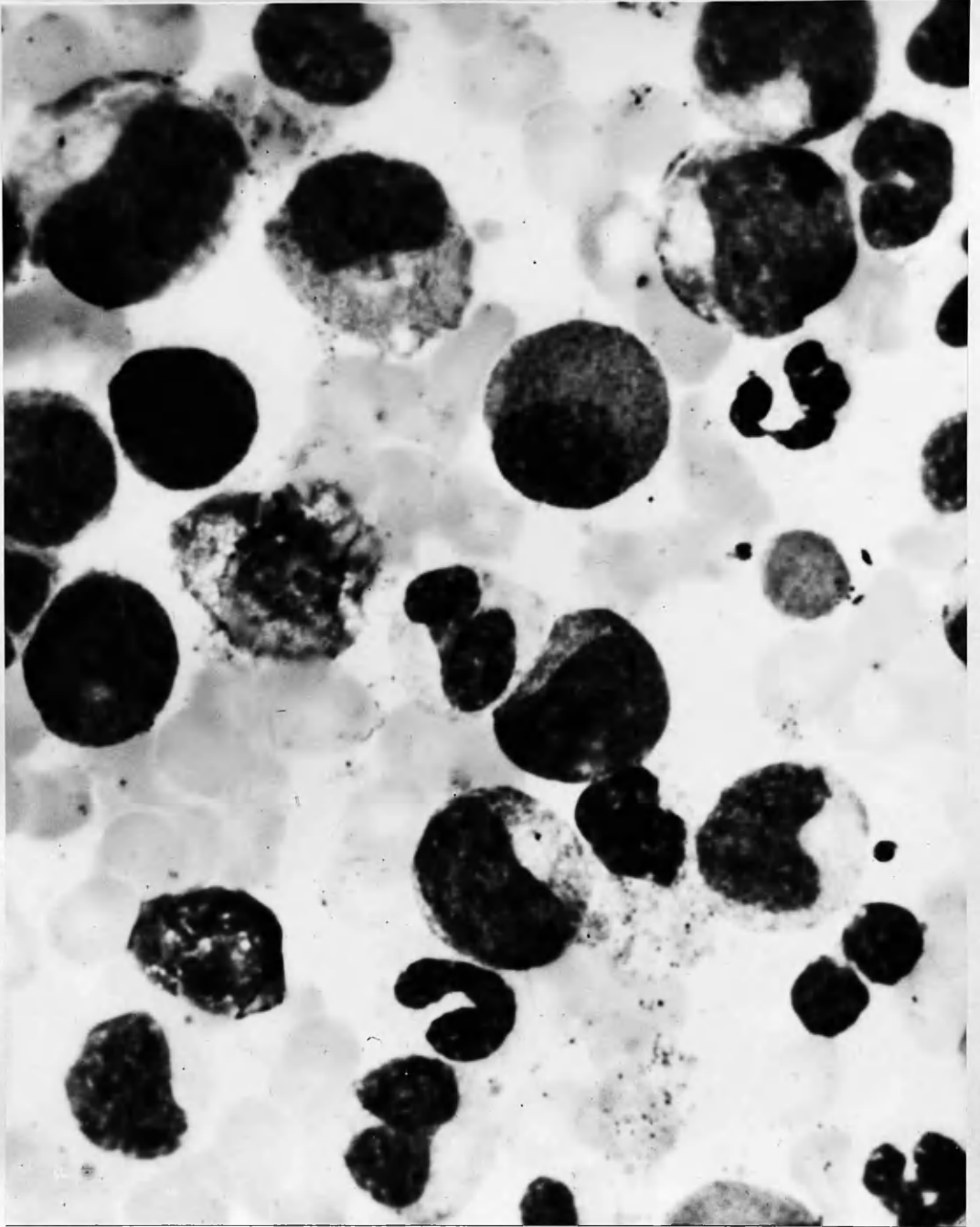
Chronic Leukaemia.

The chronic type of leukaemia usually has an insidious onset, the patient complaining of vague lassitude and anorexia for many months before the diagnosis is made, often after a chance blood examination has indicated the underlying cause of the malaise. Medical advice may be sought because of the uncomfortable splenomagaly in the myeloid type, or because of



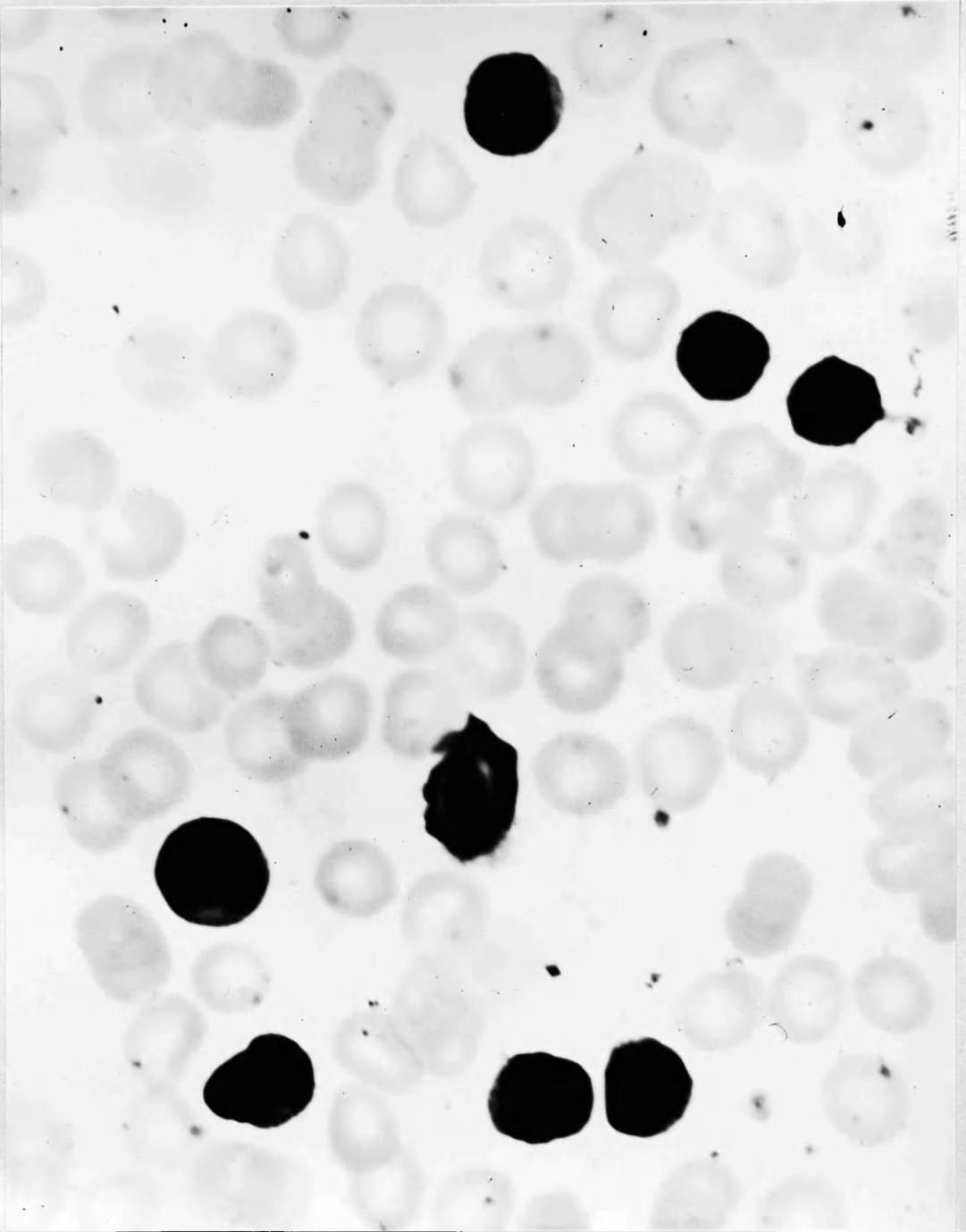
Chronic Myeloid Leukaemia - Peripheral Blood Picture

Figure 3 (a)



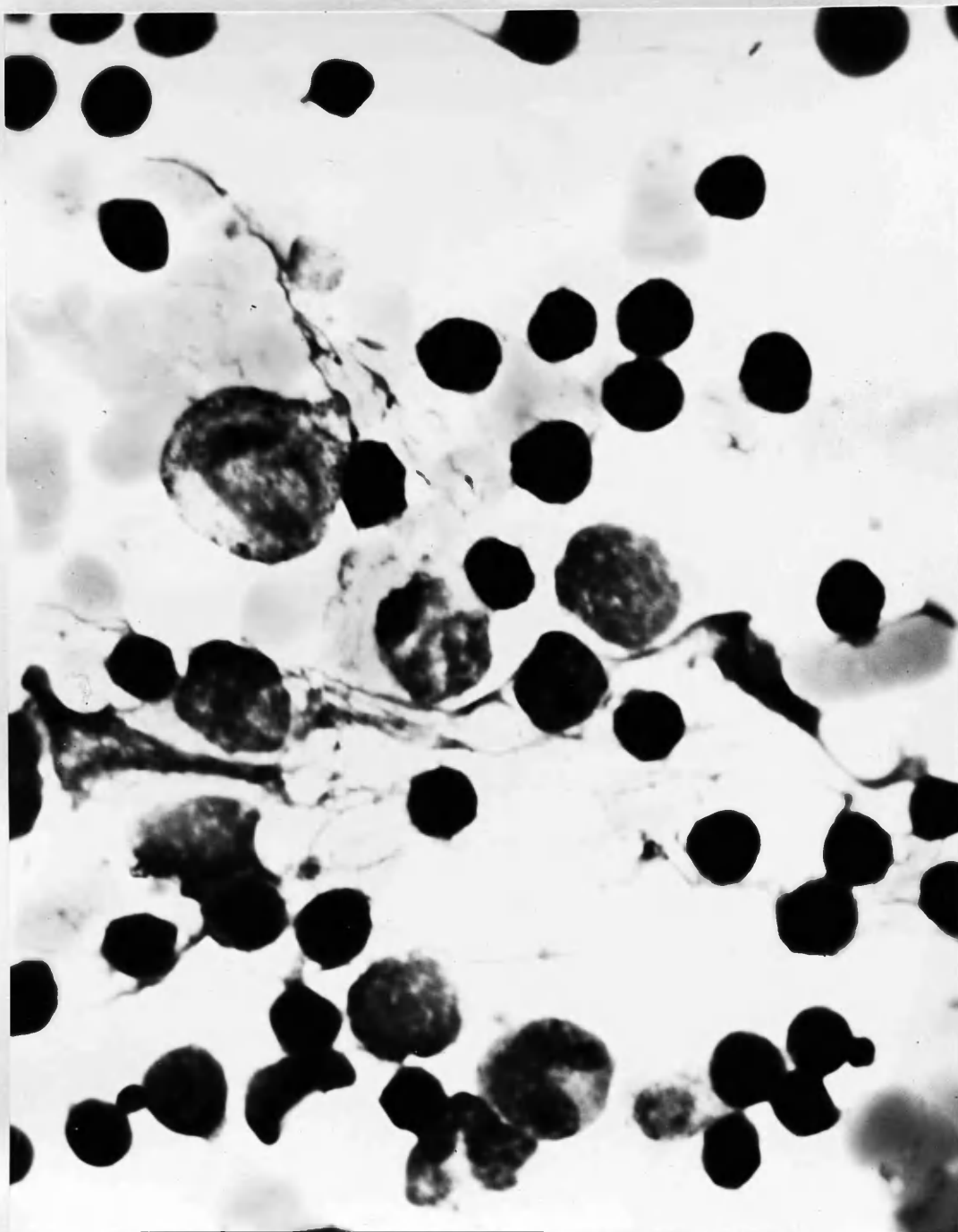
Chronic Myeloid Leukaemia - Bone Marrow Picture

Figure 3 (b)



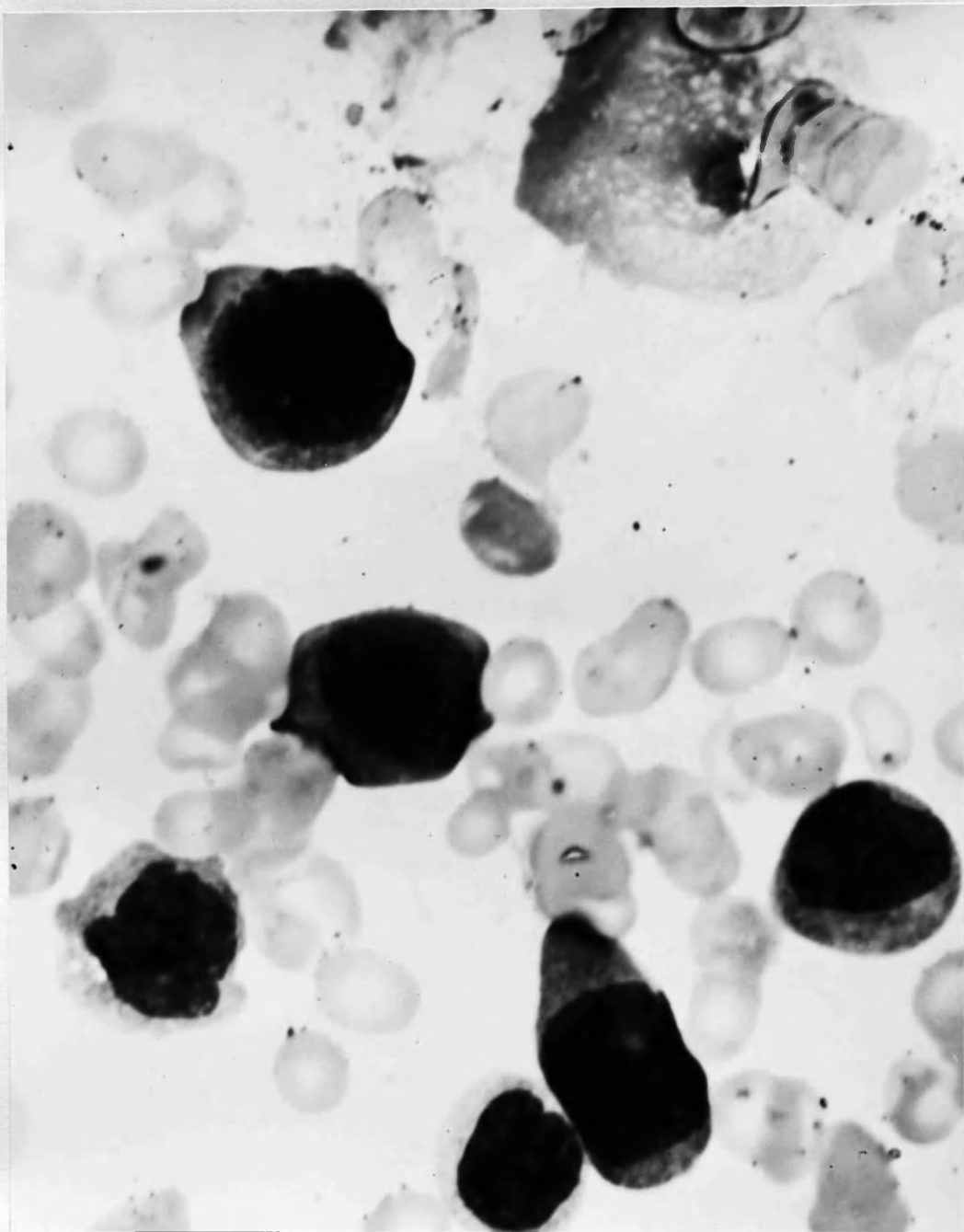
Chronic Lymphatic Leukaemia - Peripheral Blood Picture

Figure 4 (a)



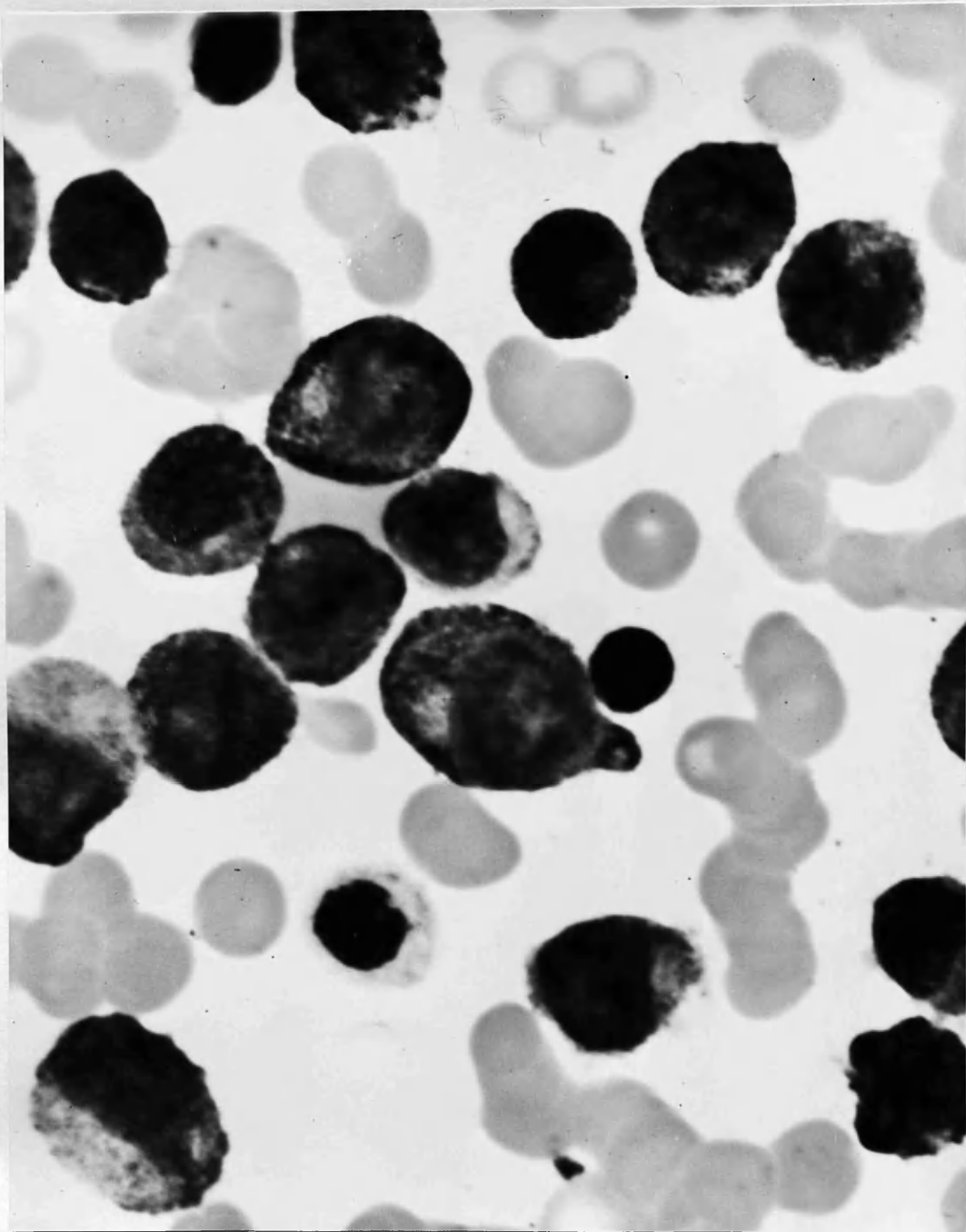
Chronic Lymphatic Leukaemia - Bone Marrow Picture

Figure 4 (b)



Subacute Monocytic Leukaemia - Peripheral Blood Picture

Figure 5 (a)



Subacute Monocytic Leukaemia - Bone Marrow Picture

Figure 5 (b)

enlarged lymph nodes in lymphatic leukaemia. Buccal ulceration in monocytic leukaemia is a not infrequent first stimulus to a medical consultation. Once the disease is suspected its diagnosis does not as a rule present much difficulty, though there are, of course, many atypical forms of leukaemia which will be briefly mentioned presently. In the typical case the peripheral blood shows an elevation of the total white cell count which may reach many thousands per c.mm. The differential white cell count (Figure 3 a) shows a greater or lesser shift to the left, with myelocytes and myeloblasts often easily recognisable in the myeloid variety. Basophils are increased and may indeed reach high proportions of the white cell count. In lymphatic leukaemia the total white cell count may consist almost entirely of lymphocytes, with once more a variable number of primitive cells - large lymphocytes, smear cells, and (in late stages) lymphoblasts (Figure 4 a). Similarly in monocytic leukaemia the preponderating cell is the monocyte with varying numbers of primitive forms of the monocytic series (Figure 5 a).

The clinical course of chronic leukaemia, with or without treatment, is very variable, though the average duration of life is about three years for the myeloid and lymphatic forms. Monocytic leukaemia being usually acute or sub-acute,

the duration of life is often measured in weeks or at most a few months.

The bone marrow in chronic leukaemia is hyperplastic, with islands of erythropoietic activity. In myeloid leukaemia (Figure 3 b) myeloblastic areas are surrounded by large numbers of promyelocytes and myelocytes in all stages of development. A common feature is the presence of numerous megakaryocytes in the marrow associated with a high platelet count in the peripheral blood. In lymphatic leukaemia (Figure 4 b) the bone marrow is characteristically infiltrated with lymphocytes, but erythropoietic activity is not disturbed by replacement until late in the course of the disease, so that anaemia is not an early feature of this type of leukaemia as it is with the myeloid type. Megakaryocytes are usually diminished with reduced platelet counts in the peripheral blood. Monocytic leukaemia, which is rarely chronic, usually presents a bone marrow picture (Figure 5 b) not unlike an acute myeloblastic leukaemia or invasion by reticulum-cell sarcoma. Opinions differ as to the origin of the monocytes, a Schilling variety of reticulo-endothelial origin, and a Naegeli variety of myeloid origin are described. Whitby and Britton (1950) remark that "the disease is apparently related to reticulum-cell sarcoma in the same way as lymphatic leukaemia is to lymphsarcoma".



Showing area of healed herpes zoster, and wide-spread
papular eruption (Case L 5)

Figure 6 (a)



Photomicrograph of papule showing infiltration of
dermis with lymphocytes (Case L 5)

Figure 6 (b)

The spleen in myeloid leukaemia can be a source of distressing symptoms. Not only does the size of the organ produce abdominal discomfort and an unpleasant dragging sensation which it is sometimes impossible to alleviate, but splenic infarcts may cause considerable pain, and pyrexia associated with prostration may suggest that an acute termination of the leukaemic process is imminent. The spleen in lymphatic leukaemia is usually somewhat smaller than in myeloid leukaemia, and in the monocytic type the spleen is usually scarcely if at all palpable.

The enlarged lymph nodes in chronic lymphatic leukaemia can be a source of real distress, and may be very large, florid and unsightly, forming a collar of nodes around the neck. On the other hand, there may be no palpable lymphadenopathy in spite of well-established lymphatic leukaemia. Eustachian deafness is a common finding, but unlike the acute form in children, the generalised lymphadenopathy causes little in the way of pressure symptoms, presumably because the nodes are so soft. The writer (1954) found no case of vena caval compression, phrenic or recurrent laryngeal paralysis in a study of the thoracic manifestations of chronic lymphatic leukaemia. Histologically the gland architecture is lost, germinal centres cannot be seen, and the entire node is filled with a mass of lymphocytes.

The skin manifestations of the leukaemias have been described by Forkner (1938) and more recently by Twiston-Davies (1955). Since the skin is well supplied with the undifferentiated mesenchymal cells from which all the cellular elements of the blood may be derived, either intra- or extra-medullary according to circumstances, it is clear that the leukaemic process might well affect the skin. The fact that Hodgkin's disease, Brill-Symmers' disease, mycosis fungoides, lympho- and reticulo-sarcoma may also affect the skin only serves to underline the basic reticulo-endothelial origin of these diseases. The author finds it difficult, however, to believe that there is any skin lesion which is truly specific to any of the reticuloses, with the sole exception perhaps of mycosis fungoides. It is true that monocytic leukaemia frequently presents with skin manifestations, but these lesions are not, in my view, characteristic in appearance.

That bones may be affected by leukaemia was first noted by Heschl only two years after Hughes Bennett and Virchow had first described the leukaemic disease. As Griffiths (1955) has remarked, it is curious that Heschl should have failed to observe the bone-marrow changes in leukaemia which were not reported until twenty years later by Neumann. Widespread lesions of the skeleton are frequently found in the acute

lymphoblastic leukaemia of children, often simulating acute rheumatism. Chronic leukaemia affects bone much less frequently, and when it does it is more commonly seen in the lymphatic type. The bone changes produced by leukaemia may be destructive (translucent zones in the metaphysis, focal bone erosion, diffuse infiltration) or formative (subperiosteal ossification, or osteosclerosis) and indeed both are often seen in the same patient or even in the same bone. As Griffiths observes, it is surprising that the extensive disorder of haemopoietic marrow in leukaemia is so seldom associated with changes in its covering shell.

The neurological complications of leukaemia have been described in detail by Forkner (loc. cit.) and by Leidler and Russell (1945). Neurological abnormalities are especially common in acute leukaemia, and, as already said, focal haemorrhage may produce protean manifestations, from retinal damage and nerve-deafness to transverse myelitis. Spinal root pain or complete paraplegia may occur as a result of vertebral collapse, even in chronic lymphatic leukaemia. It has been the experience of those who regularly come in contact with malignant disease that many cancer patients develop herpes zoster sooner or later. (Figure 6 a and b). The same experience with leukaemic patients has led some workers to

believe that herpes and even varicella are in some way associated with leukaemia, and the virus theory of leukaemogenesis comes to mind with each new herpetic patient. The truth seems to be that herpes zoster is a most common disease and its incidence in the general public is quite unknown. It appears to be "induced" by a great variety of non-specific debilitating diseases and episodes in the lives of men, women and children of all ages.

Anaemia is perhaps the most important single abnormality associated with the leukaemic process, and the patient's general health and sense of well-being are more closely tied to his haemoglobin level than to any other single factor. Anaemia may not be obvious in the early stages of the disease, but it is almost invariably a terminal feature of leukaemia, both acute and chronic. The nature of this anaemia is still debatable, but as with any anaemia it is true to say that it can only be due (a) to an inadequate production and/or (b) to an abnormally rapid loss of red cells.

(a) Inadequate production of red cells in leukaemia (apart from possible associated intercurrent factors such as dietetic, infective or surgical abnormalities), has long been attributed to "marrow invasion" by leukaemic cells. The early anaemia in myeloid leukaemia is undoubtedly associated

with large areas of myeloid hyperplasia in the bone marrow. In lymphatic leukaemia, on the other hand, high haemoglobin levels are commonly maintained for long periods, and it is only with the advent of anaemia that the bone marrow is found to be populated by large numbers of lymphatic cells. That erythropoietic tissue is thus "crowded out" by white cells is, however, too facile and mechanistic an explanation of the leukaemic patient's anaemia, especially since other causes can be demonstrated which are surely more important. By studies of iron metabolism Huff et al. (1952) have demonstrated that the anaemia of leukaemia is in fact usually associated with increased red cell production, and not decreased as the "crowding out" theory would suggest.

(b) Abnormal loss of red cells may be due to haemorrhage, haemolysis, or a shortened life-span of these cells. Haemorrhage is undoubtedly a striking feature of the acute phase of leukaemia, though it is of course itself a manifestation of the abnormal blood, including e.g. low platelet levels. (Bleeding may in fact occur with normal platelet counts). Though profuse haemorrhage may be the proximate cause of death in some leukaemic patients this is unusual, and gross degrees of anaemia are common without associated haemorrhage of any magnitude.

Significant shortening of the life-span of erythrocytes in leukaemia has been demonstrated by many workers, both by Ashby's agglutination method (1921) and by isotopic techniques (Berlin et al. 1951; Huff et al. 1950). As Crosby and Damashek have said (1955) "shortened erythrocyte survival is synonymous with haemolytic disease", though abnormally rapid haemolysis is not always evident, and indeed a patient with an adequately reacting marrow may conceal an "occult" or compensated haemolytic disease. The fact that normal erythrocytes transfused into a leukaemic patient may be destroyed too rapidly, while leukaemic red cells transfused into normal subjects have a normal life-span, suggests that the erythrocytes themselves are not abnormal. If the erythrocytes are not abnormal why and how are they destroyed? Auto-antibodies can undoubtedly be demonstrated in some cases, especially in lymphatic leukaemia, associated with a progressive anaemia refractory even to massive transfusion of carefully matched blood. This "immunological heresy" which leads to haemolysis of the patient's own red cells may cause rapid death, but there are cases in whom a similarly refractory anaemia occurs and no antibodies can be demonstrated by existing techniques. This problem requires much further study, especially concerning qualitative abnormalities in the haemoglobin.

The colour index during the anaemia is usually less than 1.0, occasionally greater than 1.0, and while the marrow is capable of reacting there are many signs of erythropoietic activity in the form of nucleated red cells, reticulocytes, polychromasia, poikilocytes, etc. Aplasia is a common but by no means constant terminal feature.

ATYPICAL FORMS OF LEUKAEMIA.

(1) Aleukaemic leukaemia is one of the commonest of the atypical forms of leukaemia. As its name suggests, the conspicuous finding is a normal or subnormal total white cell count, though the other signs of leukaemia are demonstrable - a shift to the left, with primitive cells of the myeloid or lymphoid series, progressive anaemia, splenomegaly and lymphadenopathy. The disease, with atypical symptoms, frequently presents difficulty in diagnosis and is often confused with pernicious anaemia, aplastic anaemia, or diseases of the cardiac, skeletal, genito-urinary or other systems. Marrow biopsy is, however, often diagnostic, but it is important to examine marrow from several different sites because of the patchy involvement sometimes seen - especially in the lymphoid form.

(2) Eosinophil leukaemia may occur, in which case eosinophils are the preponderating cell-type. This is a rare disease, it

runs a more chronic course than the "typical" forms of leukaemia, and a curious feature is the eosinophilic infiltrations of muscles. Charcot-Leyden crystals are found in the liver. Neutrophil, Basophil, and Megakaryocyte leukaemias have been described but their existence is debated.

(3) A plasma cell leukaemia has been described, among others by Reiter and Freeman (1937). The very nature of these plasma cells is in doubt, and Moeschlin (1940) believes them to be reticulum cells of the bone marrow. The relationship of myeloma to plasma cell leukaemia is a close one, though a debatable one. Damashek (1957), on the other hand, considers this to be simply "another name for multiple myeloma, more or less aleukaemic".

(4) Leukosarcoma is the name given by some to the condition in which an infiltrating lymphosarcoma is associated with a lymphatic leukaemic blood picture. In the writer's opinion many frank lymphatic leukaemias display soft-tissue masses of "sarcoma" at some stage in the course of the disease. Furthermore, many so-called lymphosarcomas which later develop leukaemia can be found in retrospect to have had relatively high lymphocyte counts initially. The last decade has seen a growing demand amongst histologists and oncologists for more sharply defined diagnostic criteria, and "lymphosarcoma" is

becoming an increasingly uncommon disease in some centres.

Many lymphosarcomas of the past have probably been Hodgkin's disease or subleukaemic chronic lymphatic leukaemia - the type that runs a course of ten or more years. This is a fascinating subject, but cannot be pursued here.

(5) Chloroma is a haematological curiosity because, though a rare lesion, it attracts so much attention when seen. The typical chloroma is a greenish tumour mass, usually subperiosteal, in the skull or thorax, and associated with acute leukaemia. It is naturally most commonly seen in children but may in fact be seen in adults. As well as bone, soft tissues may be involved - breast, muscle, brain, bone-marrow, etc. The tumours are sometimes not coloured. Chloroma is regarded as an atypical form of myeloid leukaemia, of the acute myeloblastic type.

(6) Leukaemic Erythrodermia is characterised by a generalised redness of the skin which French writers have named "l'homme rouge". In addition to the curious dusky erythema there is usually generalised enlargement of lymph nodes and spleen, (all rather small) and a blood picture which is not always typical of lymphatic leukaemia. This disease is regarded as a very chronic and slowly progressive form of lymphatic leukaemia with lymphocytic infiltration of the dermis.

(7) A Mikulicz Syndrome in lymphatic leukaemia is described

by Whitby and Britton (loc. cit.) but though seen in one or two cases of acute lymphoblastic leukaemia in children, the writer has seen no such case in a series of some two hundred patients with chronic lymphatic leukaemia. It must be a distinctly uncommon condition.

Leukaemoid Blood Pictures

A consideration of leukaemoid blood-pictures almost amounts to a discussion of the differential diagnosis of leukaemia, at least from the purely haematological aspect. It is clear that a leukaemic blood picture is not sufficient evidence to justify the diagnosis of leukaemia, and until all possible causes have been excluded the blood changes alone should be considered only "leukaemoid".

A leukaemoid blood picture suggesting lymphatic leukaemia is not unexpected in measles, chicken pox and whooping cough - the latter sometimes persisting for a year or two. Glandular fever may cause confusion with lymphatic or monocytic leukaemia. Septicaemic conditions, not forgetting subacute endocarditis, may produce high white cell counts with myelocytes in fair numbers. Pneumonia and meningitis may do likewise, and similar changes are reported in plague, eclampsia and even malaria (aleukaemic). Tuberculosis may even produce leukamoid reactions which are myeloid in type, as well as lymphoid.

Poisons of various kinds have been reported to cause leukamoid changes - mercury, mustard gas, sulpha drugs of various types - and even bee stings have been reported to produce a leukocytosis of 120,000 per c.mm. with 69 per cent myelocytes and myeloblasts. (Parrisius and Heimberger, 1924).

A leuko-erythroblastic anaemia occurs when the bone-marrow is "irritated" into excessive and disordered function either by the implantation in it of foreign tissue, such as malignant metastases, or by abnormal changes in the skeleton. As its name implies, this type of anaemia is characterised by a shift to the left of both erythropoiesis and leukopoiesis, so that nucleated red cells and many primitive leukocytes are found in the circulating blood.

The bone-marrow changes will depend on the underlying cause of this dyshaemopoiesis. When neoplastic metastases are the source of the disordered function, the sectioned bone reveals deposits of tumour surrounded by hyperplastic red marrow which microscopically displays excessive erythroblastic and myeloblastic activity. A high leukocytosis in the peripheral blood is uncommon. The primary tumour is frequently found in the breast, prostate, kidney, or thyroid, though almost any malignant disease may occasionally invade the bone-marrow widely enough to upset haemopoiesis in this fashion. Even

Hodgkin's disease, a related reticulosis, may produce this "irritation anaemia".

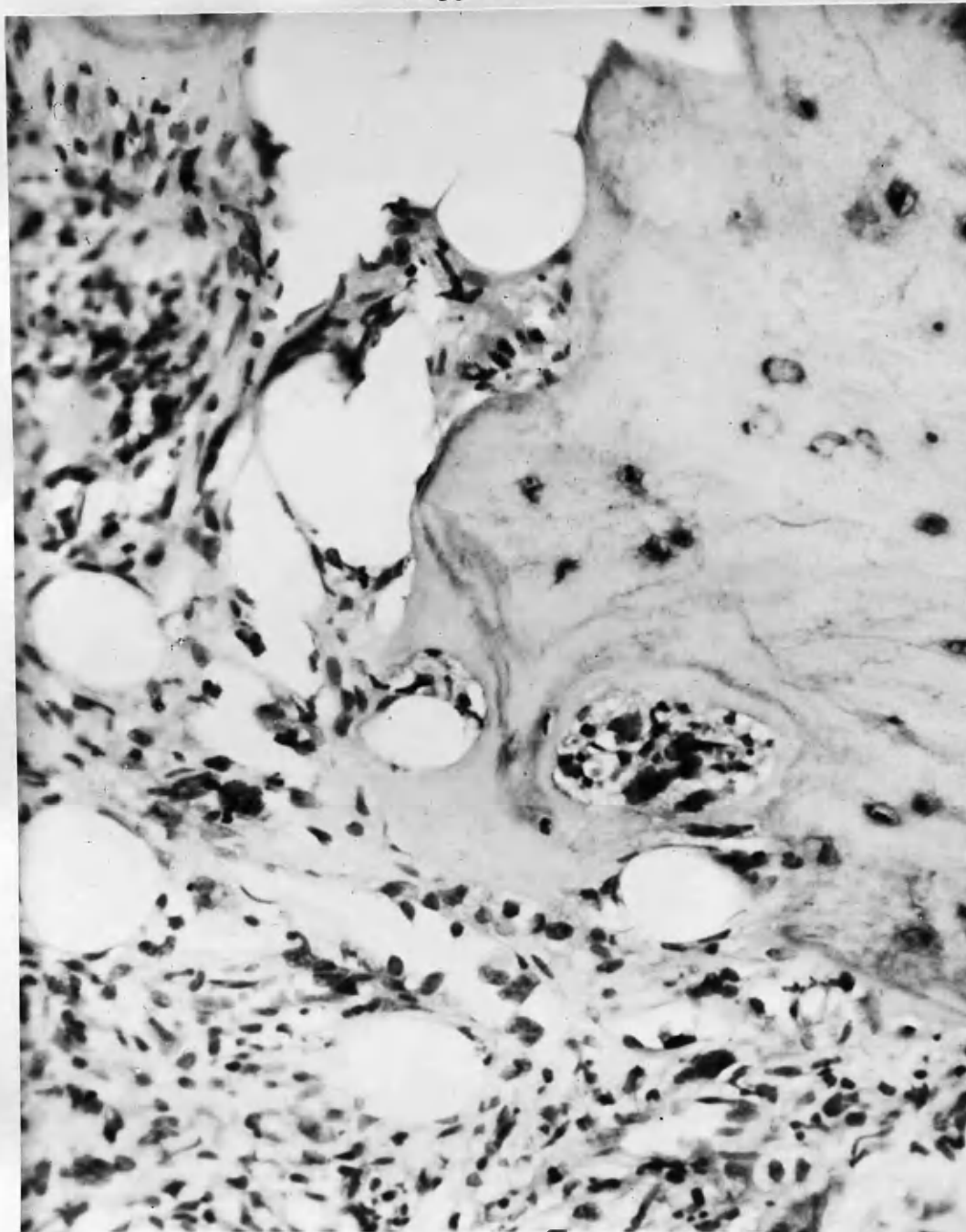
The skeletal changes associated with a leuko-erythroblastic anaemia are (1) osteopetrosis, and (2) myelofibrosis. The first of these, the so-called Marble-bone disease of Albers-Schonberg, is indeed a rare disease. A hereditary condition, it usually declares itself in childhood, and the increasing thickening of the bone progresses until it becomes virtually solid with no marrow cavity. Extramedullary haemopoiesis develops to compensate for the loss of active marrow mass, splenomegaly and hepatomegaly are characteristic, and radiographs of the skeleton are quite diagnostic. The disease is a primary dyscrasia of the mesenchyme resulting in excessive bone formation.

Myelofibrosis is perhaps a more interesting and important cause of leukamoid blood pictures if only because it is much more common than osteopetrosis. This condition is characterised by a fibrosis of the bone marrow which is progressive and leads to the usual compensatory extramedullary haemopoiesis in liver, spleen, kidney, etc. The syndrome has been recently reviewed in an excellent paper by Korst et al. (1956). They stress the close relationship of myelofibrosis to chronic myeloid leukaemia and especially to polycythaemia



X-ray films of a normal and myelofibrotic spine

Figure 7 (a)



Photomicrograph of bone biopsy from case of myelofibrosis

Figure 7 (b)

vera, and they insist that "at certain stages in this disease their separation as distinct entities may be difficult or impossible". A dry tap on attempting marrow aspiration from the sternum or elsewhere is often the first clinical indication that the patient may not have myeloid leukaemia but rather myelofibrosis. A section of bone and bone marrow from the iliac crest for histological study is then a wise procedure, and without procrastination. Circulating fragments of megakaryocytes and an unusual number of nucleated red cells are also tell-tale diagnostic signs.

The diagnosis of the infective and drug- or toxin-induced leukaemoid reactions is not usually difficult, depending mainly on careful history-taking. Myelofibrosis is often much more difficult to differentiate, even when the clinician is conscious of the possibility of this diagnosis. Indeed, to be conscious of the possibility is to be more than half way towards establishing the diagnosis. (Figures 7 a and b).

But diagnosis is essential, since x-ray treatment of e.g. a spleen which is enlarged only as a compensatory effort at haemopoiesis would be disastrous. Such spleens have in fact been excised in error, though Korst (loc. cit.) describes two patients who benefited from splenectomy after careful studies had revealed a progressive haemolytic anaemia.

The value of estimations of alkaline phosphatase in the leukocytes is discussed under Clinical Pathology.



Case of chronic myeloid leukaemia with concurrent gout.

Case M 21.

Figure 8

CLINICAL PATHOLOGY.

In the realm of clinical pathology many deviations from the normal have been found in the leukaemias. The explanation for these various changes is uncertain, but having regard to the studies in radiosensitivity discussed in Section V it is appropriate to enumerate at least the well-established features.

The Basal Metabolic Rate is increased during the active phases of leukaemia and it is said that measurements of the B.M.R. can in fact herald the end of a remission before the blood picture or other clinical symptoms and signs. This fact might help to explain the sweating, irritability and nervousness in some leukaemic patients.

The total lipins are significantly increased in all leukaemias regardless of the number of circulating leukocytes, and purine metabolism is also known to be abnormal. Blood uric acid levels are elevated, frank gout may co-exist (Figure 8), and an acute attack of gout has been precipitated by irradiation therapy, presumably by the rapid liberation of more uric acid from disintegrated leukocytes. (e.g. Shorvon, 1946, and Case M 21). The effectiveness of colchicine both in gout and in leukaemia is noteworthy. Phosphorus and glutathione levels in the blood are also elevated in leukaemia

(Whitby and Britton, loc. cit.) and in the leukocytes of acute leukaemia at least the content of folinic acid is some five times that of normal leukocytes. This high folic acid requirement for white cell mitosis underlies the value of antifolic chemotherapy, and Girdwood (1956) has suggested that this diversion of folic acid for leukopoiesis might explain the folic acid-deficient megaloblastic anaemia sometimes seen in leukaemia. Though the total plasma proteins are not significantly altered, there is generally an increase in the gamma globulin fraction, easily demonstrable by electrophoresis. The zinc content of leukaemic cells is also lower than normal while the disease is active, but returns to normal during remission. (Hughes and Gibson, 1947).

Though achlorhydria in the general population is much more common than one might guess, Meyer (1938) has demonstrated a histamine-fast achlorhydria in 53% of chronic lymphatic leukaemia cases, in 13% of chronic myeloid and 33% of aleukaemic cases. It was also found in two out of every five acute cases. Meyer himself doubts the significance of these findings, except perhaps in lymphatic cases. Witts, however, (1956) draws attention to the importance of the vitamin B complex in the metabolism and replacement of all rapidly multiplying cells. He points out that rapidity of replacement of cells is a factor

common to gastro-intestinal tissues and to blood, and the common association of alimentary and haematological symptoms may be due to a common denominator in a chain of enzyme reactions.

In 1943 Miller and Turner described substances isolated from the urine of leukaemic patients (and normal ox liver) which influence leukopoiesis and maturation. A myeloid substance (named myelokentric acid) is responsible for myeloid proliferation, but myeloid maturation occurs only in the presence of a lymphoid substance (lymphokentric acid). Conversely, lymphoid proliferation is controlled by lymphokentric acid, and lymphoid maturation by small amounts of myelokentric acid. Acute myeloblastic leukaemia is thus caused by an excess of myelokentric acid but an absence of lymphokentric acid. A normal amount of lymphokentric acid in such a case would result in chronic myeloid leukaemia, i.e. by promoting more maturation. The opposite arrangement would cause acute lymphoblastic or chronic lymphatic leukaemia respectively. This work has not apparently been confirmed, nor has it excited the interest which it first seemed likely to do.

Wachstein (1946) and Valentine et al. (1952) demonstrated that the alkaline phosphatase content of granulocytes in chronic myeloid leukaemia was distinctly lower than normal.

Maloney (1955) has indeed claimed that a fall in this phosphatase content was the earliest indication of incipient leukaemia in humans exposed to ionising radiations from the nuclear bombing of Japan in 1945. This diagnostic feature has attracted curiously little attention so far. Leonard (1957) has demonstrated that the alkaline phosphatase of leukaemic granulocytes is as far below the normal level as it is above it in infective leukocytosis. The level is also well above normal in leukaemoid states and polycythaemia, variable but not low in myelosclerosis, and normal in the granulocytes of chronic lymphatic leukaemia.

This is interesting also in the light of Bierman's conclusions (1956) that the life span of chronic myeloid leukaemic granulocytes is greatly increased. Bierman's technique for separating white from red cells and returning the latter to the patient's circulation allowed the white cell mass to be properly depleted and the rate of replacement to be more accurately measured. As Osgood and colleagues showed (1954) "more of the body's leukocytes are located extravascularly at any one time than are present in the blood stream", a fact which made Bierman's method particularly useful for life-span studies.

AETIOLOGY OF LEUKAEMIA.

In the great majority of cases no cause, either immediate or remote, can be discovered to explain the onset of leukaemia. A small minority do, however, seem to have some antecedent exposure to "agents" of various kinds that have come to be regarded as leukaemogenic. These will be discussed presently.

The Occurrence of Leukaemia. So far as is known no race is immune to leukaemia, though of course detailed statistics are available in only a few western countries, and even these are less reliable the farther back in time the enquiry goes. Indeed, the International List of the Causes of Death reveals a changing concept of leukaemia, since it was only in 1920 that leukaemia and Hodgkin's disease were separately classified. Not only are humans widely affected but the disease has been known since 1858 to occur in animals. Leukaemia has been reported, in one form or another, in dogs, cats, cattle, horses, guinea pigs and mice. An epizootic leukaemia is at present being studied in the Canadian pike, and a transmissible leukosis is well known in fowls. Leukaemia in mice and leukosis in fowls have been the source of much experimental work over many years. Jarmai (1934) has written an extensive monograph on

the occurrence of leukaemia in domesticated animals.

Incidence. (a) Total. (b) Age. (c) Sex.

(a) Total incidence. It has recently been pointed out by Hewitt (1955) that the past decade has seen a distressing and dramatic increase in the incidence of three lethal diseases, more than any other - lung cancer, coronary thrombosis, and leukaemia. The national mortality statistics for England and Wales (Table I) show a steady rise in annual death rates for leukaemia in both sexes from 17 per million living persons in 1931 to 49 per million in 1954. The incidence in other countries shows a similar trend. (Table II). Paterson E. (1956) has shown that this increased and increasing incidence applies to both acute and chronic forms of the disease, i.e. in children as well as adults.

(b) Age Incidence. Leukaemia may occur at any age and indeed the disease has been reported in new born infants. Acute leukaemia is well known as affecting children more than adults, and the disease in children is nearly always of the acute type. Chronic lymphatic leukaemia is also known to be commoner in the older age groups whilst the myelogenous type occurs more often in the middle decades. These distinctions in age incidence, firm impressions with clinicians, are confirmed by statistical examination such as that shown in Table III.

Death Rate from Leukaemia per million persons:

England and Wales, 1931 - 54

Year	Death rate per million persons		
	Men	Women	Both Sexes
1931	19	15	17
1932	20	16	18
1933	20	17	19
1934	23	18	20
1935	23	19	21
1936	25	21	23
1937	25	20	22
1938	28	22	25
1939	28	23	25
1940	30	23	26
1941	29	22	25
1942	34	24	28
1943	38	25	30
1944	38	26	31
1945	40	29	34
1946	41	30	35
1947	38	32	35
1948	40	31	35
1949	44	35	40
1950	47	37	42
1951	47	41	41
1952	52	41	46
1953	53	44	48
1954	54	44	49

Table I

Death Rate from Leukaemia per million persons:

Various Countries, 1940 - 54

Year	Death rate per million persons				
	Canada	Denmark	Eire	Scotland	U.S.A.
1940	30	48	15	38	39
1941	31	44	16	28	39
1942	31	39	16	27	40
1943	30	52	24	32	41
1944	36	51	22	32	43
1945	33	57	16	32	45
1946	36	52	22	34	47
1947	37	57	17	32	51
1948	39	58	24	30	53
1949	45	61	20	39	55
1950	46	59	26	39	59
1951	46	62	32	43	61
1952	46	64	32	44	63
1953	53	69		38	63
1954	51	71		48	

Table II

Age Incidence of Leukaemia
(Forkner, 1938)

Table III

Sex Incidence of Leukaemia

(Forkner, 1938)

All ages to age of	Acute Leukaemia		Chronic Lymphatic		Chronic Myeloid	
	M.	F.	M.	F.	M.	F.
5	60	40	-	-	-	-
10	65	35	-	-	-	-
15	69	31	75	25	60	40
20	72	28	80	20	61	39
25	71	29	83	17	55	45
30	71	29	81	19	52	48
35	70	30	76	24	52	48
40	69	31	86	14	52	48
45	68	32	75	25	53	47
50	68	32	77	23	55	45
55	67	33	75	25	54	46
60	67	33	77	23	56	44
65	-	-	73	27	56	44
70	-	-	74	26	56	44
75	-	-	74	26	56	44
80	-	-	75	25	56	44
85	-	-	-	-	56	44

Table IV

(c) Sex Incidence. Different authorities quote slightly different sex incidences, but Table IV demonstrates not only that males predominate but that the relationship varies at different age periods. This latter fact might, with different proportions of males and females, explain some of the slight differences of overall sex incidence in the literature.

(d) Season. Sceptical as one might be on possible seasonal influences on malignant disease Lambin and Gerard (1934) describe 54 cases of acute leukaemia, 37 of whom had their onset between October and May, while only 17 had their onset between May and October. The crux of this problem lies in the definition of the word "onset", though this is admittedly less difficult with acute leukaemia, the onset of which is usually sudden.

Relationship of Leukaemia to Other Diseases.

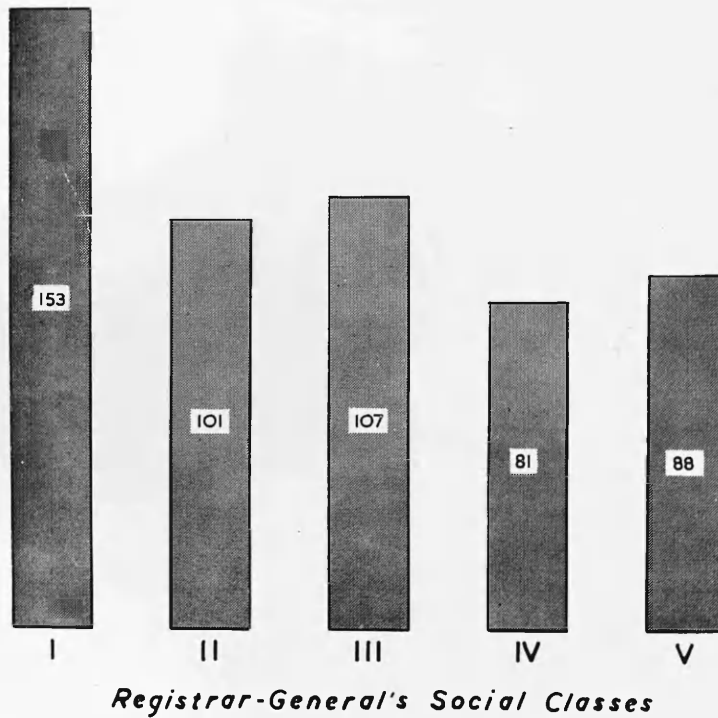
(a) Infection. The original concept of leukaemia by Hughes Bennett was that leukaemia is a pyemia following some infective process. In addition to an association with malaria many authors claimed to have isolated cocci, bacilli, diphtheroids, tubercle bacilli, and viruses. Sir Robert Muir once wrote "In the absence of knowledge regarding the agent producing the excessive proliferation of leukocytes, we cannot definitely

assign the place of leukocythaemia in the category of disease. On the whole it presents most points of analogy to the growth of tumours; but on the other hand, it is not absurd to suppose that it may yet prove to be due to a microparasite". Apart from continuing interest in the virus hypothesis, recently revived with considerable interest by Gross (1953), little enthusiasm now exists for an infectious origin of leukaemia. The similarities between the anaemia of chronic infection and that of leukaemia has been noted for many years, but this fact alone does not prove any causal relationship.

(b) Other Diseases of the Blood-forming Organs. The close relationship between the leukaemias and other reticuloses is well established and has already been described as "The Borderlands Dim". Polycythaemia vera may be seen in association with chronic myeloid leukaemia, sometimes preceding leukaemia and sometimes following it. (Vide Section VI, Case M 13). The close relationship, however, between polycythaemia and myelofibrosis, and the tendency of the latter to produce confusing leukamoid blood-pictures has already been mentioned. Lymphosarcoma and lymphatic leukaemia, reticulum-cell sarcoma and monocytic leukaemia, and myelomatosis and plasma cell leukaemia are three commonly accepted transitions much discussed in the literature. The immunological distinction between

lymphosarcoma cells and lymphatic leukaemia is interesting, but an additional therapeutic distinction seems clear from the author's experience. The great radiosensitivity of lymphosarcomatous nodes is well known. This cannot be said of the lymph nodes of chronic lymphatic leukaemia where relatively higher doses of x-rays are required to produce resolution which, in addition, is usually incomplete, the nodes becoming smaller but remaining palpable. Lymphosarcomatous nodes resolve completely and are no longer palpable after small doses of x-rays. The histological distinction between a lymph node which is the seat of lymphosarcoma and one involved in chronic lymphatic leukaemia is notoriously difficult, and many histologists report that both diagnoses are possible and that "the blood picture is necessary to distinguish". Thus a "normal" blood picture is often considered to exclude leukaemia. The author has followed the course of several such cases for periods of six or seven years and has noted (a) the relative insensitivity of lymph nodes to x-ray treatment and (b) a very gradual inversion of the polymorph/lymphocyte ratio and increasing total white cell count to leukaemic levels. Such cases have clearly been examples of very chronic lymphatic leukaemia and not lymphosarcoma. The latter diagnosis would imply that patients with manifestly generalised sarcoma were capable of surviving

LEUKAEMIA & ALEUKAEMIA
Standardised Mortality Ratio by Social Class
for Men aged 20-64
England & Wales 1950
(Standard = All Males = 100)



Social Gradient in Leukaemia Incidence in Great Britain

(Paterson, E., 1956)

Figure 9

many years. All other experience suggests otherwise. It is indeed easy to be wise after the event, but it is also wise.

The relationship of the leukaemias to abnormalities of the vitamin B complex has already been mentioned in the section on clinical pathology. Biochemical studies in the field of nutrition are throwing increasing light on the enzyme systems concerned in common with the health of e.g. the central nervous system, mucosal, and erythropoietic tissues. It is hard to resist a feeling that many lines of enquiry are gradually converging, bringing to this vast field a sense of imminent discovery.

Relationship of Leukaemia to Noxious Extrinsic Factors.

(a) Toxins and Drugs. There must be many toxic and leukaemogenic substances to which humans are exposed which are still unknown to us. There is no doubt that workers exposed to benzol (C_6H_6) may develop leukaemia, as well as the more common aplastic anaemia. Exposure to benzol may occur in such manufacturing processes as leather, rubber, celluloid, enamels, lacquers, paint-removers, silvering and bronzing liquids, dry-cleaning, electroplating, photography, aeroplane and sulphite pulp industries. Tar and indol are also suspect, and no doubt in many other occupations the hazards are unknown. Wilkinson (1955) has suggested that adulterated and contaminated food may

play a part in explaining the increased incidence of leukaemia. Paterson E. (1956) has drawn attention to the social gradient in leukaemia incidence in Great Britain (Figure 9), and suggests some dietary factor may be operating here, quoting White and Mider who showed that a diet deficient in sulphur-containing amino acids clearly inhibits leukaemogenesis in mice. So far as drugs are concerned, Wilkinson (loc. cit.) has repeatedly drawn attention to the leukaemogenic propensities of the sulphonamide drugs, the leukaemia sometimes following an agranulocutic phase.

(b) Ionising Radiations - occupational, medical and military.

(1) Occupational. According to Forkner (loc. cit.) lymphatic leukaemia was described by Jajic and co-workers as early as 1911 in a patient who had been engaged for eight years in diagnostic and therapeutic work with rontgen rays. They had known three other similar cases. The literature on this subject has since become voluminous, one of the more recent surveys being that of Pellar and Pick (1951). The incidence of leukaemia amongst radiologists is undoubtedly higher than with non-radiological medical workers. (But see below). Recent enquiries by the author into the code of practice of physicians using diagnostic x-ray apparatus in the North-West of England make this occupational hazard more understandable. For example, it seems only too clear that some physicians have

acquired the reprehensible habit of embarking on the screening of patients' chests without troubling to adapt their eyes to the darkness: the prolonged exposures that follow are harmful to the patient, the doctor, and other staff in the vicinity. It is hoped that the recent Medical Research Council Report on the Hazards to Man of Nuclear and Allied Radiations (1956) will see the enforcement of a safer code of practice. The industrial problems of ionising radiations were discussed as long ago as 1931 by Martland, who described the tragedy of luminous dial painters, many of whom acquired significant body burdens of radium and developed aplastic anaemia. It seems likely, as remarked in the Research Council report just mentioned, that some of these dyscrasias were leukaemic in type rather than simply aplastic. Again, one cannot but be concerned at the rapid employment of radioactive sources of all kinds in an ever-widening field of industry with little apparent concern or even knowledge of the potential hazards to health.

(2) Medical. The leukaemogenic effects of radiations used therapeutically have also been recognised for some time though renewed interest has been stimulated in this field by van Swaay's report (1955) of aplastic anaemia and leukaemia following the radiation of the spine for ankylosing spondylitis. This problem was also mentioned by the author, (Sharp and Easson, 1954), and has become the subject of a nation-wide

survey by a Medical Research Council Group for the study of radiation hazards, (Court-Brown and Abbatt, 1955; Court-Brown and Doll, 1956; Court-Brown, 1956; Abbatt and Lea, 1956). The increased risk of leukaemia (and also cancer of the thyroid) as a result of the irradiation of the thymus gland in babies has been stressed by Simpson et al (1955), though a baby with a large thymic tumour presents such an emergency that a risk of leukaemia could scarcely justify the withholding of the only known approach to treatment. Leukaemia has also been reported following therapeutic doses of radioactive iodine (I^{131}) for thyroid disease (Pochin et al., 1956). Diagnostic x-ray exposures have also been recently impugned, and the evidence of leukaemogenesis due to pre-natal obstetric radiography seems almost beyond question. (Stewart et al., 1956). A similar general conclusion was reached (though by statistically less acceptable methods) by Faber (1956) and no doubt further data will be sought and found in the near future.

(3) Military. The leukaemogenic properties of ionising radiations received further confirmation by the increased incidence of leukaemia in survivors of the atom-bombing of Hiroshima and Nagasaki in 1945. This has been described by Maloney (1955) and Maloney and Kastenbaum (1955) and their study demonstrates the important effect of dosage of radiation,

in that incidence bore a direct relationship to the distance of the patient from the epicentre. It is interesting also to note that the lymphatic type of leukaemia did not show an increased incidence. This is curious, in some ways, and would certainly tend to reduce the degree of risk which is claimed, e.g. amongst radiologists, since the removal of lymphatic cases from the total number of instances of leukaemia in such workers would significantly reduce this risk. It would not, however, remove it.

A study of the aetiology of leukaemia, indeed of all malignant disease, involves a study in human ecology. Though many environmental factors are known for cancers of various sites, few are well established so far as leukaemia is concerned. It has been said of Darwin that his work caused zoologists to flock indoors where they stayed for fifty years instead of doing essential field-work. With leukaemia, the same might be said of Ehrlich from whom so much of our morphological preoccupations stem. One major problem, however, lies in the relative rarity of leukaemia, so that statistical studies of large populations at risk are quite indispensable. This matter has been recently reviewed by Witts (1957) who points also to the need for higher standards of diagnosis.

SECTION II

General Therapeutic Background

- (i) **Aim in Management.**
- (ii) **Evolution of Treatment Methods.**

THERAPY IN GENERAL

Aim in management of the leukaemic patient

In spite of recent advances in chemotherapy and radioactive isotope therapy leukaemia remains an incurable disease. Much can be done, however, to keep the patient comfortable by controlling the symptoms associated with high white cell counts, anaemia, splenomegaly and lymphadenopathy. The criteria of good palliative radiotherapy were outlined by Tod (1952), and the management of the leukaemic patient fulfills these requirements in typical fashion. Palliative treatment should aim to relieve symptoms without creating new symptoms due to the treatment itself. The treatment should be relatively simple and of short duration - especially in relation to the overall period of symptomatic improvement. The period spent in hospital should also be short, and an out-patient method of treatment is ideal in this connection. Palliative treatment aims at the improvement in the general well-being of the patient, and the duration of this improved health is of less importance than its quality. The final criterion of good palliation is that the terminal illness should be short.

Acute leukaemia remains a desperately difficult disease to treat with any hope of worthwhile palliation, though some

temporary improvement can be looked for since the introduction of antifolic and antipurine drugs, as well as ACTH and cortisone. The antimetabolites in fact provide helpful tools for the study of the leukaemic disease and it is in that sense, rather than their true therapeutic value, that I see their main importance.

Chronic leukaemia can be usefully palliated over several, and in some cases over many years. Many methods can be employed to induce a remission, both clinically and haematologically, though some may be considered better than others because they involve less hospitalisation, some cause less toxic side effects than others, some induce their beneficial effects quickly, some more slowly - all factors to be carefully considered with each individual patient, and in the light of the criteria described above.

The Evolution of Treatment Methods.

The evolution of treatment methods for leukaemia, as indeed with many other diseases, is inseparably linked with our understanding of the disease itself, its pathology and symptomatology, as well as to the growth of pharmacology. The confusion, for example, between the clinical pictures of malaria and leukaemia during the 19th century was perhaps the main if not the sole reason for the use of quinine as a therapeutic agent.

Apparently it was seldom used alone, and "authentic" cases of improvement may be ascribed to the concomitant use of arsenic. Efforts to produce splenic contraction by cold douching, or by painting the overlying skin with iodine seem no more curious than treatment by prolonged inhalation of oxygen or hypodermic injections of ergotine. Some rationale was advanced for all the treatment methods adopted, though empiricism, combined with an optimism born of despair, ruled the day. It is a chastening thought that we are still no nearer curing this disease, and though we believe we understand it better than a hundred years ago, a historian may well smile a hundred years hence at our confident empiricism.

Chemical Methods

Lissauer, in 1865, is credited with the first observations on the value of arsenic for leukaemic patients. Since this was in the days before blood counting he regarded the improvement as due to the general tonic effect of Fowler's Solution. Cutler and Bradford (1878) were among the first to carry out a detailed haematological study of the effects of arsenic on the blood of normal as well as leukaemic patients. A mixture of iron and arsenic rapidly became a popular approach to the treatment and care of chronic leukaemia.

In his exhaustive monograph on leukaemia Forkner (1938)

quotes the claims of many authors for successful treatment with such widely diverse agents as antimony, silver and lead, Coley's toxin, tuberculin, naphtholene tetrachloride, cinnamic acid, and amidopyrine. Most of these chemotherapeutic agents were in fact found to be valueless in the hands of careful and critical workers. Colchicine was tried many years ago but its toxic effects led to its being abandoned. However Moeschlin (1954), and Leonard and Wilkinson (1955), have described their experience with a new alkaloid of colchicine (desacetylmethylcolchicine) which promises to have some value in chronic myeloid leukaemia. Benzol (C_6H_6) was found to have a depressent effect on bone marrow as long ago as 1900 and was used as an anti-leukaemic agent from time to time from about 1912 onwards. Its serious toxic side-effects, however, including aplastic anaemia and widespread fatty degeneration, finally led to its gradual abandonment.

Arsenic remained the most effective chemo-therapeutic agent until the discovery of a series of nucleo-toxic anti-mitotic drugs during and just after the Second World War. Haddow and Sexton (1946) discovered the anti-tumour effects of urethane (ethyl carbamate), and Paterson et al. (1946) followed this up by demonstrating the value of "this tantalisingly simple radio-mimetic drug" in chronic leukaemia. Wilkinson and

Fletcher (1947) described the value of nitrogen mustard in chronic leukaemia and other reticuloses and Gardikas, Leonard and Wilkinson (1955) have discussed in detail the place of many nitrogen mustard derivatives which have been tested during the past ten years. Another group of radio-mimetic "cross-linking" chemicals is the ethylene imine drugs such as T.E.M., T.E.P.A., and Thio-T.E.P.A. (Paterson and Boland, 1951). These chemicals had been used in Germany and the U.S.S.R. long before the War in the textile industry for binding textile fibres together. It has been thought that their capacity to bind amino acid chains leads to chromosomal cross-linkage and break-down in mitosis, though Bacq and Alexander (1955) suggest that change of shape of the D.N.A. molecule is the initial reaction. In addition to the epoxide B.E.P. (bisethyleneiminosulphyl propane), yet another cross-linkage agent was discovered by Haddow and Timmis (1953) and described in clinical practice by Galton (1953). This was the sulphone Myeleran (1:4-Dimethanesulphonyloxybutane). Now called Busulphan, it has a selective action on cells of the myeloid series, though it also depresses platelet formation. Another of the recent products of the Chester Beatty Laboratories is p-bis(2 chloroethyl) aminophenylbutyric acid. This drug, known as C.B. 1348, and more recently as chlorambucil, seems to be more effective against lymphatic leukaemia than myeloid,

though some workers have been unduly enthusiastic about it.

An international conference on the subject of alkylating agents was recently sponsored by the New York Academy of Sciences (March, 1957) and in conclusion Professor A. Haddow "doubted whether they (alkylating agents) would have any ultimate or permanent place in the chemotherapy of malignant disease." (Haddow, 1957).

A different approach to the chemotherapy of the leukaemias is by the anti-metabolic drugs. Farber and his co-workers (1948) found that folic acid made acute leukaemia worse, and on testing folic acid antagonists (the pterins) they succeeded in controlling acute leukaemic cases for significantly longer periods than hitherto. Not only did these drugs increase the duration of life of acute leukaemic patients, they provided a new tool for the study of the disease. A second attack on the metabolic processes of leukaemic cells was that of the purine antagonists. The synthesis of 6-mercaptopurine was the result of a ten-year study of possible antagonists of precursors of nucleic acid by Clarke et al. (1953). The effect of this agent on leukaemia was quickly established, and yet another new weapon was provided, of especial value in acute leukaemia. It can also be effective even after resistance has been established to other antileukaemic drugs, and even in chronic leukaemia in an acute terminal phase.

Resistance is acquired to all of these chemotherapeutic agents, presumably by enzymic adaptation, and it is also to be noted that they are by no means free from toxic side-effects such as buccal ulceration, diarrhoea, nausea and vomiting, purpura, aplastic anaemia, etc. Dosage control is of great importance and idiosyncrasy has to be anticipated.

The steroid hormones A.C.T.H., cortisone, and its newer derivatives, also have a real place in the treatment of the leukaemias, but almost entirely in the acute lymphoblastic type. They seem to be valueless in acute myeloblastic and monocytic leukaemia, and in chronic leukaemia too they have no effect except occasionally in the control of the haemolytic features sometimes seen in chronic lymphatic leukaemia.

Ionising Radiations and Radio-mimetic Chemicals.

The voluminous literature on this physico-chemical borderland has been recently reviewed by Bacq and Alexander (1955). There is no doubt that the biological effects of ionising radiations can be closely simulated by certain radio-mimetic chemicals such as those just described - especially the nitrogen mustards, T.E.M., Myeleran, etc. They all produce chromosomal breaks, and can kill both dividing and resting cells. They are both mutagenic and carcinogenic. They can suppress

anti-body formation, cause acute or chronic degenerative changes in bone-marrow, intestinal mucosa and testis, and can inhibit the growth of certain tumours. Many of these superficial similarities, however, have differences in detail. For example, the period of maximum sensitivity for the production of chromosome aberrations is during early interphase with chemicals, but just before prophase with x-rays. There are also differences in the site of action of these agents on the chromosomes. Furthermore, nitrogen mustards produce much more frequent mosaics in *Drosophila* than do x-rays. It is interesting to note also that though cysteine and cysteamine protect animals against the lethal effects of both x-rays and nitrogen mustard (Peczenik, 1953), this is not true for T.E.M. (Nadkarni, 1954).

So far as leukaemia is concerned Elson et al. (1955) claim that chlorambucil produces the same effect as x-radiation on lymphoid tissues, while myeleran produces similar effects on myeloid tissue. Both chemicals together are claimed to induce a total effect which is identical to x-radiation, in animals at least.

Radiation Methods.

Heliotherapy was at one time claimed to be useful in leukaemia, but probably did little more than help general supportive measures, so necessary with any course of treatment.

It is quite remarkable, however, how quickly after the discovery of roentgen rays, and the radioactivity of radium, the biological effects of ionising radiations were appreciated. The effects on the blood were noted within a year, skin erythema and necrosis were soon recognised as hazards of fluoroscopy, and by 1902 Pusey described the use of x-rays in the treatment of various diseases including leukaemia. This was only seven years after the discovery of x-rays, and by 1905 the literature on this subject was already becoming voluminous.

Mode of action. It would be out of place to discuss here the detailed theories of radiobiology, though some consideration must be given to a few of the more commonly advanced hypotheses concerning the antileukaemic effects of ionising radiations.

One of the earliest observations of the effects of ionising radiations was their power to depress the leukocyte count, and if the exposure to the rays was long enough a depression of all the blood elements took place, and death followed from aplastic anaemia. Heinecke was one of the first to carry out careful studies of the different sensitivities of tissues and blood cells to radiations, and it was soon generally realised that though all living cells were vulnerable, those in active mitosis were especially so. Thus the bone marrow was more sensitive to radiations than muscle tissue, even though the

latter could also be damaged by larger doses. However, that this is not the whole answer is clear from the radioresistance of some tumours, and indeed some types of leukaemia, in which active mitosis is taking place. Thus the old 'Law' of Bergonié and Tribondeau is no longer accepted as an adequate explanation of the fact that the stem cells in the marrow are more sensitive than fully differentiated cells of other tissues. Recent work by Hevesy (1956) on the existence of different soluble fractions of D.N.A. possessing different radio-sensitivity in radioresistant tumours might throw new light on this old problem. The fact that the lymphocytes disappear from the blood after irradiation more quickly than neutrophils, and the latter more quickly than red cells, has been explained as due to the differing life spans of these three types of cell. Once again, this explanation is not quite so simple and authorities are still sceptical. The facts remain.

There is much evidence, from in vivo as well as in vitro experiments, to support the theory of a direct action of radiation on leukaemic white cells. There is, however, even more interesting and compelling evidence in favour of an indirect action. The production of leukopenia in animals following the injection of serum from irradiated leukaemic patients was demonstrated as early as 1905 and has been repeated on many

occasions (Forkner, 1938). Antimitotic effects in the bone marrow of the sternum have been reported by Gunz (1953) following irradiation of the spleen, care having been taken to avoid any scattered irradiation of the sternum. Levitt (1948) has emphasised that since splenectomy does not have the same effect as irradiation of the spleen, the radiation effect cannot be due to simple depression of activities which have their seat in the spleen. There is thus strong opinion in favour of the production of some leukolytic substance in the irradiated spleen of leukaemic patients. Presumably any such substance would act by inhibiting the synthesis of nucleic acid by one of many possible pathways. Much work on this subject is still called for, and may yet provide further tools in the search for a final cure of leukaemia, or its effective control.

Whatever its precise mode of action irradiation therapy leads to a depression of the excessive leukopoiesis, with a concomitant increase in erythropoiesis, diminution in the size of the spleen and lymph nodes, and an improvement in the general condition of the patient. Furthermore, this improvement may last for many months, or even for some years, a fact which argues an actual reduction in the activity of the underlying disease process.

X-ray Therapy

The earliest attempts at irradiation therapy for leukaemia consisted of whole body radiation - so-called spray-radiation. Soon other workers tried and advocated the irradiation of different portions of the body - sometimes the long bones only, aimed at treating the active bone marrow; others would treat the enlarged spleen alone, with or without the lymph nodes in lymphatic leukaemia; others suggested the irradiation of the thorax, or of the heart to treat only the circulating blood; still others suggested treating the vegetative nervous system which was considered the seat of the underlying defect causing hyperactivity of leukopoietic tissue. There were those also who argued that irradiation of the kidneys was important in order to promote excretion of uric acid. There are those who adopt a less dogmatic view and agree that when one method of treatment appears to be losing its effect it is reasonable to attempt further treatment by other means. With the advent of various chemotherapeutic approaches to leukaemia the failure of a radiation method of treatment would seem to call for a chemotherapeutic approach, rather than continued use of one antimitotic agent. If it be assumed that even radiation therapy acts by virtue of a chemical blocking of nucleic acid synthesis, then, on the analogy of bacterial resistance, it is

undoubtedly preferable to use when necessary a new agent which will perhaps interfere with cell metabolism in a different way. Attempts at synergism have been made and x-rays have been combined with arsenic or with benzol. Magnin et al. have more recently reported favourably on the synergism of cortisone and antifolics in acute leukaemia. (1953).

Radium Therapy

Radium has been used in the treatment of leukaemia (e.g. White, 1933) and its gamma radiation does of course have biological effects similar to x-rays. The problem with radium therapy is that in order to attain a usable beam of radiation a substantial quantity of radium is necessary. This has been available for many years in the form of the so-called radium bombs. These telerradium units are now being replaced by even more effective bombs of radiocobalt (Co^{60}). The penetrating quality of this gamma radiation is equivalent to x-rays generated at over a million electron volts, and so far as leukaemia is concerned this is needlessly high. However, there is no doubt that such units have been and can be used in leukaemia treatment. Radium in much smaller quantities has been used under emergency conditions when no other form of radiation has been available. Melville (1950) has described the use of a surface application

of radium amounting to only a few hundred milligrammes (all that was available) placed over the spleen of a leukaemic patient. The response was very satisfactory and a good remission was induced. Many writers have made claims for the superiority of radium over other methods but one rather suspects that no other agent was available to them.

The indications for the use of radium are clearly similar to those for the use of x-ray therapy. The latter is much simpler and is certainly safer, for the operator as well as for the patient.

Thorium Therapy

The radioactive decay products of the thorium family have been used in the treatment of leukaemia, the two members most commonly used being radiothorium and thorium-X. Both of these substances have been found to remain in the body, in liver, spleen and bone, for long periods, and aplasia is a dangerous side effect. The poor prognosis of leukaemia, however, tempted many workers to continue to use these thorium derivatives, though they have been abandoned in Britain for many years.

Radioactive Isotopes in the Treatment of Leukaemia

Since this is the main subject of this thesis it is appropriate to consider the matter in some detail.

Thanks to the pioneer work of Gustave de Hevesy in the

study and development of the method of biological tracers, using natural stable and radioactive isotopes, the scene was set for the arrival of artificial radioactivity in 1934. The discovery of artificial radioactivity by the Joliot-Curies introduced a new, vast, and still expanding chapter in the history of radiology. Hevesy and his co-workers had already shown that tissues will concentrate metabolites whether they be radioactive or not. Tissues are unable to distinguish between stable and radioactive isotopes of any element, so that cells will absorb, metabolise, and excrete radio-isotopes depending only on the affinity of the cells in question for the element presented to them. For example, phosphorus is an ubiquitous cellular metabolite, the concentration of which in any tissue depends on metabolic activity; thus the distribution of phosphorus throughout the body is not uniform since the metabolic activity of tissues varies so widely. Strontium, being the biochemical analogue of calcium, is on the other hand selectively concentrated in the skeleton, and is thus confined largely to one organ system. Iodine is another example of an element which is selectively absorbed and concentrated in one organ system, namely the thyroid gland. When these elements are radioactive, the organ in which they are deposited, or more properly, through which they pass, will be irradiated continuously until the

isotope leaves the tissue in question and/or until the isotope decays into an inert element.

So far as leukaemia is concerned, radioactive phosphorus (P^{32}) in the form of the sodium acid phosphate, was used as early as 1937 by Lawrence and his co-workers (1939). The importance of the chemical compound in which the isotope is incorporated was shown by studies in the distribution of insoluble chromic phosphate. This material was selectively taken up by the reticuloendothelial system, mainly the liver and spleen. (Low-Beer, 1950). The size of the particles were found to be of importance, and though Lawrence and Dougherty (quoted by Low-Beer, loc. cit.) tried treating five cases of chronic myeloid leukemia by chromic phosphate, they met with unfavourable responses and abandoned this approach.

Radioactive sodium (Na^{24}) was considered on theoretical grounds to be an ideal source of general body radiation, since sodium is an extracellular metabolite with no special selective uptake by any tissue. Hamilton and Stone (1937) were, however, disappointed with their first trials on leukaemic patients and, though Evans et al. (1948) were somewhat more enthusiastic, radiosodium has nevertheless been generally superceded by radiophosphorus.

Though Shepperd et al. (1947) have studied radioactive

gold (Au^{198}), so far as its distribution in the body is concerned, and some workers, e.g. Hahn et al. (1956) have in fact used this isotope enthusiastically in leukaemia, it has been generally abandoned. The importance of the colloidal particle size is again seen with Au^{198} and the selective uptake by spleen and liver is characteristic.

Indications for Treatment

This is commonly the title to a section in most monographs on leukaemia, but a much more desirable attitude of mind is to consider the mode of management, and only as a distinctly different problem, the indications for positive anti-leukaemic treatment in some form or other. It cannot be too strongly stressed that a mere elevation of the white cell count with some primitive white cells in the peripheral blood is no indication for dosing the patient with mustard drugs or radioactive isotopes. As was said at the outset to this section on therapy, the aim in management is to improve the quality of a patient's health and living by improving his blood and removing symptoms associated with his high white cell count and low red cell count. If a patient is kept under observation it will generally be found that his white cell count slowly increases and ultimately the red cell count will begin to fall. The red cell count sometimes is found to fluctuate, and action should be delayed until there

is no doubt that the count is falling. The errors inherent in blood counting are significant. (Williams, 1954).

Apart from a falling red cell count as an indication for positive treatment, it may be necessary to consider treating a leukaemic patient because the spleen is assuming unpleasant and uncomfortable proportions. In the writer's experience there is an interesting group of subleukaemic (rather than aleukaemic) cases in whom a painfully large spleen occurs in association with only a moderately elevated white cell count. In this type of case it is possible to provide considerable relief of discomfort, though curiously little splenic resolution, by small doses of x-rays to the spleen. It will be found, incidentally, that the white cell count in such cases falls slowly and can indeed be reduced to very low levels with impunity. As well as a large spleen, treatment may be indicated for large and mechanically troublesome lymph nodes in lymphatic leukaemia. In this connection, the writer's experience has already been mentioned that the lymph nodes of lymphatic leukaemia are by no means as sensitive to x-rays as lymphosarcomatous nodes, or indeed any of the other reticulososes.

Sometimes a patient whose white cell count is slowly increasing but whose red cell count is well maintained, may complain of vague malaise. Even in the absence of any discoverable cause for this, it is often wise to institute a

course of treatment. The patient himself is often able to indicate deterioration before any clinical or haematological test will do so.

Indications for Resuming Treatment

After the successful induction of a remission, there are two schools of thought as to further treatment. Some believe that frequent repeated treatment should be given by small exposures of x-rays to the spleen or elsewhere, or by small doses of P^{32} (Osgood et al., 1955), or by maintenance doses of one of the chemotherapeutic agents. The other school of thought is that the greatest improvement possible should be achieved, and then the patient should be allowed to live a life as free of hospital control as possible. The patient who lives, as it were, in the shadow of the hospital for the remainder of his life does, I believe, lose one of the greatest advantages of his palliative treatment.

As a member of the second school of thought, what are the indications for re-treatment? Once more the red cell count or haemoglobin level is the most important single index of the patient's well-being. Provided the haemoglobin level is rising, or static, further treatment should be withheld, but as soon as the physician is quite certain that the level has dropped significantly further treatment should be considered.

As with the initial treatment, other factors such as splenic discomfort, large lymph nodes, or the vague but definite deterioration in the patient's general condition may call for special consideration, even with a good and steady haemoglobin level.

Contra-indications for Treatment

Here again, by treatment is meant the application of some positive antileukaemic agent, since significant assistance may be given to a patient even when there exists some accepted contra-indication to, for example, x-ray therapy. It is agreed that acute leukaemia is aggravated by radiation therapy in all its forms, and the same applies to most of the chemical agents of known value in chronic leukaemia. Thus when a chronic leukaemic patient begins to show any signs which may herald the onset of an acute phase of his disease it is wise to withhold treatment. Such signs as pyrexia, mucosal bleeding and petechial haemorrhages, considerable increase of stem cells in the peripheral blood, sudden drop in the platelet count, (especially in myelogenous leukaemia), and severe splenic pain, are all indications for exercising the utmost caution. In the past, such an acute phase of a previously chronic leukaemia was regarded as the end of the struggle, and apart from transfusions, often badly tolerated, nothing could be done for these patients.

Fortunately it is now possible to exhibit 6-mercaptopurine with some hope of success in the form of another remission, albeit a short one.

The Refractory State

Much has been written about the so-called refractory state of leukaemia, the condition at which a previously responsive chronic leukaemia fails to show much or any response to the same agent. Low-Beer (1950) asserts that this so-called radioresistance, in the sense of induced metabolic change, has not been proved, and he believes that since there is a gradual increase of primitive cells in the bone marrow and blood of chronic leukaemic patients, associated with a progressive replacement of erythropoietic and megakaryocytic elements, it is this increasing activity of the malignant disease and not radioresistance which is responsible for the lessened response to radiation in the later stages of chronic leukaemia. The complete lack of response of acute leukaemia to radiation is cited as substantiating this view. Variation in radiosensitivity in the same patient at different phases of his disease is, however, a different problem from the variation in sensitivity seen between different patients. This matter is discussed in detail in Section V.

Synergism

Much has been written on the synergistic value of combined methods of treatment. In a recent "Round-Table Discussion on Therapy" of leukaemia (Rebuck et al., 1957), many speakers claimed "undoubted" improvement from combinations of chemical, isotopic, steroid or x-ray therapy. Mitchell (1953) in discussing the potentiating effects of Synkavit has emphasised the importance of a planned pharmacological approach to this difficult subject of synergism, and the author deems it wise to avoid further discussion here. Suffice it to say that few of the many claims in this field would stand up to a critical examination. The subject does, nevertheless, call for most careful and detailed study, and is closely linked to the problems of acquired cell-resistance.

General Supportive Measures

It has long been appreciated that much can be done for the leukaemic patient in addition to specific anti-leukaemic treatment.

An important feature in the management of the leukaemic patient is the avoidance of fuss over such matters as diet, work and rest. A common-sense attitude should prevail, and provided the diet is well-balanced, and work is not such as to tax the strength of the patient, some occupational activity should be pursued as long as possible. Though acute differences of

opinion exist, the author believes firmly that it is rarely in the patient's interests to know the nature of his disease, since he can so readily discover the hopelessness of his prognosis. Such a realisation greatly undermines the quality of a clinical remission, and rare indeed is the patient who can adjust well to the knowledge of his approaching death. The avoidance of undue fussing is an essential part of reassurance.

Iron tonics for leukaemic patients have been in vogue for at least a century. However, in a haemolytic phase of leukaemia the patient may take up iron which he can neither use nor excrete, and further iron supplies can only increase the embarrassment of his siderotic organs. Crosby and Damashek (1955) condemn iron therapy in haemolytic anaemias, and caution is clearly required with the leukaemic patient.

The theoretical value of the vitamin B complex has already been mentioned, and the author feels that this vitamin, combined with vitamins A, B and C, (as well as liver in the diet) are wise if still empiric adjuvants.

Infection is often a great problem, especially in the acute forms of the disease, and also commonly in chronic lymphatic leukaemia. Antibiotics are of inestimable value, and many patients who would otherwise have succumbed to advancing pulmonary infections have been kept alive and well for several years longer. It is true to say that antibiotics have

significantly extended the life-expectancy of chronic lymphatic leukaemia apart altogether from specific anti-leukaemic agents.

Bone marrow injections have been tried and found wanting, but blood transfusions have an undoubted place in the general care of leukaemic patients. Most clinicians have had experience of remissions of leukaemia following blood transfusion, remissions which were qualitatively better than could have been expected from the quantity of blood transfused. Sabin et al. (1924) have in fact reported maturation of myeloblasts in a case of subacute myeloblastic leukaemia following blood transfusion, and Schwind (1947) had the same experience following transfusion of fresh plasma. In acute leukaemia in children the author has seen remarkable though temporary improvement after exchange transfusion. It should be mentioned, however, that though blood transfusion can be helpful, it is often open to doubt whether the clinician is justified in using precious blood for the temporary support of a patient whose very need for blood is usually an indication of approaching and inevitable death. Rarely does transfusion of the grossly anaemic patient permit subsequent useful specific treatment with radiation or radio-mimetic drugs.

Splenectomy in Leukaemia

It was natural that the size and discomfort of the spleen in leukaemia should tempt surgeons to remove the organ,

and Forkner (loc. cit.) quotes Bryant as having done so as long ago as 1866. The results were disastrous, though a few of the many subsequent reports were more favourable. With all the present-day excellence of surgical technique the removal of a large and adherent leukaemic spleen may still prove extremely difficult, and since palliation is the sole intent of such an operation few surgeons are willing to embark on splenectomy even with the most favourable case. Though splenectomy may be valuable in certain haemolytic anaemias, such a phase in the course of leukaemia is usually a terminal one, and the patient would not be considered suitable for operation.

The author has yet to see a leukaemic patient for whom splenectomy has at any time seemed worth contemplating.

Heterologous Marrow

Though discussion of animal research has been deliberately avoided in this thesis, it would be unwise not to mention the recent and fascinating work of Loutit and his colleagues, (Barnes et al., 1956). By whole-body irradiation of leukaemic mice to lethal dosage levels Loutit aimed to kill off all leukaemia cells and stem cells, and at the same time to inhibit antibody-formation in the irradiated mice. Then he injected heterologous marrow from non-leukaemic mice, or even from rats, and the implanted marrow did successfully repopulate the

haemopoietic system of the irradiated mice with non-leukaemic blood cells. This entirely new and bold approach to leukaemia therapy has rightly earned for Loutit the Leukaemia Society's Award for 1956. The possibilities of applying this principle to human leukaemia are being considered, though confirmation in other laboratories is still awaited.

Causes of Death in Leukaemic Patients

Life has been defined as the ensemble of functions that resist death, and this is particularly apt when consideration is given to the causes of death in leukaemic patients. It is of course often difficult at autopsy to understand how any patient has survived so long with so much obvious anatomical derangement.

It is not an uncommon experience at autopsy to find an unsuspected chronic lymphatic leukaemia, clearly asymptomatic before death, and not significantly related to the sequence of events which culminated in death. This must be rare with chronic myeloid leukaemia.

Infection is a frequent terminal feature of acute leukaemias and chronic lymphatic leukaemia, and may well be an important contributory cause of death. The value of antibiotics in this connection has already been mentioned.

The author has seen substantial haemorrhage from the

nasopharynx and from the intestine resulting in death, but this is a distinctly uncommon event with chronic leukaemia. Small mucosal bleedings and petechial haemorrhages are not a significant cause of the anaemia of leukaemia. That very low levels of haemoglobin are compatible with a moderately active life is common experience in tropical countries where nutritional anaemias are almost endemic. It may also be seen in children with congenital hypoplastic marrows, where death may be delayed until adolescence or early twenties, and is in any case largely due to extensive haemosiderosis. Thus it seems that anaemia alone is not a necessary cause of death in leukaemia though it may well be a contributory cause in many cases.

That aplasia is not a constant terminal finding in leukaemia is well established. Even in the presence of a gross anaemia the erythropoietic activity of the marrow can be seen microscopically, and can also be demonstrated by radioactive iron studies. The author has found this latter feature in several patients whose iron turn-over was measured. Some have proved quite aplastic and have died within a few weeks: others have had active erythropoiesis suggesting haemolysis though this was not confirmed by serological studies. The latter group of patients also died rapidly with a gross and refractory anaemia which did appear to be the main cause of death. (This work has not been published, but accords well with the experience of

other workers, such as Huff et al., 1952).

"Iatrogenic death" is a more common jibe than a fact. That myelofibrosis and marrow exhaustion may be induced, e.g. by irradiation of the bone marrow has often been suggested, but many writers (e.g. Korst et al., 1956) have equally emphasised that myelofibrosis may occur at any stage of treated or untreated leukaemia or polycythaemia vera. That a chronic leukaemia may become acute as a result of treatment has been described from time to time, but though the association in time is sometimes interesting it is no proof of a causal relationship.

That any organ may be infiltrated with leukaemic cells, and that haemorrhage may occur into any tissue has already been mentioned, and such anatomical derangements might lead to a breakdown in function incompatible with continued life.

Whatever its cause, it is unfortunately still true that death is inevitable for the leukaemic patient.

SECTION III

Pharmacology of Radiophosphorus.

- (i) Physical and Chemical.
- (ii) Radiation Effects.

THE PHARMACOLOGY OF RADIOACTIVE PHOSPHORUS ($^{32}\text{P}_{15}$)

Forkner (1938) draws attention to the report of Roger and Josué (1899) of the leukaemogenic properties of stable phosphorus, but also discusses several studies of the results of treatment of the leukaemias by oral phosphorus. The pharmacological similarities of arsenic and phosphorus are noted as a possible explanation of this antileukaemic effect, but no study of stable phosphorus seems to have been published during the past fifty years.

We are concerned here, however, with radioactive phosphorus, the biological effectiveness of which depends on its radioactivity. It is relevant, therefore, to discuss its pharmacology from the physical as well as the biochemical point of view.

Characteristics of therapeutic usefulness. Radioactive isotopes may emit alpha or beta particles and/or gamma rays. Alpha particles are in fact emitted by only a few artificial isotopes and consist of helium nuclei ejected with great velocity from the nucleus of the isotope. They are rapidly stopped in tissues, and even in air, liberating all their energy in the former within a fraction of a millimetre. Beta "rays"

are high speed electrons, with greater penetrating power, but still a range limited to a few millimetres in tissues. Gamma rays are truly penetrating electromagnetic radiations capable of passing through several feet of concrete.

Clearly, the gamma rays released in a given gram of tissue will produce only a small amount of ionisation locally, most of their energy being expended elsewhere along their paths. Beta rays, on the other hand, expend all their energy in the immediate vicinity of their site of emanation. The ideal therapeutic isotope, therefore, is one which emits beta rays and which will be selectively absorbed into a particular tissue. Radio-phosphorus is one of the few isotopes possessing these requirements in some measure.

A further therapeutically important characteristic is the effective half-life of the isotope in question. It is biologically and posologically undesirable to employ a compound which disintegrates very slowly over several years, and which is also retained in the body during that time - whether in the diseased tissues or elsewhere. The contrary is also true, in that an isotope may decay so rapidly as to be useless by the time it reaches the physician from the distributor.

Physical characteristics of radioactive phosphorus

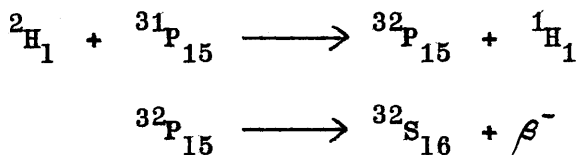
The element phosphorus occurs in nature in only one form - $^{31}\text{P}_{15}$. Five isotopes can be produced by nuclear excitation - $^{29}\text{P}_{15}$, $^{30}\text{P}_{15}$, $^{32}\text{P}_{15}$, $^{33}\text{P}_{15}$ and $^{34}\text{P}_{15}$. Since all six isotopes of phosphorus have the same number of protons in their nuclei (15), they are chemically identical. ^{29}P and ^{30}P are positron emitters, but with a half-life of 4.6 seconds and 2.3 minutes respectively, they are of no value in biological work. ^{33}P has a half-life of 25 days, and though this could be a useful feature, the beta particles emitted have a very low maximum energy of only 0.27 Mev. ^{34}P has a good high energy beta emission (5.1 Mev.) but has a therapeutically useless half-life of only 12.4 seconds. ^{32}P on the other hand, emits energetic beta particles of 1.70 Mev maximum energy, and with a disintegration rate of 4.8% per day has a half-life of 14.3 days. This isotope has therefore physical characteristics of obvious biological value and has been put to considerable use. It is with this particular isotope that this thesis is concerned.

$^{32}\text{P}_{15}$ can be produced either in the cyclotron or in the nuclear reactor. The cyclotron method requires the bombardment of stable phosphorus with deuterons of relatively low energy, only the neutron entering the phosphorus atom to produce $^{32}\text{P}_{15}$. When the $^{32}\text{P}_{15}$ ultimately regains stability by emitting a beta

particle the nucleus consists of 16 protons and 16 neutrons, that is stable sulphur, $^{32}\text{S}_{16}$. The cyclotron was the source of $^{32}\text{P}_{15}$ used by Lawrence and his co-workers (1939) in the first clinical studies of this isotope in medicine.

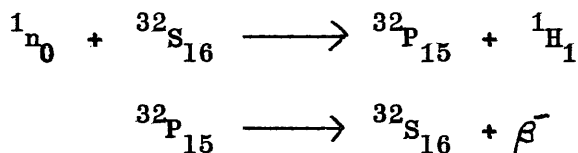
The explosion of the atom bombs over Hiroshima and Nagasaki in 1945 ushered in a new epoch of medical science, however, and isotopes of many different kinds have now become available in large quantities, and considerably cheaper than the cyclotron-produced isotopes. $^{32}\text{P}_{15}$ is now produced in the nuclear reactor, stable sulphur being bombarded by neutrons, so that $^{32}\text{S}_{16}$ becomes $^{32}\text{P}_{15}$.

The cyclotron method of production may be symbolised thus:-



The reactor method of production may be symbolised

thus:-



The specific activity of the radioactive phosphorus (i.e. the ratio of $^{32}\text{P}_{15}$ to admixed $^{31}\text{P}_{15}$ "carrier") is much higher with the reactor-prepared isotope than with the cyclotron

isotope. This fact is at least as important as its cheapness and ready availability.

Finally, the radioactivity on which the usefulness of this isotope depends consists of a negatively charged electron emitted with a maximum kinetic energy of 1.70 million electron volts, the average energy being approximately 0.6 Mev. The maximum range of these beta particles in air is about 7.05 metres, while in tissues of unit density their average range is 2 mms. with a maximum of 7 mms. Thus most of the ionising action is localised to the tissue which takes up the isotope.

Biochemical Characteristics of Radioactive Phosphorus

The metabolism of stable phosphorus was of course studied chemically long before its radioactive isotopes were discovered. Nevertheless, since $^{32}\text{P}_{15}$ is biochemically indistinguishable from $^{31}\text{P}_{15}$ all the subtleties of radioactive tracer studies have added greatly to our understanding of the dynamics of this ubiquitous element in living tissues. The literature is already voluminous and continues to expand.

Radiophosphorus has been used clinically both externally (to irradiate skin and eye lesions) and internally. The latter only concerns us here. Colloidal suspensions of chromic phosphate have been injected intravenously in leukaemic patients, as well as into the peritoneum and pleura. It has now been

abandoned. Sodium and magnesium phosphate was prepared by Scheer (1952) as a compound for interstitial use, depending on its capacity to remain localised in tissues at the site of injection. It has no place in leukaemia therapy.

The compound with which this thesis is concerned is the inorganic soluble sodium phosphate, and the biochemical characteristics of this compound alone will be discussed.

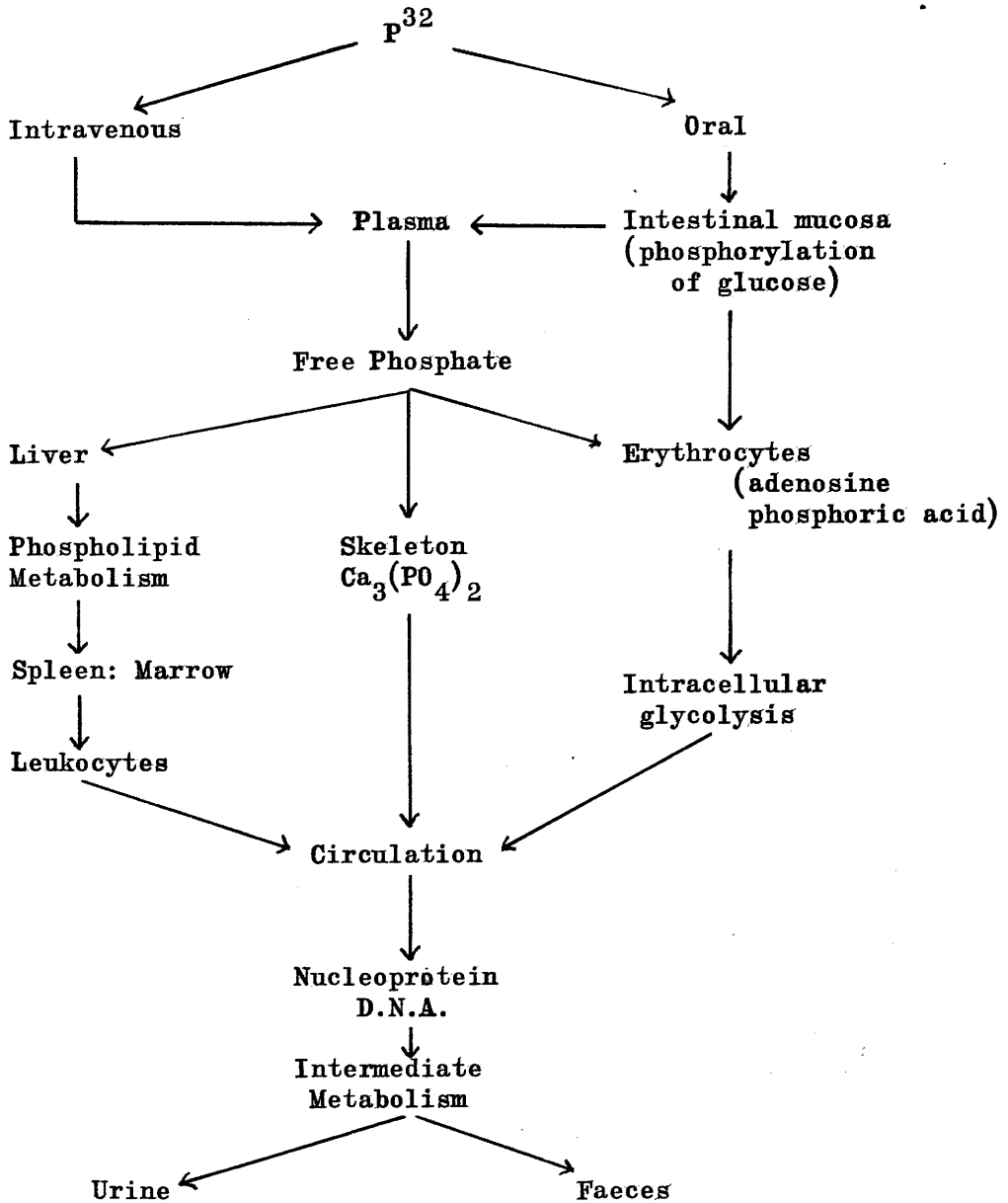
Absorption and excretion. For therapeutic use the P^{32} is oxydised to phosphoric acid, neutralised with sodium hydroxide to a pH of 7.0, and administered as a mixture of sodium acid and basic phosphates. This may be given orally or intravenously. After oral administration in the normal subject about 75% of the given dose is absorbed, the remainder appearing in the faeces. Renal excretion is rapid, being the main route of elimination, and up to 50% of an absorbed oral or intravenous dose is excreted in the urine during the first 4 to 6 days. Thereafter excretion falls to less than 1% of the administered dose per day (Goodman and Gilman, 1955). In leukaemic patients urinary excretion may be reduced, as it is also in polycythaemia vera.

The combination of radioactive decay and excretion results in a radiobiological half life of about eleven days, according to measurements made by Easson, Mackenzie and Jones

(1952, unpublished). This is in agreement with the findings of Mitchell (1951), though Osgood (1956) would disagree in some details.

Distribution. Phosphorus is a constituent of all cells and tissues, and its metabolic pathways are consequently extremely complex. A phosphate radical taken up from the food may participate in the phosphorylation of glucose in the intestinal mucosa; it may instead enter the circulation as free phosphate where it may then enter a red cell and become incorporated into an adenosine phosphoric acid molecule and participate in glycolytic processes within the cell, later appearing in the plasma. From the plasma it may return to the liver to take part there in the formation of a phospholipid molecule which in turn may be carried in the circulation to the spleen or other organs to be incorporated into a leukocyte. Alternatively, the phosphate radical may pass directly into the skeleton from the plasma. Such are the dynamics of metabolic processes that the phosphate radical may return again to the circulation, after following any of its possible paths, and participate in the formation of nucleoproteins, desoxyribose nucleic acid, or other products of intermediate metabolism.

The above outline of possible metabolic pathways was described by Low-Beer (1950), and is expressed diagrammatically



Possible Metabolic Pathways of an absorbed phosphorus atom.

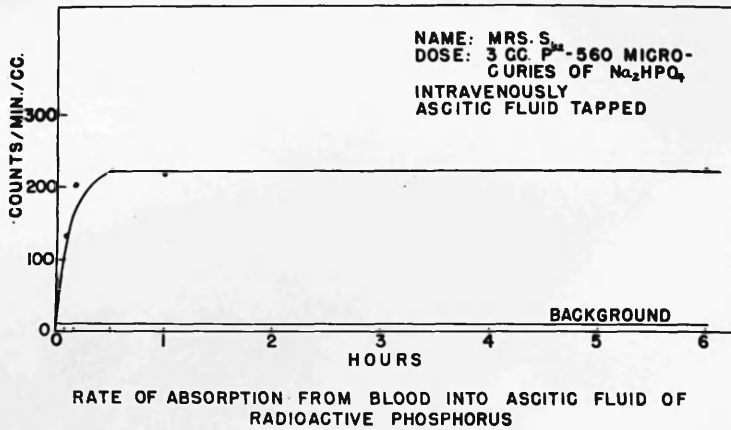
Figure 10.

in Figure 10.

The differential uptake of phosphorus by cells depends on at least three factors: (1) the total amount of phosphorus in exchangeable form in the tissue being studied, (2) the rate of turnover of phosphorus by that tissue, and (3) the rate at which new tissue is being formed.

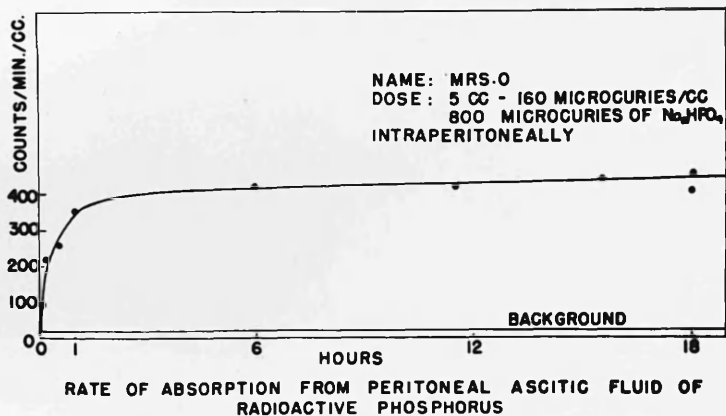
For example, the total amount of inorganic phosphorus in bone is high, so that eventually a large proportion of an administered dose of phosphorus will find its way there. The effect of the rate of turnover of phosphorus is exemplified by liver and brain tissues. Both organs have approximately the same phosphorus content, but the higher rate of turnover by liver leads to a much greater uptake of radiophosphorus by the liver than by the brain. The third factor is exemplified by the higher rate of uptake of radioactive phosphorus by neoplastic tissue as compared with the same tissue when growing normally. This fact is so marked in the case of certain brain tumours that localisation of a tumour is possible because of the relatively high differential uptake of radiophosphorus. (Morley and Jefferson, 1952; Selverstone et al., 1949).

A vast literature now exists on the subject of phosphorus uptake by various tissues, both human and animal, and the accumulated findings clearly indicate the preferential uptake of P^{32} in all neoplastic as well as leukaemic tissues. So far



Rate of transfer of P^{32} from blood into ascitic fluid

Figure 11.



Rate of transfer of P^{32} from ascitic fluid into blood

Figure 12.

as leukaemia is concerned, it has been shown by Kenny et al. (1941), Reinhard et al. (1946), Warren (1943), and many others, that P^{32} is absorbed most actively into the liver, spleen, lymph nodes, bone marrow and kidney. Low-Beer (loc. cit.) points out that the longer the interval between administration of P^{32} and death the greater is the concentration of P^{32} in bone, though Osgood (1956) emphasises that in human adults this deposition is so slow relative to radioactive decay "that progressive accumulation does not occur even in patients who have been treated for years".

In leukaemic patients, during the first 48 hours after administration of P^{32} , the red cells contain more P^{32} than the leukocytes. Within nine or ten days, however, the leukocytes contain four or five times the amount of P^{32} in erythrocytes, and this is even higher if the P^{32} is given intravenously.

Low-Beer has also shown (Figures 11 and 12) that though phosphorus is mainly a cellular metabolite, P^{32} administered intravenously can be detected in ascitic fluid as soon as five minutes after injection, and equilibrium between blood and ascitic fluid is reached within 30 minutes. Diffusion in the opposite direction has also been demonstrated, and P^{32} injected intraperitoneally appears in the blood within five minutes, though equilibrium in this case takes about 60 minutes. The

same author reports similar diffusion of radiophosphorus between blood and pleural effusions. The absence of selective concentration in tissue fluids is important, and demonstrates the futility of treating metastatic carcinoma in these regions with soluble P^{32} .

The Biological Effects of Radioactive Phosphorus

The histological changes produced by P^{32} are due to its beta radiation. These changes would not be expected to differ significantly from those observed after irradiation with x- or gamma rays. Platt (1947) has described in detail the histological appearances in 43 patients suffering from various reticuloses, all of whom were treated with P^{32} before death. The tissues of patients dying of similar diseases but not treated with P^{32} were used as controls.

The histological changes described by Platt may be summarised as showing:- varying degrees of cellular disintegration; abnormal mitoses producing giant irregular nuclei; generalised tissue fibrosis; hyalinisation of collagen; vascular changes characterised by thickening and hyalinisation of small blood vessels. The most extensive changes were noted in bone marrow, spleen and lymph nodes, as would be expected from the high selective uptake of phosphorus by these tissues - a fact which explains the striking effect of therapeutic dosage

of P^{32} in leukaemia. Changes of a lesser degree were also observed, however, in kidneys, lungs, gastro-intestinal tract, ovaries and testes.

A hitherto unreported finding, which may well be an important effect of P^{32} on the bone marrow, has been described by Dr. Helen Russell. This is a curious bright red colour of the marrow throughout the length of the femur, instead of the usual fatty yellow-grey colour seen in untreated leukaemia. Microscopically it resembles the naked eye picture of the megaloblastic marrow of pernicious anaemia, but histological examination shows that the colour is due to wide vascular spaces with haemorrhagic degeneration and capillary stasis. This picture is reminiscent of the effects of lethal whole-body irradiation as seen for example in the bone marrow of monkeys irradiated to LD 50 levels with x-rays. The similarity between these two marrow pictures is sufficiently striking to call for more detailed study. It is of interest that such a disorganised marrow has been seen as soon as three weeks after a dose of P^{32} (Case E 11), and as long as 160 weeks after the start of P^{32} therapy (Case M 14). In the latter case a total quantity of 40 mcs. of P^{32} had been given, while in the former only 6.0 mcs. had been given. It is not easy, therefore, to

see any immediate explanation for this marrow effect, though it has not been observed in patients treated by other methods at this hospital.

(1) Isolation of a Single Series

(11) Prediction Method of Isolation

SECTION IV

Author's Experience with Radiophosphorus

(i) Evolution of a Dosage System

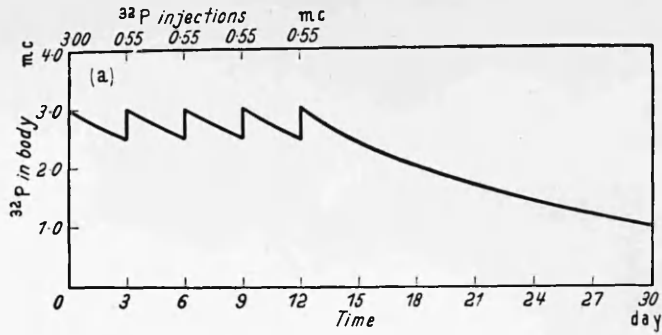
(ii) Prediction Method of Dosimetry

Evolution of a Dosage System for Radioactive Phosphorus Therapy

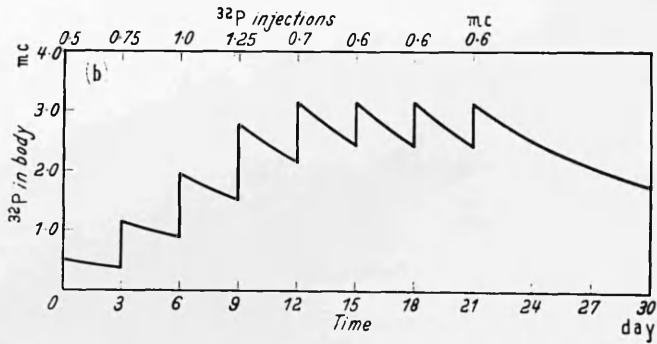
Before discussing dosage of radiation or techniques of treatment it must be re-emphasised that, short of actual cure, the object of any therapeutic regimen is to improve the well-being of the patient. This general improvement of the patient (as will be shown later) is closely concerned with the improvement in his anaemia, though the reduction in size of an uncomfortably large spleen or of lymph nodes must also contribute to the general subjective improvement. Nevertheless, during a course of anti-leukaemic treatment, whether by chemotherapeutic or radiotherapeutic means, what the clinician requires is some guide to the patient's response. Shrinkage of the spleen is too slow and coarse a criterion for control of dosage, and in practice the white cell count has become the usual index of effectiveness of treatment - at least in the earlier phases of a course of treatment. As the treatment progresses, the response of the red blood count and platelets, splenic resolution, and improvement in general health all provide further valuable guides. Experience shows that in the favourable case the red cell count rises towards normality *pari passu* with the falling white cell count. This improvement in anaemia is also closely linked with the response of the spleen, the type of leukaemia

and the stage of the disease. The treatment of chronic leukaemia may, however, be regarded as effective when, provided none of the contraindications to treatment have meanwhile arisen, the total white cell count falls sufficiently far to permit these favourable concomitant changes to take place.

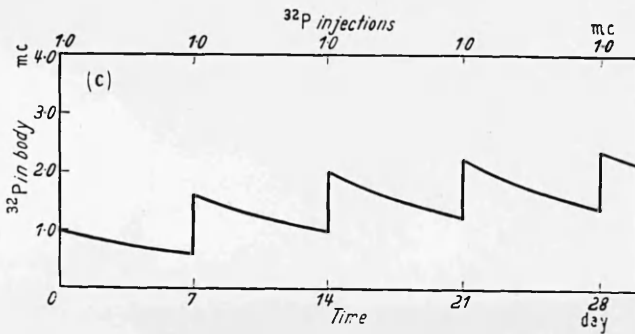
The literature on the use of radioactive phosphorus for chronic leukaemia is now extensive but there is still considerable difference of opinion as to the therapeutic problems imposed by variations in the sensitivity to irradiation. P^{32} was first used in the treatment of leukaemia by Lawrence in 1937 and since then interest has grown in the many possible methods of dosage. Lawrence and his co-workers (1939) began tentatively by giving small repeated doses of P^{32} over a period of many weeks, carefully observing the haematological response. This approach was essential with a new therapeutic agent, especially since its action, once the P^{32} had been administered, was a prolonged one, and could not be controlled after absorption. However, with increasing experience of the response to be expected from injected or ingested P^{32} it became possible to consider different courses of treatment and methods of fractionation. Kenny (1942), Low-Beer et al. (1942), Reinhard et al. (1946), Hall et al. (1947), and many others described various approaches to this problem, but all of the methods described can in fact be reduced to one of the following three types:-



(a)



(b)



(c)

Three Possible Approaches to P^{32} Dosimetry

Figure 13.

1. A method by which the initial dose of P^{32} is followed at intervals of a few days by further amounts designed to maintain the initial activity level and hence the initial average dosage-rate - a maintenance technique. (Figure 13a).
2. A method by which a small amount of P^{32} is given initially, followed by progressively increasing amounts, until a desired maximum dosage-rate is established and then maintained as in Method 1, - a crescendo technique. (Figure 13b).
3. A method somewhat similar in effect to Method 2, by which equal amounts of P^{32} are given at rather longer intervals (e.g. one week) with the effect of building up the dosage-rate over a period - a simple fractional technique. (Figure 13c).

In each of the above methods the treatment was continued until the total white cell count had fallen to an arbitrary level (usually above 20,000 per c.mm.) and thereafter no further P^{32} was given, the residual radioactivity at that time being expected to depress the white count to the desired minimum level.

The long term programme of "titrated", regularly spaced doses of P^{32} described by Osgood et al. (1955) comes into a

different category from the three just described, and aims at inducing a remission and then maintaining it by judicious increments of P^{32} .

If only for geographic reasons, there is no doubt that expediency must have dictated an even greater variety of unpublished methods of administering P^{32} , all resulting nevertheless in the ultimate reduction of the leukocyte count and more or less of a clinical remission of the disease.

The author's first personal responsibility for the management of leukaemic patients began early in 1946 when he treated chronic leukaemia by the method of splenic irradiation, using medium voltage x-rays (250 K.V.). In April 1949 the first consignment of P^{32} was received from the isotope division of the Atomic Energy Research Establishment at Harwell, as a solution of sodium phosphate. Individual injections were made up in 5 to 10 mls of a buffered solution, sterilised by autoclaving, and administered intravenously in all cases.

What might be called Phase 1 in the author's search for a dosage system was the tentative approach similar to that first used by Lawrence. A base-line experience was gained by giving serial low doses of 2 to 3 mcs. at intervals of one to three or four weeks. Having learned the sort of response to be expected the Phase 2 method of treatment was adopted in the

P³² Dosage Table for "Diminuendo" Technique

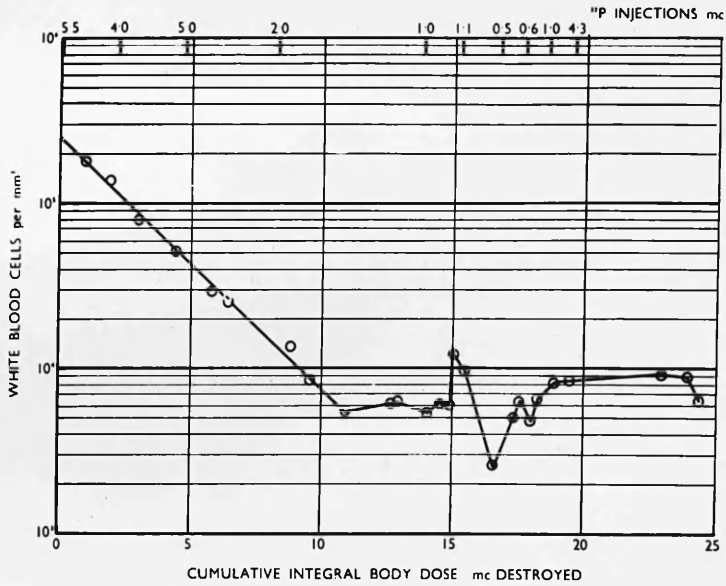
$$\text{Dose in mC} = \frac{\text{Total WBC}}{100,000} \times \frac{\text{Body wt. in kgm.}}{70} \times 10$$

WBC 1000's Wt.kgm.	10	20	30	40	50	60	70	80	90	100
30	0.43	0.86	1.29	1.71	2.14	2.57	3.0	3.43	3.86	4.29
40	0.57	1.14	1.71	2.29	2.86	3.43	4.0	4.57	5.14	5.71
50	0.71	1.43	2.14	2.86	3.57	4.29	5.0	5.71	6.43	7.14
60	0.86	1.71	2.57	3.43	4.29	5.14	6.0	6.86	7.71	8.57
70	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0
80	1.14	2.29	3.43	4.57	5.71	6.86	8.0	9.14	10.29	11.43
90	1.29	2.57	3.86	5.14	6.43	7.71	9.0	10.3	11.6	12.9
100	1.43	2.86	4.29	5.71	7.14	8.57	10.0	11.43	12.9	14.3

Table V.

autumn of 1949. It was argued that as the white cell count fell from several hundred thousand cells per c.mm. to less than 100,000, so the need for sustained radiation dosage should be reduced. Thus a table of dosage was drawn up (Table V) partly related to body weight and partly related to the total white cell count. It was decided that if for example a patient weighed 70 kilogrammes he should be given an initial dose of 7.0 mcs. of P^{32} . This dose was to be repeated each week until the white cell count fell to less than 100,000 cells per c.mm. Then the dose was to be reduced proportionately so that if the patient's white cell count on the treatment date had fallen to 70,000 he would then receive 7/10ths of his initial dose. If the following week his count was 30,000 he then received 3/10ths of his initial dose. This "diminuendo" treatment seemed to work satisfactorily, though it is now clear that in the early stages of treatment the dose-rate was unnecessarily high, while towards the end of a course - especially if the white cell count fell slowly from the 100,000 level - the dose-rate became progressively less, being less vigorously 'topped up' each week.

About this time a further decision was made which yielded interesting results. It was decided to endeavour to depress the white cell count to very low levels, i.e. to about 2,000 white cells per c.mm. (This decision was based partly on the view that longer remissions result from depressing the

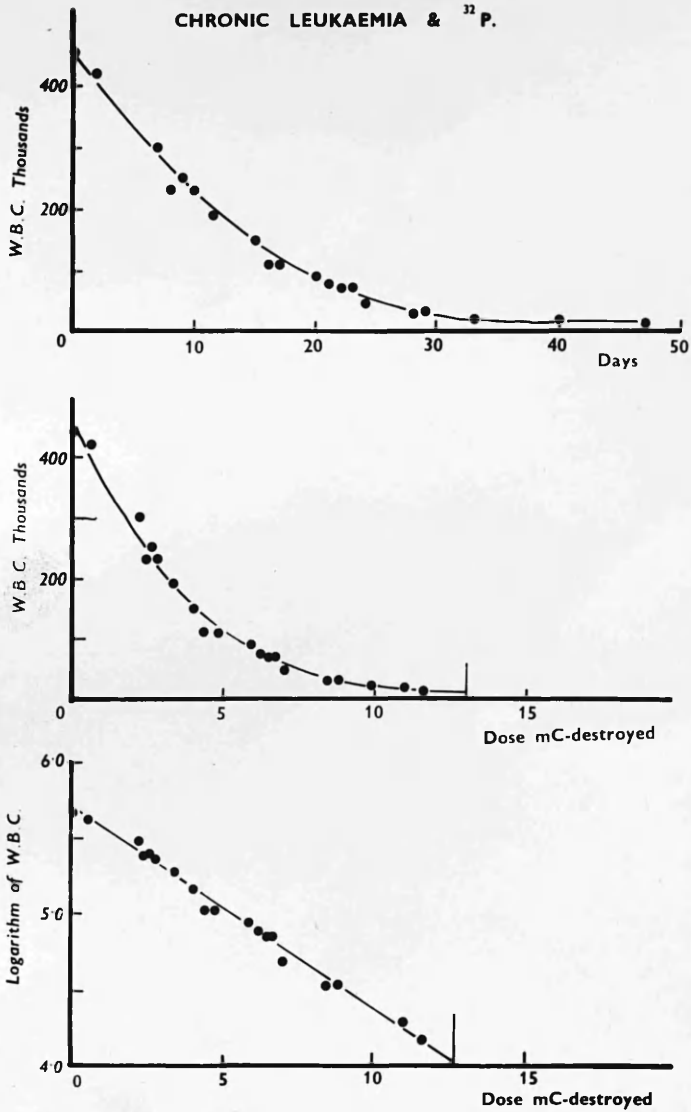


Case M 8, showing initial exponential fall of W.B.C. to normal range, and resistance to further P³² radiation.

Figure 14.

white cell count to at least 10,000 per c.mm., and partly on the view that since a sub-lethal dose of x-rays will cause a temporary disappearance with subsequent recurrence of a squamous carcinoma of e.g. the skin, perhaps a more lasting effect on leukaemia would follow a more vigorous attempt at reducing the white cell population to near zero. This idea has, I believe been attempted by other workers with as little success). The effect of this approach to treatment is illustrated in Figure 14. As the white cell count approached normal levels the weekly increments of dose were already diminishing too much, it seemed, to be effective. Accordingly a substantial increment was given in an effort to depress the white cell count still further, but without success. It was concluded that as the leukaemic white cell population is reduced the 'normal' leukopoietic tissue is more resistant to the effects of P^{32} . Very far from agreeing with Low-Beer, that a few hundred microcuries may exert a truly depressive effect, the author's experience led to the conclusion that a dose of less than 2 mcs. was of little demonstrable value in the treatment of chronic leukaemia. Several other workers in this field (e.g. Tubiana, 1950) have expressed agreement with this point of view.

The above experience led to the third phase of treatment, when it was decided to abandon the "diminuendo" approach and to start with a single dose of P^{32} , based only on body weight (at



- (a) Shows WBC plotted against time - non-exponential.
- (b) Shows WBC plotted against dosage from P^{32} - exponential.
- (c) Shows log WBC plotted against dosage from P^{32} .

Figure 15

the rate of 1 mc. per 10 kilos) followed at weekly intervals by half the initial dose until the white cell count fell to about 20,000 per c.mm. Since the radiobiological half life of P^{32} in leukaemic subjects is approximately 11 days, this Phase 3 treatment led, by its 7 day increments to a gradual build-up of dose-rate similar to type 3 in Figure 13 (c).

This dosage method was continued until the end of 1953 when the author and his physicist collaborators (L.A.Mackenzie and B.E. Jones) reviewed the patients treated up till that time. It was decided to seek any possible correlation between dose, time, fractionation, and effects on the leukocyte count. If only because it had never been mentioned in the literature, we were surprised to find that in the majority of cases the relationship between the effect on the white cell count and the dose of P^{32} utilised was an exponential one (Easson, Jones and Mackenzie, 1954 and 1955). It may be said that this is only to be expected, and is a common cause/effect phenomenon with biological material. Nevertheless, the immediate value and the clinical implications of this finding seemed to be considerable, and the absence of any published comment on such an 'expected finding' was the more surprising. The interesting relationship between the WBC and P^{32} dosage is seen in Figure 15. Figure 15 (a) shows the falling white cell count plotted against time, Figure 15 (b) shows the effects of plotting the daily white cell

$$\lambda = \frac{0.693}{11} \text{ days}^{-1}$$

<i>T</i> days	$\lambda \int_0^t e^{-\lambda t} dt$ mc destroyed
0	0.00
1	0.06
2	0.12
3	0.17
4	0.22
5	0.27
6	0.32
7	0.36
8	0.40
9	0.43
10	0.47
11	0.50
12	0.53
13	0.56
14	0.59
15	0.61
16	0.64
17	0.66
18	0.68
19	0.70
20	0.72
21	0.73
22	0.75
23	0.77
24	0.78
25	0.79
26	0.81
27	0.82
28	0.83
29	0.84
30	0.85
∞	1.00

Body-integral dose in mc destroyed from an initial 1 mc ³²P injection.

Table VI.

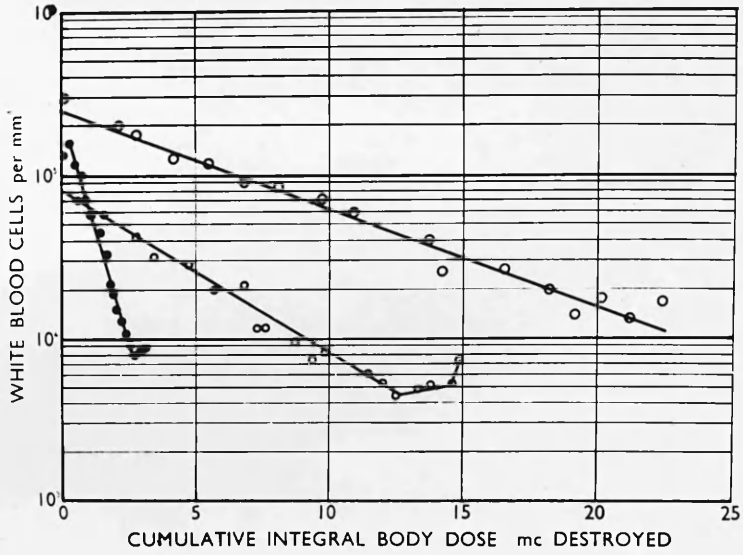
count against the radiation dose (expressed in millicuries-destroyed) while Figure 15 (c) shows the straight line obtained by expressing this exponential semi-logarithmically.

Definition of Radiation Dose

Before considering the implications of this finding it is important to describe the details of the analysis.

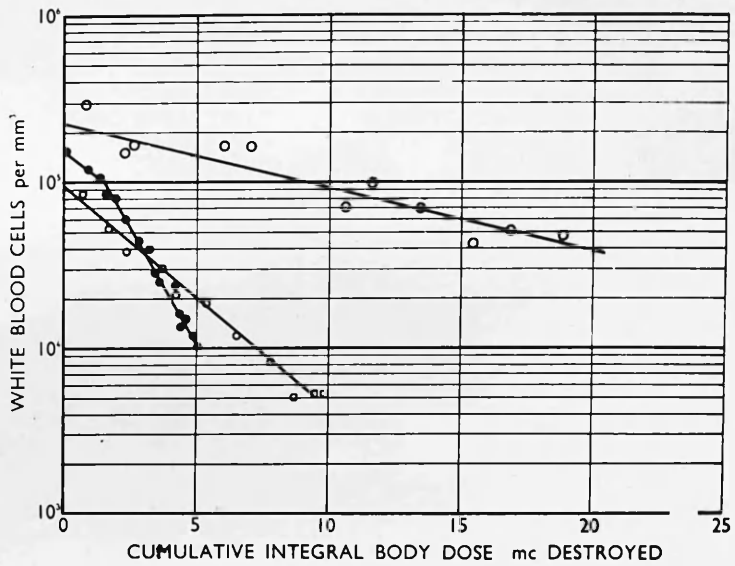
In assessing the response to P^{32} therapy, calculation of the integral dose received by the body must take into account the activity that is lost by excretion as well as radioactive decay. Measurements of the urinary excretion of P^{32} in humans have been made by the author (unpublished) and many other workers (e.g. Mitchell, 1951). From these it may be assumed that following an injection of P^{32} the activity remaining in the body falls approximately exponentially with a half-life of about 11 days. Thus, after a single injection of C mcs. of P^{32} the integral body radiation dose (I.B.D.) will build up at an exponentially decreasing rate, and after T days will be proportional to $C \lambda \int_0^T e^{-\lambda t} dt$, where $\lambda = (0.693/11) \text{ days}^{-1}$, and $t = \text{time elapsed after injection}$.

The above expression gives the I.B.D. directly in mcs.-destroyed, and to facilitate calculations a table of the values



Chronic myeloid leukaemia. Three cases showing variation of sensitivity.

Figure 16.



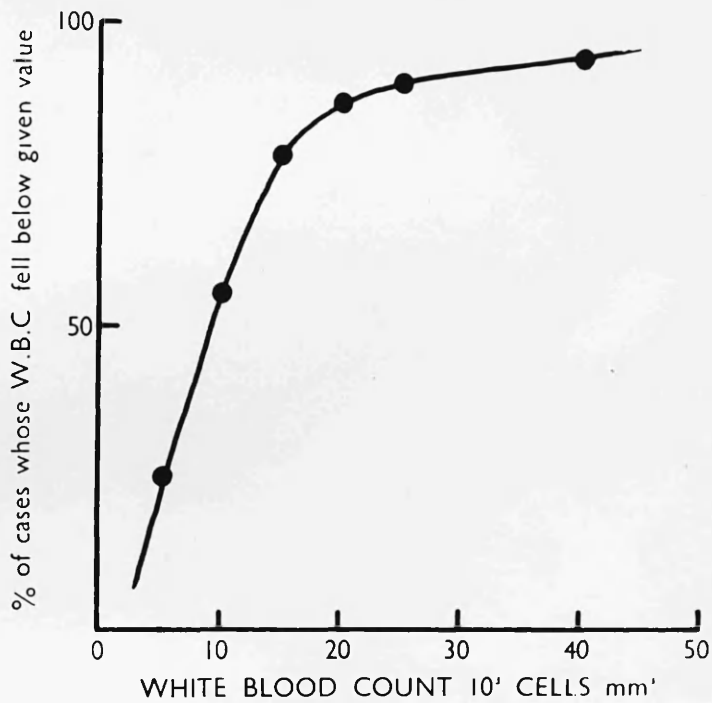
Chronic lymphatic leukaemia. Three cases showing variation of sensitivity.

Figure 17.

of $\lambda \int_0^T e^{-\lambda t} dt$ was prepared and is shown in Table VI. It can be shown that one mc.-destroyed is equivalent to 6.21×10^5 gm-rep, or a mean dose of 9.55 rep to a standard man of 65 kilos body weight. Thus the I.B.D. could be expressed in gm-rep, but it has been found more convenient for routine calculations to use mc destroyed.

Prediction Method of Dosimetry

The first implication of practical importance which suggested itself was the possibility of predicting the total dose required for any one patient by extrapolating the straight line obtained early in treatment. The slope of these straight lines, indicating differences in individual radiosensitivity (vide Section V) varies from patient to patient and Figures 16 and 17 show typical examples. Much has been written about the need for individualisation of treatment to meet the uncertainties of response to any anti-leukaemic drug, and some early index of individual sensitivity would clearly be of great value to the clinician. Furthermore, to reduce to a minimum any adverse effects it would seem desirable to administer as little of any anti-leukaemic drug as possible, consistent with the induction of a satisfactory clinical and haematological remission. That is to say, each patient should receive the appropriate Minimum Effective Dose (M.E.D.) and this can in



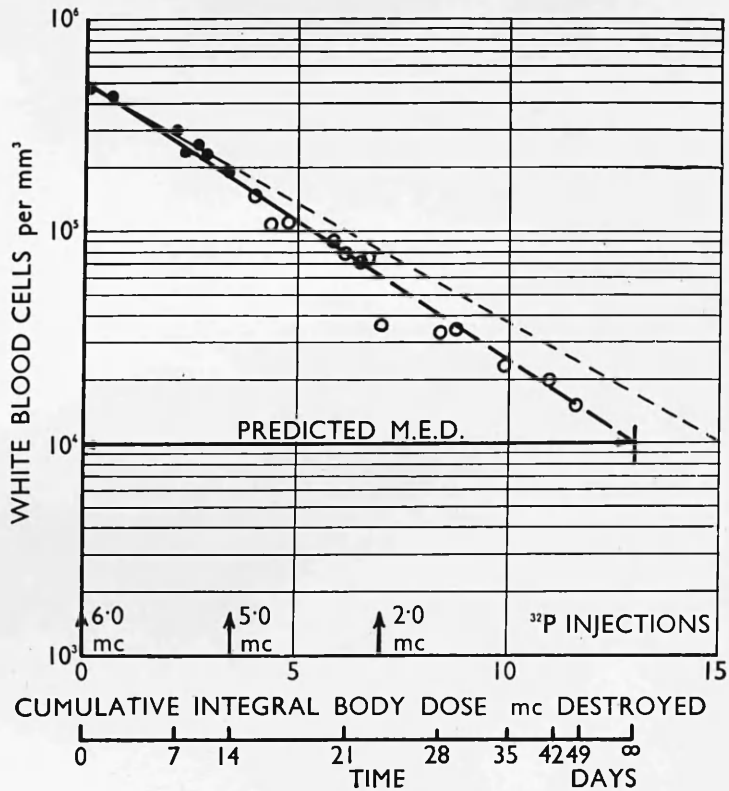
Showing various levels at which WBC ceased to fall
in spite of adequate residual radioactivity from P³².

Figure 18.

fact be determined as follows:-

- (a) An initial dose of P^{32} is given.
- (b) The fall in the white cell count is plotted for two weeks.
- (c) The M.E.D. is then predicted by extrapolating the two-week line down to a normal range.
- (d) If any further P^{32} is indicated it is given in suitable fractions.

With x-ray therapy, still the well-established base-line experience, some writers consider 30,000 white cells per c.mm. as an adequate lower level, (e.g. Burchenal et al., 1954), while others would regard a count of 10,000 or less as conducive to longer remissions (e.g. Levitt, 1948). This latter point of view has in fact been held at the Christie Hospital and Holt Radium Institute for many years. Data for 30 patients treated with P^{32} were reviewed, and it was found (Figure 18) that though there was a variation in the level at which the WBC ceases to fall (in spite of high residual radioactivity in the body) only a small percentage of cases failed to fall below 20,000 and about fifty per cent of cases fell to 10,000 or less. Thus, since the initial straight line must be extrapolated to some definite lower level, the author's experience with both P^{32} and x-ray therapy led to the decision to adopt a lower index level of 10,000 total leukocytes per c.mm. It would have been



- Response to initial dosage.
- - - Preliminary prediction at 14 days.
- Improved prediction at 24 days.
- Subsequent response to predicted dosage.

Graph of Typical Prediction of Minimum Effective Dose of P³²

Figure 19

equally possible, of course, to predict the dose for a lowest level of, say, 15,000 or 20,000 per c.mm.

The M.E.D. for P^{32} for this series of cases can therefore be defined as that minimum integral body dose required to reduce the leukocyte count from its value at the commencement of treatment down to 10,000 per c.mm.

DETAILS OF PREDICTION METHOD.

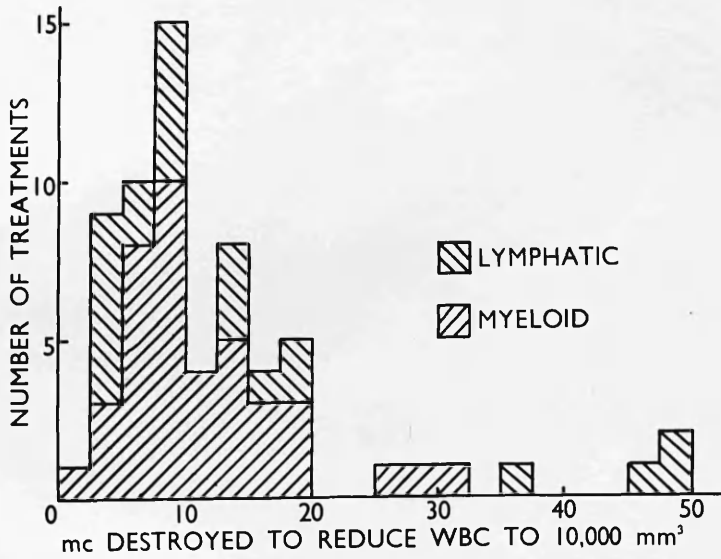
The method of predicting the M.E.D. can best be described in detail by considering the typical case shown in Figure 19. This patient received an initial injection of 6 mcs. and 14 days later the most appropriate straight line was drawn through the known points and extrapolated to a white cell level of 10,000 per c.mm. This gave a predicted M.E.D. of 15 mcs-destroyed. An additional amount of 5 mcs. was given at this time and the continuing fall in the white count permitted a more accurate prediction to be made at the 24th day, the value now being 13 mcs-destroyed. Of this 13 mcs., 11 had already been given and the additional 2 mcs necessary were given on the 24th day. The points obtained subsequent to the preliminary prediction (o) show the close agreement between the estimated and the actual fall in the white cell count.

The values of the I.B.D. were calculated from Table VI. Thus, during the 14 days after the initial injection of 6.0 mcs.

the I.B.D. delivered was $6.0 \times 0.59 = 3.5$ mcs.-destroyed. The activity remaining on the 14th day was therefore 2.5 mcs. and this was raised to 7.5 mcs. by the second injection of 5 mcs. The I.B.D. from this 7.5 mcs. from the 14th to the 24th day (ten days) was $7.5 \times 0.47 = 3.5$ mcs.-destroyed. Thus the total I.B.D. by the 24th day was $3.5 + 3.5 = 7.0$ mcs.-destroyed. An alternative method of calculation is to summate the doses delivered by each injection separately, but for a series of injections the method described above is simpler.

When the predicted M.E.D. is more than 12 mcs., the second injection should not exceed 6 mcs. and the continuing fall in the white cell count permits, by successive approximations, a more accurate final prediction. In the case of a second course of treatment, information about the patient's response to the first may be a guide to the value of the initial injection.

It is interesting to note that the exponential relationship between the white cell count and I.B.D. held (with some exceptions shortly to be described) for all the treatment methods described above - i.e. Phases 1, 2 and 3. In addition, data have been examined from a further six unselected courses of treatment carried out at other centres (Low-Beer et al., 1942; Hall et al., 1947, and Thurgar, 1953) and all of these showed



Histogram showing range of M.E.D. for chronic myeloid and lymphatic leukaemia.

Figure 20.

the same characteristic response, despite the use of treatment systems differing in detail from the author's. It is obvious, therefore, that this exponential relationship holds over a considerable range of dosage-rates - as much as a factor of ten in any one patient - so that the effect of P^{32} on the leukopoietic tissue is also independent of dose-rate over a wide range.

The histogram shown in Figure 20 demonstrates the variation in minimum effective dosage for this series of patients. This further underlines the fact that there can be no universally fixed dose approach to P^{32} therapy for leukaemia. Nevertheless, Figure 20 does show that an initial injection of 6 mcs. to all patients, regardless of differences in body weight, will depress the white cell count sufficiently for a satisfactory prediction of the M.E.D. to be made after 14 days. This quantity might in fact be in excess of the M.E.D. in a small percentage of cases, but the experience embodied in Figure 14 suggests that such excess carries no risk.

Exceptions

Of the sixty patients treated by P^{32} , twelve failed to show the regular exponential relationship described above. Exceptions to any rule deserve special analysis, and these have been separated in Section VI under the code letter E (1 to 12).

One of these patients (E 2) had three completed courses

of P^{32} therapy, and thrice showed no exponential response, though good remissions were achieved, and indeed further remissions by splenic x-ray therapy followed the third P^{32} treatment. Another exception, (E 12), failed to show a regular response, no reason for this was apparent, and her overall response to treatment cannot be considered to have been favourable. Case E 5 also failed to respond exponentially, though in fact there was scarcely any response in the white cell count at all. An excellent remission was, however, obtained in this case by splenic x-ray therapy. A further exception was Case E 7. He responded irregularly to P^{32} , he also failed to derive much benefit from this treatment, and died 6 months later.

In none of the four patients just described was there any apparent reason for their failure to respond like the majority. Of the remaining eight patients in this group of twelve exceptions there did seem to be a possible contributory feature. Two patients, E 8 and E 9, were given substantial blood transfusions before their initial dose of P^{32} , and the absence of an exponential fall in the white cell count could reasonably be explained on the basis of a mixed population of cells in the peripheral blood. Cases E 4 and E 10 were at least subacute, and in retrospect would have been better managed by blood transfusion rather than anti-mitotic agents of any kind. Case E 3 was also ill at the time of treatment, and developed pneumonia

early in the course of treatment. It is probable that this microbic infection would also produce a mixed white cell population, leukaemic and "infective", so that differing average life-spans of white cells could account for this exceptional case. Two more cases, E 1 and E 11, died three weeks after the start of P^{32} therapy, the first of these when his white cell count was only just beginning to show some response. The last patient in this group, E 6, was another whose whole behaviour suggested a subacute, and consequently unfavourable phase of leukaemia.

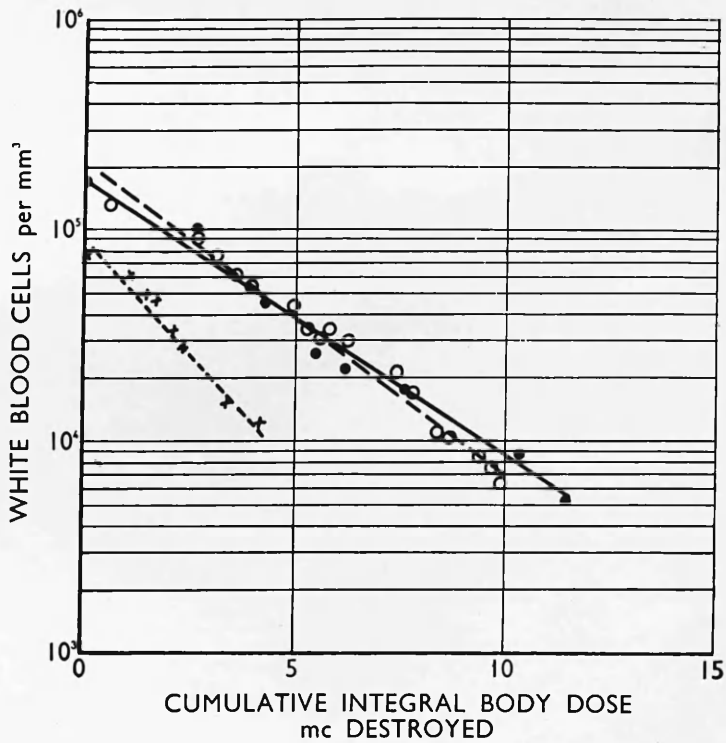
Conclusions

Consideration of the exceptions quoted above would suggest that a regular exponential relationship may be expected between the falling white cell count and the integral body dosage from P^{32} in the vast majority of cases (at least 55 out of 60), provided they are carefully selected. Thus, if this prediction method of dosimetry is to be employed, with the object of administering the Minimum Effective Dosage, care must be taken to avoid those patients whose initial haemoglobin level is such that blood transfusion is a necessary first step to treatment. Any suggestions of a change towards a subacute phase of the disease - suggested by mucosal bleeding, pyrexia, splenic pain, increase of blast cells, rapidly falling platelet or haemoglobin levels, or simply poor general health - would also justify the

avoidance of this approach to dosimetry, or indeed to any form of antimitotic therapy. With this careful selection of patients, accurate predictions of the Minimum Effective Dose can be made in over 90% of cases.

It has been said that a non-exponential response does not necessarily herald a poor remission, and it would be wrong to suppose also that a regular exponential response in the white cell count will guarantee a good remission. Five patients who responded exponentially (Cases M 5, M 24, L 3, L 7 and L 14) all died within three months of treatment. In all of these cases there were features which might well have indicated that P^{32} should be avoided (See Section VI), though it is this very problem of the uncertainty of the leukaemic patient's response to treatment that makes some early index of individual sensitivity so necessary.

Most of the patients whose white cell response to P^{32} was exponential did enjoy a satisfactory remission of their leukaemia. Following recurrence of symptoms, 15 patients have so far received a second course of P^{32} , and of these seven have had a third, and one a fourth course. From this limited group the response of the white cell count to second and third treatments is remarkably similar to the first. Though the number is small there seems to be a tendency towards an increase



Responses seen in three successive courses
of P^{32} therapy (Case L 8)

Figure 21.

in sensitivity with each repeated course of P^{32} . Figure 21 shows the responses of a typical patient to three successive courses of treatment. This latter finding is surprising since most workers in this field would expect leukaemic patients to become increasingly refractory. The truth of this finding lies, I believe, in the fact that leukopoietic sensitivity has not hitherto been expressed quantitatively, and this specific cell-sensitivity is not synonymous with the term "refractoriness". The latter term rather connotes the combination of clinical and haematological responses which are collectively concerned in the induction of a remission.

It is obvious, of course, that satisfactory remissions can be obtained in leukaemia by any of the more tentative approaches to dosimetry, but since adopting the prediction method described above, the average dose of P^{32} required to induce a remission has been reduced by nearly 4 mcs per patient. Naturally, only a long term study will tell whether this method of treatment will give the best remissions, but it certainly does provide an accurate method of reducing the white cell count to the desired low level with the minimum of treatment. As already stated, it would seem reasonable to suppose that there is an advantage in giving no more of any potentially harmful drug than is therapeutically necessary. The search for optimum

dosage must continue, and only time will tell whether the M.E.D. of P^{32} , using an index point of 10,000 white cells per c.mm., is more or less than the optimum dose for chronic leukaemia.

The fact that repeated courses of treatment can be expected to follow a pattern similar to the first presents an opportunity for the comparison and measurement of the effects of adjuvant forms of therapy and of radiation protective substances. This study has not yet been made by the author, though the next section of this thesis is concerned with the quantitative study of radiosensitivity made possible by this exponential phenomenon.

SECTION V.

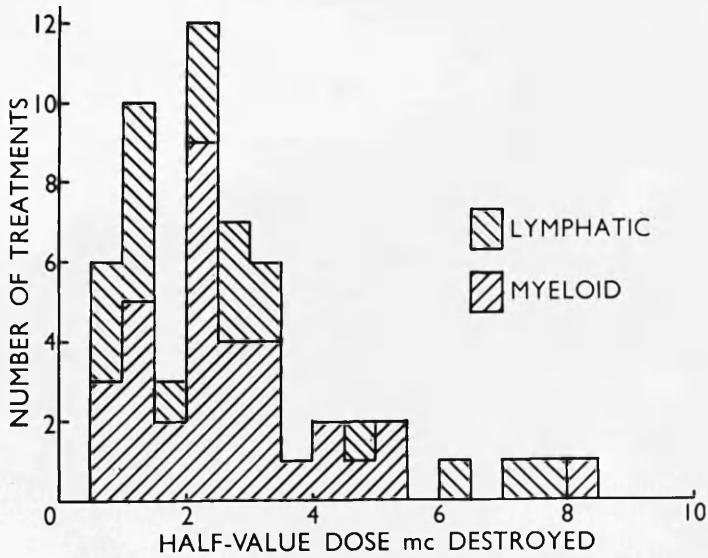
Author's Experience with Radiophosphorus:

A Quantitative Study of Radiosensitivity.

A QUANTITATIVE STUDY OF RADIOSENSITIVITY TO P³².

Apart from its therapeutic applications the exponential relationship between P³² dosage and white cell response has several heuristic possibilities already mentioned. This section is concerned with a study of individual variations in leukopoietic radiosensitivity.

The slope of the graph, expressing the rate of fall of the white cell count in response to each millicurie utilised, is an index of the sensitivity for that patient. The slope may be expressed in various ways. It could, for example, be expressed simply in degrees, or as the tangent of the angle of slope. Alternatively, being exponential, the relationship between the initial white cell count and the count in response to a given dose of P³² is found from the equation $C_2 = C_1 e^{-kd}$ where C_1 is the initial white cell count, d is the dose required to depress that count to the level C_2 , and k is the sensitivity constant for that patient. A simpler expression, however, is the Half Value Dose, which may be defined as that integral body dose (IBD) which will reduce the white cell count to 50% of its pretreatment level. The Half Value Dose (HVD) is related to the sensitivity constant k by the equation $k = 0.693/\text{HVD}$, and since it can be expressed in millicuries-destroyed it is a



Histogram Showing Range of H.V.D.s for Chronic
Myeloid and Lymphatic Leukaemia.

Figure 22.

convenient method of measuring sensitivity. As with the Minimum Effective Dose discussed in the preceding section, the HVD could be expressed in gram-reps, gram-roentgens or rads, but there is no advantage in so doing.

The HVD is clearly related to radiosensitivity in that the lower the value the greater the sensitivity and vice versa. Figure 22 shows the wide range in the sensitivity of the different patients in this series. It is of particular interest to note that the sensitivity of white cells in chronic lymphatic leukaemia to P^{32} therapy, when compared by this quantitative method, seems to be remarkably similar to those in the myeloid variety of the disease. Most radiotherapists familiar with the more conventional x-ray methods of treating leukaemia might have expected a significantly greater sensitivity in the lymphatic type. This finding probably indicates once more that a different mechanism operates with these two methods of treatment, even though ionising radiation is being employed in both cases.

The HVD is, therefore, a quantitative expression of each patient's white cell sensitivity, and this being so, treated cases of leukaemia can be arranged in order of the radio-sensitivity of their leukopoietic tissue by tabulating their HVDs. It then becomes possible to look for correlations between

leukopoietic sensitivity and various clinical and haematological data. In fact, it now becomes possible, on a quantitative basis, to seek the factor or factors on which the in vivo radio-sensitivity of human white cells depend.

Material

The cases analysed consist of 27 patients with chronic myeloid and 21 with chronic lymphatic leukaemia. To avoid extraneous factors which might influence their response to P³² these cases were selected in that none had been previously treated in any way, and this study is concerned with the first remission of their disease.

Having tabulated the HVDs for all patients in order of decreasing leukopoietic sensitivity, details were also tabulated (Tables VII and VIII) of those factors believed to reflect in some degree the activity of the underlying disease process. General health, degree of anaemia, immature white cells, size of spleen and lymph nodes, age, sex, duration of remission - all have been tested, but in no case has any correlation with white cell sensitivity been demonstrated.

Discussion and Results

That sex might influence the response to treatment of malignant disease had not been fully appreciated until Russell's

CHRONIC MYELOID LEUKAEMIA

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	F	74	10.0	25	150	68	14	0	0	1	44	30	4.3	0.55
2	M	64	2.1	20	224	66	28	1	0	1	75	55	10.9	1.1
3	F	64	3.0	25	185	45	43	4	1	2	34	55	21.9	1.9
4	F	62	7.5	27	80	65	23	3	0	2	72	57	10.5	2.2
5	F	45	6.5	39	70	62	2	2	2	0	74*	67	14.0	2.2
6	F	54	2.0	60	280	58	40	3	0	1	42	66	19.2	2.2
7	M	61	1.5	27	130	65	33	3	1	2	46*	68	12.7	2.2
8	M	52	1.0	38	200	65	29	2	0	2	23*	52	25.5	2.3
9	F	59	3.0	32	457	68	32	2	0	2	51	46	15.0	2.3
10	F	62	5.0	32	150	62	24	2	1	2	52	59	12.6	2.4
11	F	32	10.0	38	250	48	64	2	0	2	55	48	18.1	2.5
12	F	69	0	4	33	80	22	2	0	1	5 1/2 yrs	49	10.0	2.6
13	F	65	0	10	76	56	56	3	2	2	32	36	17.5	2.7
14	M	50	1.0	55	300	56	66	3	0	1	160	64	27.6	2.9
15	M	72	2.5	24	340	40	50	3	1	1	39*	67	21.6	2.9
16	F	56	1.0	53	440	48	34	4	2	1	23	54	29.0	3.1
17	F	64	2.0	51	510	58	34	3	1	2	58*	55	22.4	3.2
18	F	61	1.0	7.5	90	80	16	3	3	1	79*	40	12.0	3.2
19	M	56	1.0	19	320	62	38	3	0	2	56	70	17.0	3.5
20	F	25	1.0	37	260	58	34	3	0	2	61	60	25.5	3.6
21	F	58	1.5	28	140	65	17	4	3	1	121*	54	18.9	4.5
22	F	31	1.0	38	200	68	59	3	0	2	62	51	20.0	4.5
23	F	64	2.0	11	31	63	63	3	1	2	128	51	12.5	4.6
24	M	72	1.0	12	100	26	4	1	0	0	4*		12.6	5.0
25	M	46	0.5	32	300	46	34	4	1	2	14*	60	27.0	5.2
26	F	41	0.2	5	460	62	28	3	1	2	27	62	22.5	5.5
27	F	12	4.0	78	590	44	38	4	3	2	23		12.6	8.4

Column 1. Sex of patient

Column 2. Age

Column 3. Initial percentage of myeloblasts.

Column 4. Initial percentage of all immature cells of granular series.

Column 5. Initial W.B.C. in thousands per c.mm.

Column 6. Initial haemoglobin level.

Column 7. Percentage improvement in haemoglobin level.

Column 8. Spleen size before treatment: 0=not palpable.

1=just palpable

2=enlarged to near umbilicus.

3=enlarged to iliac crest.

4=gross enlargement to right.

Column 9. Maximum diminution of splenomegaly during first remission—0 to 4.

Column 10. General condition after treatment—i.e. before second treatment or death: 0=not improved, or worse.

1=improved.

2=distinctly improved.

Column 11. Time in weeks to second treatment (or death—marked thus*).

Column 12. Body weight in kilogrammes.

Column 13. Total quantity of ³²P administered during first treatment.

Column 14. Half-value dose in millicuries destroyed.

Table VII

CHRONIC LYMPHATIC ÆEUKAEMIA

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	M	69	L	12.5	56	66	14	1	0	1	1	2	57*	63	10	0.9
2	F	43	S	3.1	144	84	18	2	1	1	0	2	64	45	6.4	1.1
3	F	51	S	7.5	70	76	8	-	-	1	1	0	10*	74	12	1.3
4	M	55	S	3.0	100	66	24	0	-	1	1	2	100	56	11.5	1.4
5	M	53	BSL	0.5	500	68	34	2	1	2	2	2	74	59	14.5	1.4
6	M	66	BSL	0.5	570	59	34	2	2	2	1	1	38†		12	2.0
7	M	49	S	3.0	210	70	0	0	0	0	0	0	1*		5	2.0
8	M	56	BS	4.5	165	84	20	1	0	1	0	1	113.	71	20	2.3
9	M	67	S	3.5	100	60	28	3	2	1	0	2	156	49	12.5	2.3
10	M	62	S	1.0	96	84	22	2	2	1	0	2	107†	68	9.7	2.5
11	M	62	S	3.0	266	58	70	2	0	1	0	2	119†	57	17.1	2.7
12	M	61	SL	1.0	934	66	28	1	0	2	1	1	60†		18	2.7
13	M	46	BS	4.5	196	90	8	2	0	2	1	0	78	67	14	2.8
14	M	27	BSL	10.0	17	52	10	1	1	0	0	0	11*	63	9	3.3
15	F	58	S	4.0	167	68	0	2	0	2	0	0	17*	59	16.5	3.3
16	F	62	SL	0.5	680	60	36	1	0	1	1	2	38†		5+ XRT	4.0
17	M	52	S	4.0	178	98	6	1	0	2	1	2	79	76	20	4.7
18	M	55	BS	1.5	230	72	0	1	1	1	1	0	17*	66	17.8	6.4
19	M	71	S	3.0	260	74	10	2	1	2	1	1	112	68	20	7.2
20	M	69	BSL	3.5	300	52	32	4	0	2	0	2	180	63	40.6	7.7
21	M	67	SL	3.5	127	96	0	1	1	1	1	1	18*	70	18	15.0

Column 1. Sex of patient.

Column 2. Age.

Column 3. Presence of immature cells of lymphoid series: B=blast cells present.

S=smear cells present.

L=large lymphocytes present.

Column 4. Percentage of polymorphs in initial W.B.C. (i.e. remainder=lymphocyte series).

Column 5. Initial W.B.C. in thousands per c.mm.

Column 6. Initial haemoglobin level.

Column 7. Percentage improvement in haemoglobin level.

Column 8. Spleen size before treatment: 0 to 4 as in Table I.

Column 9. Maximum diminution of splenomegaly during first remission (0 to 4).

Column 10. Lymph nodes before treatment: 0=none palpable.

1=small nodes.

2=florid enlargement.

Column 11. Lymph nodes after treatment: 0 to 2, as above.

Column 12. General condition after treatment—i.e. before second treatment or death. 0 to 2 as in Table I.

Column 13. Time in weeks to second treatment (or death, marked thus *).

Column 14. Body weight in kilogrammes.

Column 15. Total quantity of ³²P administered during first treatment.

Column 16. Half-value dose in millicuries destroyed.

† indicates remission continuing at time of analysis.

Table VIII

analysis (1954) showed clearly that females had a more favourable prognosis, other things being equal, than did males with the same types of cancer. With this in mind the sex of this series of patients has been tabulated, but it will be seen from Tables VII and VIII that in neither the myeloid nor the lymphatic form of the disease is there any correlation between sex and radio-sensitivity of the leukopoietic marrow.

Age, so well known as a factor in the simple anaemias, might also have been expected to have some influence on the sensitivity of the marrow to radiation from P^{32} , but no association with white cell sensitivity is demonstrated.

Immature cells appear in large numbers in the blood of acute leukaemic patients and it is well established that the irradiation of such patients makes matters worse rather than better. This fact has perhaps led to the belief that with chronic leukaemia the greater the number of immature cells in the peripheral blood the more sensitive the response to radiation. So far as available data would permit, this question has been tested by tabulating the percentage of blast cells and also the percentage of all primitive white cells in the peripheral blood (columns 3 and 4, Table VII). In the case of lymphatic leukaemia it was not possible to record actual numbers of primitive cells, but the presence of blast cells, smear cells, and large immature lymphocytes was noted and has been recorded

in table VIII as "B", "S", or "L", singly or in combination. Again it will be noted that there is no clear correlation between the radiosensitivity of the leukopoietic tissue and the degree of shift to the left.

The initial white cell count, being very high in some cases and relatively low in others, might be considered to give some indication of the activity of the disease and to show some relationship to white cell sensitivity. No correlation is apparent.

The anaemia of chronic leukaemia is still not adequately explained, but whatever its cause, its degree might reasonably be considered some index of the extent of the underlying leukaemia. The initial haemoglobin level in each case has been recorded and so also has the improvement in the haemoglobin level at its maximum during the first remission. The latter might be considered a good indication of the marrow's capacity to respond to treatment, an index of marrow depression. The radiosensitivity of the leukopoietic tissue shows no correlation to these erythropoietic data.

The size of the spleen may be of importance, providing a reservoir of cells or a source of delay in the general diffusion of P^{32} . It is not easy to describe and compare the size of the spleen, but for quantitative purposes an effort has

been made to assign a value to each patient's spleen. Neither the initial splenomegaly (Column 8) nor the degree of splenic resolution after treatment (Column 9) shows any clear correlation to white cell sensitivity.

Lymph node enlargement in chronic lymphatic leukaemia varies with different patients from generalised florid lymphadenopathy to impalpable nodes. Tabulation of the initial size of the lymph nodes and also of their resolution in response to treatment, reveals no correlation to the lymphocyte sensitivity.

The general condition of the patient is all-important. The main object of treatment is to improve the sense of well-being, to remove symptoms due to a high white cell count and low haemoglobin, and the uncomfortable size of the spleen and lymph nodes. It is reasonable, therefore, to look for some correlation between the quality of a patient's remission and the radio-sensitivity of his leukopoietic marrow. No such relationship is apparent.

The duration of remissions (as measured between times of treatments) is also found to bear no relation to the white cell response to P^{32} .

The body weight will be seen to bear no relationship to the HVD, nor, indeed, does the total quantity of P^{32} necessary

to induce a remission. Since the marrow is considered the "target tissue" in such cases, this lack of correlation is interesting when considered in the light of Osgood's confirmation (1954) of earlier anatomical measurements showing the remarkably constant ratio between total marrow mass and body weight.

So far, consideration has been given only to leukopoietic sensitivity and potentially related factors. It is interesting to consider whether any correlation can be seen between the other data presented in Tables VII and VIII. For example, it is usually believed that the improvement in a leukaemic patient's general condition is more dependent on the improvement in his haemoglobin level than on anything else, and this view is clearly confirmed by correlation studies on the appropriate columns in Tables VII and VIII. Similarly, a positive correlation can be seen between the degree of splenic resolution and the percentage improvement in haemoglobin level.

Conclusions

So far as the available haematological and clinical data would permit, it has been demonstrated that no correlation exists between the radiosensitivity of the white cell count and a variety of data which are commonly considered to reflect the activity of the leukaemic process. This study would seem to

suggest that the leukaemic white cells, or the leukopoietic marrow from which they arise, respond to radioactive phosphorus therapy with a sensitivity which bears no relationship to the underlying disease process. In other words, the prognosis in any case, both in terms of the quality of a remission and the duration of survival, bears no relationship to intrinsic white cell sensitivity.

On what then does the sensitivity of leukopoietic tissue depend? The effects of oxygen on the radiosensitivity of various biological materials have been known since 1921 and were recently reviewed by Bacq and Alexander (1955). Many protective agents are also known whose presence before irradiation will reduce the damaging effects of ionisation. The potentiating effects of Synkavit have been described by Mitchell (1953) and are of great interest. Nevertheless, none of these agents can be said to explain the leukopoietic sensitivity with which we are here concerned. Indeed the wide variations seen in different animal and insect species in response to whole body irradiation are likewise impossible to explain by these known factors (Bacq and Alexander, loc. cit.).

It seems probable that differences in mean life-span of leukocytes might explain the differences in HVDs in this series of cases, and this might be worth further investigation.

However, the next problem to arise would be to discover what factors influenced variations in leukocyte life-span! The work of Leonard and Wilkinson (1955) suggests that the difference between the sensitivity of leukocytes to colchicine in myelosclerosis and in myeloid leukaemia might be related to the phosphatase content of the granulocytes. It was hoped that a quantitative approach to this histochemical abnormality might be informative when compared with HDVs of P^{32} , but unfortunately the small differences in alkaline phosphatase likely to be found in different leukaemic patients could not be expected to be measurable, by present techniques, within the limits of experimental error.

Perhaps some of the many other known changes described in the section on clinical pathology (Section I) would be worth testing.

SECTION VI.

Summaries of Case Histories

M 1 to 27, Myeloid Leukaemia.

L 1 to 21, Lymphatic Leukaemia.

E 1 to 12, Exception Cases.

SUMMARIES OF CASE HISTORIES

The serial numbers of the patients described in this thesis have been made to conform to the numbers in Tables VII and VIII. Since these tables are two of the main tables in this study, it seemed best to adhere to the serial numbers used therein. The sixty treated cases have therefore been divided into three groups under the code letters, M, L or E. The 27 cases of myeloid leukaemia are first described (M 1 to M 27), followed by the lymphatic cases (L 1 to L 21). The remaining 12 patients, as already shown, were exceptional in showing non-exponential relationship between their falling white cell count and the IBD from P^{32} . These cases are described in the third group (E 1 to E 12).

None of these patients had received any known anti-leukaemic treatment before admission to the Christie Hospital, and unless otherwise stated, none received blood transfusion before or during treatment.

All blood-counting at the Christie Hospital was carried out by one technician for each patient, as far as possible, and always at approximately the same time of day - between 9 and 11 a.m. All cell-counts and haemoglobin estimations were done on capillary blood obtained by finger-puncture. Haldane's

method was used for haemoglobin measurement, the technique being checked against a Medical Research Council standard every three months. Two hundred white cells were counted for differential purposes.

Case M 1.

Miss G.P. aged 74, weight 30 kilos, became rapidly weak in May 1951. She was referred to Park Hospital in November 1951 and extensively investigated. In April 1952 her Hb was 76% and white cell count was 28,800 per c.mm. Sternal marrow suggested "early leukaemia". She was finally referred to the Christie Hospital on 10.6.52 by which time the Hb was 68% and the WBC 150,000 per c.mm. The differential count showed 10% myeloblasts and 25% total primitive white cells. The spleen and liver were not palpable, there was no lymphadenopathy, no petechiae or ecchymoses. The sternal marrow confirmed the hyperplasia of myeloid cells, and active erythropoiesis. On 16.6.52 a single dose of 4.3 mcs. of P^{32} was given intravenously and the WBC fell exponentially with a HVD of only 0.55 mcs.-destroyed. By 2.7.52 the WBC was 8,200 and Hb 72%. The Hb rose to a maximum of 82% on 6.10.52 by which date the WBC had also increased to 73,000 per c.mm. During this period the general weakness improved significantly and she gained several pounds in weight. However, by 22.4.53 the Hb was 56%,

the WBC 142,000 and a further 6.4 mcs. of P³² were given. The WBC again fell exponentially with a HVD of 0.7 mcs.-destroyed, the Hb rose to 70% by 20.7.53 but the WBC by that time had again risen to 77,000 after being only 11,000 on 6.5.53. The spleen and liver remained impalpable all this time. By 24.9.53 a further injection of 6.3 mcs. was necessary, the WBC again falling exponentially with a HVD of 0.6 mcs.-destroyed. The Hb rose from 64% to 88% on 28.12.56 and the general condition improved remarkably. The final treatment was given on 17.8.54 (2 mcs.) and 31.8.54 (3 mcs.) but on this occasion the WBC fell less exponentially though with a HVD of about 0.6 mcs.-destroyed. On this occasion the Hb fell slowly from 60% and suddenly collapsed on 3.1.55 to 18%. The WBC on this date was 125,000, the spleen became grossly enlarged and the patient died on 11.1.55.

It is of interest that this patient's four courses of P³² therapy showed HVDs of 0.55, 0.70, 0.60 and 0.60 mcs.-destroyed.

Case M 2

Mr. J.T.H., aged 64, weight 55 kilos, developed a corneal ulcer in June 1952, and investigation in Burnley Hospital disclosed a leukaemic blood picture. He was referred to the Christie Hospital on 31.8.52 and by that time his Hb was 66%, platelets plentiful, and WBC 224,000 per c.mm., 2.1% being myeloblasts and 20% immature granulocytes of all types. Sternal marrow confirmed myeloid leukaemia with active

erythropoiesis. There were no haemorrhagic features, and no lymphadenopathy. On 2.9.52 an intravenous dose of 7.9 mcs. of P^{32} was given. The white cell count fell exponentially with a HVD of 1.1 mcs.-destroyed, and on 17.9.52 a second dose of 3.0 mcs. was given. The WBC fell to a lowest level of 9,300 by 24.9.52, the Hb on that date being 78%. The Hb rose to a maximum of 94% by 9.3.53, the WBC by that date having risen to 16,700 per c.mm. The spleen was just palpable before treatment and was impalpable by 20.10.52. The patient's general health improved rapidly during treatment but began to deteriorate as did the blood picture, until further P^{32} therapy was instituted on 29.1.54, i.e. 75 weeks after his first treatment. The Hb had fallen to 74% and the WBC had reached 170,000 per c.mm. 6.0 mcs. were given on 29.1.54 and 3.0 mcs. on 26.2.54, the HVD on this occasion being 1.2 mcs.-destroyed. Again the Hb rose, this time to a maximum of 106% by August 1954, though the WBC had not fallen as "predicted" to 10,000, but had flattened out at 27,000 per c.mm. The general condition improved and remained so in spite of a progressive rise in the WBC, the Hb falling only slowly. A third course of P^{32} was begun on 26.10.55 with a dose of 5.0 mcs. followed by similar doses on 29.11.55 and 29.11.55. The HVD on this occasion was 2.6 mcs.-destroyed. At the start of treatment the Hb had been

54%, the WBC 250,000 and platelets were scarce. A small transfusion was given after the last P^{32} dose and the Hb increased to 90% by February 1956. By July, however, the general health and blood picture began to deteriorate, and since the spleen was now enlarging and causing discomfort some tentative doses of x-rays were given to the spleen. The organ became almost impalpable by 29.8.56 but the Hb showed little response and the patient died on 3.10.56. Autopsy was not permitted.

Note here the increasing HVDs during the three courses of treatment - 1.1, 1.2 and 2.6 mcs.-destroyed.

Case M 3.

Mrs. M.E. aged 64, weight 55 kilos, developed vague malaise towards the end of 1949. Investigation at Wigan Infirmary in March 1950 disclosed leukaemia. On admission to the Christie Hospital on 30.3.50 she was a pale thin woman with enormous splenomegaly, but no hepetic or lymph node enlargement, no petechiae, ecchymoses or mucosal bleeding. The WBC on 11.4.50 was 185,000 per c.mm. with 3.0% blasts and 25% total primitive white cells. The Hb level was 45%. A dose of 8.0 mcs. of P^{32} was given on 14.4.50, followed by 5.0 mcs. on 21.4.50, by 2.7 mcs. on 28.4.50, by 0.64 mcs. on 5.5.50, by 0.5 mcs. on 12.5.50, by 1.0 mc. on 19.5.50, another 1.0 mc.

on 26.5.50, and finally 3.1 mcs. on 31.5.50. This was an example of the "diminuendo" technique. The WBC fell and the HVD was 1.9 mcs.-destroyed, the lowest WBC being 1,600 per c.mm. on 15.5.50. The Hb rose during the first remission period to a maximum of 88% on 18.10.50. The WBC at that date was 16,000 per c.mm. During this remission the general health improved considerably and the spleen resolved to about 5 cms. below the costal margin by 22.6.50. By November 1950 the general condition was deteriorating, the spleen enlarging, the Hb was 76% and the WBC 73,000. A second remission was induced by splenic x-ray therapy given between 7 and 21.12.50, but though the patient improved, further x-ray therapy was deemed necessary on 20.3.51. On this occasion, after a short and unsatisfactory remission the general health went downhill rapidly and the patient died on 13.8.51.

It is worth noting that though the WBC in this case was deliberately depressed to a very low level (1,600) by the first anti-leukaemia treatment, the interval to the second necessary treatment was only 34 weeks - certainly not superior to other less vigorously treated patients.

Case M 4.

Mrs. A.M., aged 62, weight 57 kilos, felt tired for a year, was referred to Salford Hospital in December 1948, and early leukaemia was diagnosed. On admission to the Christie Hospital on 6.4.49 the general condition was fair, the spleen was enlarged to the iliac crest, the liver was impalpable, there were no nodes to be felt, no petechiae, ecchymoses or mucosal bleeding, and no pyrexia. The WBC on 6.4.49 was 80,000 per c.mm. with 7.5% blast cells and 27% total primitive white cells. The Hb on that date was 65%. The sternal marrow confirmed the excessive granulopoiesis, and red-cell activity was considered to be poor. 3.0 mcs. of P^{32} were given on 13.4.49, again on 20.4.49 and on 27.4.49, ending with 1.5 mcs. on 6.5.49. The WBC fell exponentially, with a HVD of 2.2 mcs.-destroyed, to a lowest level of 3,600 on 16.8.49, and the Hb rose to a maximum of 88% on 18.10.49. The WBC on the latter date was only 10,000 per c.mm. During this first remission the general health improved considerably and the spleen was not palpable by 18.10.49. By 31.8.50 the spleen was again down to the umbilicus, the Hb reduced to 70% and the WBC up to 86,000. A further 5.0 mcs. of P^{32} were given on 31.8.50, but there was little response, and on 13.11.50 splenic x-ray therapy was started. This was also abandoned because of continued deterioration and the patient died on 9.2.51.

Case M 5.

Mrs. A.H. aged 45, weight 67 kilos, complained of persistent weakness after the birth of a child in 1950. She was investigated at Oldham Infirmary where leukaemia was diagnosed, and she was admitted to the Christie Hospital on 2.4.52. The general condition was fair, the spleen six cms. below the costal margin, but no enlargement of the liver or lymph nodes, no petechiae or other haemorrhagic features, and no pyrexia. The Hb on 19.4.52 was 62%, the WBC 70,000 per c.mm., 6.5% being myeloblasts and 39% being primitive white cells of various types. On 22.4.52 a dose of 7.2 mcs. of P³² was given followed by 3.5 mcs. on 29.4.52 and 6.5.52. The WBC fell exponentially with a HVD of 2.2 mc.-destroyed and reached a lowest level of 8,000 on 19.5.52. The Hb showed no significant improvement, the spleen did not resolve, and by the end of May the clinical picture had deteriorated greatly. The spleen became grossly enlarged and painful, the WBC rose to 240,000 by 10.6.52 and the Hb was then down to 42%. Platelets were also scarce, and the patient died on 14.6.52.

Autopsy was carried out by Dr. Helen Russell who reported several interesting features. The femoral marrow was very cellular, definitely leukaemic, but with minimal erythropoiesis. The lungs "were very curiously eodematous and very heavy, weighing over a kilo and standing up like casts. No tubercle

was found, nor true consolidation, but the waxy solid oedema was diffusely spread through both lungs". The spleen was "enormous, bright red, and approximately 4.5 kilos in weight. A large plaque of haemorrhage lay on its postero-medial aspect in the abdominal cavity but there was no obvious rupture of the organ. A certain amount of blood was also present in the pelvis, which had apparently oozed out of the spleen. The cut surface of the spleen showed a very varied picture of infarction, fibrosis, and oedema, in which the normal spleen architecture was completely lost"..... "The liver weighed 3 kilos and was diffusely infiltrated. All sinusoids were dilated much more than is likely to be an effect of heart-failure, I think." Microscopy revealed a widespread diffuse stasis with dilatation of the capillaries and arterioles of the lung, pleura, liver and spleen.

Case M 6.

Mrs. A.H., aged 54, weight 66 kilos, complained of vague abdominal discomfort for 4 years before being referred to the Manchester Royal Infirmary where a large spleen was found and leukaemia was diagnosed. On admission to the Christie Hospital on 8.9.52 the general condition of the patient was quite good, the spleen was enlarged down to the iliac crest and across to the midline of the abdomen, but

there was no hepatomegaly, no nodes, petechiae, ecchymoses or mucosal bleeding, and no pyrexia. The Hb was 58% and the WBC 280,000 per c.mm., 2.0% being blasts, but some 60% were primitive white cells. Platelets were plentiful. A dose of 9.5 mcs. of P^{32} was given on 15.9.52 followed by 2.0 mcs. on 29.9.52, by 2.5 mcs. on 7.10.52, and 5.2 mcs. on 24.10.52. The WBC fell exponentially, with a HVD of 2.2 mcs.-destroyed, to a lowest level of 5,500 per c.mm. on 6.11.52, and the Hb rose to a maximum of 98% by 12.3.53. The WBC on the latter date had risen to 21,000 per c.mm. A second treatment became necessary by August 1953 and a single dose of 11.0 mcs. was given on 7.8.53. The WBC again fell exponentially with a HVD of 1.3 mcs.-destroyed. A good remission followed but a third course of treatment became necessary in March 1954. A dose of 6.0 mcs. was given on 23.3.54, followed by 3.8 mcs. on 7.4.54 and 3.0 mcs. on 15.4.54. The WBC again fell exponentially with a HVD on this occasion of 2.8 mcs.-destroyed. The spleen was scarcely palpable by June 1954 and the Hb rose to 92%. In August, however, the general health began to fail rapidly and though x-ray therapy to the spleen was cautiously tried on 24.8.54 there was no real improvement. Erythropoietic collapse was seen in December 1954 and the patient died on 15.1.55.

The three HVDs in this case were 2.2, 1.3 and 2.8 mcs.-destroyed.

Case M 7.

Mr. H.M., aged 62, weight 68 kilos, developed "indigestion" in July 1952 and felt generally unwell. He was admitted to Wigan Infirmary as an abdominal emergency on 13.11.52 and leukaemia was discovered. On admission to the Christie Hospital on 27.11.52 his general condition was quite good, the spleen was enlarged to the iliac crest but his liver was not enlarged, nor were there any palpable nodes. There were no petechiae, no ecchymoses or mucosal bleeding, and no pyrexia. The Hb on 16.12.52 was 65%, platelets were plentiful, and the WBC was 130,000 per c.mm., 1.5% being blast cells and 27% were primitive cells of all types. On 16.12.52 a dose of 9.7 mcs. was given, followed by 3.0 mcs. on 31.12.52. The WBC fell exponentially with a HVD of 2.2 mcs.-destroyed, to a lowest level of 6,000 on 12.1.53. The Hb rose to a maximum of 98% on 10.4.53 by which time the WBC had risen to 15,600 per c.mm. The general condition improved remarkably and the spleen was scarcely palpable on 6.3.53. Clinical and haematological deterioration was apparent, however, in September and on 14.10.53 the patient was found to have signs of cerebral thrombosis. He died on 2.11.53.

Autopsy was carried out by Dr. Helen Russell and this confirmed an extensive area of softening in the grey matter and sub-cortical white matter in the left parietal lobe. The spleen was "very large and adherent to the parietes, and burst on handling, revealing a huge necrotic cavity which contained pints of brown fluid within a necrotic lining. The lower pole of the spleen was the only healthy part, and a spleniculum was present, attached to the lower tip of the organ". No other special features were noted, but once again (vide M 5) the lungs were curiously heavy. The possibility of this whole history being due to a splenic abscess with a leukaemoid blood-picture was considered, but on review the leukaemic diagnosis was accepted.

Case M 8.

Mr. A.F., aged 52, weight 52 kilos, felt unduly fatigued about March 1949, and was investigated in Salford Hospital in November 1949, when leukaemia was discovered. He was admitted to the Christie Hospital on 1.3.50 when he was ill. The spleen was enlarged to the umbilicus, but the liver was not enlarged and there was no significant lymphadenopathy, no pyrexia, no petechiae, ecchymoses or mucosal bleeding. Platelets were plentiful, the Hb on admission was 65%, and the total WBC was 200,000 per c.mm. of which 1.0% were myeloblasts

and 38% were primitive cells of various types. P^{32} therapy began with 5.0 mcs. on 14.3.50, followed by 4.0 mcs. on 22.3.50, by 5.0 mcs. on 29.3.50, by 2.0 mcs. on 5.4.50, by 1.0 on 21.4.50, by 1.1 mcs. on 28.4.50, by 0.5 mcs. on 5.5.50 and again on 12.5.50, by 1.0 mc. on 19.5.50, and finally 4.3 mcs. on 26.5.50. The WBC fell exponentially, with a HVD of 2.3 mcs.-destroyed, and reached a lowest level of 2,500 per c.mm. on 5.5.50. This was one of the patients in whom an attempt was made, without success, to depress the WBC to still lower levels. It will be noted that even a final dose of 4.3 mcs. failed to depress the WBC any further. The Hb rose to a maximum of 94% by 9.6.50, the WBC at that date being 8,700. The spleen became impalpable by 26.5.50, and the patient's general health improved considerably. He suddenly deteriorated, however, during August 1950, he became pyrexial and the blood-picture suggested aplasia. He died on 26.8.50.

The most striking feature at autopsy was the dark crimson colour of the marrow at the centre of the femur. Dr. Helen Russell considered this was due to stasis and haemorrhage.

Case M 9.

Mrs. E.E.I., aged 59, weight 46 kilos, complained of lassitude in April 1952, first consulted her doctor in February 1954, and was investigated at Blackpool Infirmary and referred

to the Christie Hospital on 2.4.54. The spleen was enlarged to the umbilicus, the liver was just palpable, there were no enlarged lymph nodes, no pyrexia, no petechiae, ecchymoses, or mucosal bleeding. Platelets were plentiful, the Hb was 68%, and the WBC was 457,000 per c.mm., 3.0% of which were myeloblasts and 32% primitive cells of all types. 6.0 mcs. of P³² were given on 13.4.54, additional 5.0 and 4.0 mc. doses being given on 27.4.54 and 7.5.54 respectively. The WBC fell exponentially, with a HVD of 2.3 mcs.-destroyed, the lowest level being 7,000 per c.mm. on 3.9.54. The Hb rose to a maximum of 100% on 3.9.54, and the spleen was no longer palpable by 4.6.54, while the general health improved vastly. By February 1955 the spleen was again below the umbilicus and across the midline, and by April 1955 the Hb had fallen to 52%. the WBC having risen to 195,000 per c.mm. A course of splenic x-ray therapy at that time produced a short remission, and was repeated during September 1955 and again in January and May 1956. On each occasion a worthwhile improvement in general health was achieved - rather surprisingly towards the end - but myocardial insufficiency complicated the terminal picture and the patient died on 14.9.56.

Case M 10.

Mrs. E.W., aged 62, weight 59 kilos, failed to "pick up" after bronchitis in December 1951. Her lassitude was investigated at Withington Hospital and she was admitted to the Christie Hospital on 26.6.52. The general condition was quite good, the spleen was moderately enlarged, as also was the liver, but there was no significant lymphadenopathy, no pyrexia, no petechiae, ecchymoses or mucosal bleeding. The platelets were plentiful, the Hb level was 62% and the WBC was 150,000 per c.mm., 5% being myeloblasts, and 32% primitive cells of various types. P³² was given as follows:- 8.0 mcs. on 8.7.52, 2.1 mcs. on 22.7.52 and again on 7.8.52. The WBC fell exponentially, with a HVD of 2.4 mcs.-destroyed, the lowest level being 8,300 on 1.9.52. The Hb rose to a maximum of 86% on 24.11.52, the WBC at that time being 24,000 per c.mm. The spleen became just palpable by 24.11.52 and the patient's general condition very greatly improved. The Hb began to fall during the spring of 1953 and a second course of P³² was instituted with 8.0 mcs. on 3.7.53 followed by 3.0 mcs. on 17.7.53. Again the WBC fell exponentially, with a HVD on this occasion of 2.0 mcs.-destroyed, from an initial 190,000 to a lowest level of 12,500 on 27.7.53. The Hb rose during this second remission from an initial 60% to a maximum 76% on 22.9.53. Deterioration was

sudden, however, and by 15.12.53 the Hb was 64% and WBC 216,000. The spleen, barely palpable on 17.11.53 was now down to the umbilicus. A three weeks' course of splenic x-ray therapy began on 8.1.54. The WBC fell to 9,500 on 4.2.54 and the Hb rose from 60% to 82% on 2.3.54. The patient felt greatly improved, but suddenly collapsed, with splenic pain, purpura, etc. - signs of an acute leukaemic termination - and she died on 12.3.54. Autopsy was not permitted.

The HVDs in this case were 2.4 and 2.0 mcs.-destroyed.

Case M 11.

Mrs. F.M., aged 32, weight 48 kilos, felt tired and vaguely unwell several months after the birth of her second child (November 1950). She consulted her doctor in August 1951 and was referred to the Christie Hospital on 10.8.51. The general condition was good, the spleen was down to the umbilicus, the liver was not enlarged, and she had no lymphadenopathy, no pyrexia, no petechiae, ecchymoses or mucosal bleeding. Platelets were plentiful, the Hb was 48% and the WBC 250,000 per c.mm., 10% being blast cells and 38% immature cells of all types. P^{32} was given as follows:- 4.6 mcs. on 27.8.51, 2.0 mcs. on 3.9.51 and 2.3 mcs. on 10.9.51, 17.9.51, 25.9.51, 1.10.51 and 9.10.51. The WBC fell exponentially,

with a HVD of 2.5 mcs.-destroyed, to a lowest level of 13,500 on 8.10.51. The Hb rose to a maximum of 112% on 7.1.52, the WBC then being 16,000 per c.mm. The spleen became impalpable by 23.11.51, and the patient's general health considerably improved. Deterioration began in mid-1952 and a two weeks' course of splenic x-ray therapy was begun on 11.9.52. The WBC fell from 121,000 to 9,400 by 2.10.52, while the Hb rose from 64% to a maximum of 103% on 14.11.52. The general condition also improved during this period but the whole picture deteriorated again, and on 13.4.53 chemotherapy was instituted, using B.E.P. She had 10 mgs. daily from 15.4.53 to 17.4.53 with some initial improvement, but after leaving hospital she developed pneumonia. By 30.9.53 she was again considered in need of chemotherapy and had a further 14 days' course, having 10 mgs. daily. The Hb rose from 53% to 75% by 12.2.54 though the WBC was then up to 250,000. No further treatment was given apart from general supportive measures and the patient died on 13.9.54. Autopsy was not possible.

Case M 12.

Mrs. J.B., aged 69, weight 49 kilos, developed sudden weakness in March 1949. She refused investigation and remained in bed for 3 months, but finally agreed to examination in Bury Hospital in December, 1949. On admission to the

Christie Hospital on 6.1.50 the general condition was only fair, the spleen was substantially enlarged and the liver moderately so, though there was no lymphadenopathy, no pyrexia or haemorrhagic features. The Hb was 80%, platelets were plentiful and the WBC was 33,000 with no myeloblasts but 4% of immature white cells. There was a symptomless urinary infection of B. coli and an infective leukaemoid blood picture was considered. However a 2% basophilia in the peripheral blood, and also the large number of myeloblasts in the sternal marrow strongly suggested myeloid leukaemia. In addition, the large spleen (not kidney!) and liver added further weight to this diagnosis. 5.0 mcs. of P³² were given on 11.1.50 and 24.1.50 and the WBC fell exponentially with a HVD of 2.6 mcs.-destroyed. The lowest WBC level was 3,000 per c.mm. on 7.3.50 and the Hb had risen to 102% by 27.9.50, the WBC then being 6,000. The spleen was impalpable by 2.8.50 and the patient's general condition has remained excellent to date. Naturally such a remission casts doubt in retrospect on the original diagnosis. On 12.12.56 the Hb was 92%, the WBC 14,000, the spleen nearly down to the iliac crest, and the patient had what could only be called a polycythaemic facies. The peripheral blood showed a shift to the left with 10% myelocytes but no blast cells. The marrow showed active granulo- and erythropoiesis. It is of

interest that a radioiron tracer study showed a plasma clearance rate of only 13 minutes and an iron turnover rate of 8.9 mgs. per hour. This suggests very active erythropoiesis, and in the absence of obvious haemolysis, a polycythemic development in the future seems an interesting possibility.

Case M 13.

Mrs. A.H., aged 65, weight 36 kilos, was troubled by rheumatoid arthritis for many years. An attack of diarrhoea led to an abdominal examination in October, 1950 and a large spleen was found. Investigation at Leigh Infirmary confirmed myeloid leukaemia and she was sent to the Christie Hospital on 6.11.50. The general condition was rather frail, the spleen was enlarged to the iliac crest, the liver was not palpable, there was no lymphadenopathy and no haemorrhagic features. The Hb was 56% just before treatment, platelets were plentiful and the WBC was 76,000 per c.mm. 10% of the WBC were primitive cells. An initial dose of 5.0 mcs. of P^{32} was given on 10.11.50 followed by five weekly doses of half this quantity. The WBC fell exponentially, with a HVD of 2.7 mcs.-destroyed, to a minimum level of 3,800 on 23.12.50. The Hb rose to a maximum of 112% by 23.7.51. The patient then looked polycythaemic and had symptoms of visual disturbance, limb pains, and general suffusion which finally led to the administration

of 5.0 mcs. of P^{32} on 13.8.51. This was designed to reduce her erythropoeisis. The spleen, at the iliac crest in her initial leukaemic phase, had resolved to the umbilical level and persisted. The WBC at the time of this second dose of P^{32} was 28,000 per c.mm. and this fell to 6,700 by 9.11.51. The haemoglobin also fell to 100%. The problem thereafter was that of the polycythaemic patient with increasing thrombotic features - scotomata, dysarthria, headache, etc. In addition to repeated venesections, 5.0 mcs. doses of P^{32} were given on 12.2.53, 3.7.53 and 3.3.54. The response to P^{32} was always short-lived and the Hb reached a highest level of 134% in July, 1954. Whole body x-ray therapy was tried in September, 1954 with only a moderate response, and in April 1955, chemotherapy with the anti-malarial drug Daraprim was begun. For the first time the Hb was effectively controlled at levels between 90% and 100%. However, when last reviewed on 12.2.57 the general condition was not good, cerebral thrombotic signs dominated the clinical picture, and the Hb had fallen to 75%. The platelets, however, were 223,000 per c.mm. and the WBC 19,600.

This remains a most interesting case and the relationship between myeloid leukaemia, polycythaemia vera, and myelosclerosis once more comes to mind. It may well be that this has been a case of polycythaemia vera from the beginning.

Case M 14.

Mr. S.B., aged 50, weight 64 kilos, developed breathlessness in August 1950, was investigated at Wigan Infirmary and referred to the Christie Hospital on 1.1.51. The general condition was good, the spleen reached below the umbilicus, the liver was not palpable and there were no significant lymph nodes to be felt, nor any bleeding tendency. Platelets were plentiful, the Hb was 56%, and the WBC 300,000 per c.mm., 1.0% being blasts and 55% immature cells of all types. On 12.1.51 a dose of 9.2 mcs. of P^{32} was given followed by 4.6 mcs. on 19.1.51, 26.1.51, 2.2.51 and 9.2.51. The WBC fell exponentially, with a HVD of 2.9 mcs.-destroyed, to a lowest level of 4,700 on 22.2.51. The Hb rose to 100% by 26.4.51 when the WBC was 6,900, but the highest Hb recorded during this remission was 122% on 30.11.53. The spleen was impalpable by 26.4.51 and the general condition looked excellent. The patient however was something of a chronic invalid, having been off work for many years following an accident. He seldom admitted good health. By 9.2.54 the Hb had dropped to 86%, the WBC had risen to 150,000, platelets were 180,000 and the spleen was enlarged again almost to the umbilicus. P^{32} was given again:- 6.0 mcs. on 9.2.54, 3.0 mcs. on 3.3.54 and 4.3 mcs. on 16.3.54. The Hb again rose to 110% on 29.4.54 but the WBC fell

erratically, possibly because of intercurrent pyrexial episodes. The WBC remained low however, and the Hb fell rapidly from 88% on 2.11.54 to 37% on 19.11.54. It is of interest to note that during October 1954 this patient developed a patchy paresis of the right arm, affecting mainly the deltoid and biceps, associated with pain radiating to the fingers. The question of a leukaemic deposit was considered but the general deterioration called for palliative measures only, and the patient died on 27.11.54. Autopsy revealed a carcinomatous tumour of undetermined origin densely adherent to the side of the upper cervical vertebrae. This was considered to be unassociated with his myeloid leukaemia. The femoral marrow in this case again showed the dark crimson colour referred to previously.

Case M 15.

Mr. F.T., aged 72, weight 67 kilos, developed cough and dyspnoea early in 1951. Twelve months later he noted discomfort in the left hypochondrium and was referred to Crumpsall Hospital in April 1952. Myeloid leukaemia was diagnosed and he was referred to the Christie Hospital on 27.5.52. In addition to his leukaemia he had congestive heart failure and his general condition was poor. The spleen was enlarged below

the umbilicus but the liver was not felt, there was no lymph-adenopathy, and no petechiae or mucosal bleeding. Platelets were plentiful, but the initial Hb level was only 40% of normal. The WBC was 340,000 per c.mm., 2.5% being blast cells and 24% total primitive white cells. 9.6 mcs. of P³² were given on 4.6.52, 3.8 mcs. on 18.6.52, 1.45 mcs. on 25.6.52, 2 mcs. on 2.7.52 and finally 4.8 mcs. on 9.7.52. This was another example of an attempt to depress the WBC as low as possible but it fell no lower than 18,000 on 18.8.52. The WBC nevertheless fell exponentially with a HVD of 2.9 mcs.-destroyed. The Hb on 18.8.52 was 82% and it rose to 90% by 29.9.52, by which time the WBC had also increased to 27,000. At this time also the spleen was just palpable. The general condition of the patient did improve, but in view of his cardiac defect and general decrepitude this improvement was not spectacular. There was sudden and rapid deterioration in February, 1953, and the patient died on 26.2.53. Autopsy was not permitted.

Case M 16.

Mrs. A.S., aged 56, weight 54 kilos, noticed breathlessness and cyanosis of the lips and face in March, 1950. She had had a left radical mastectomy in 1947 for mammary cancer but had no sign of local or metastatic cancer. She was attending the Christie Hospital because of the breast history

and myeloid leukaemia was diagnosed in August, 1950. Marrow metastases were considered as a possible cause of her leukaemic blood picture but finally were regarded as unlikely. The general condition was good, the spleen was grossly enlarged across the mid-line, but the liver was ~~impalpable~~, there were no nodes and no bleeding or petechiae. Platelets were plentiful and the initial Hb level was 48%. The WBC was 440,000 per c.mm. of which 1% were blast cells and 53% total immature cells. P^{32} was given as follows:- 7.5 mcs. on 23.8.50 and 30.8.50, 4.5 mcs. on 7.9.50 and 14.9.50, 1 mc. on 21.9.50 and 3.5 mcs. on 28.9.50 and 6.10.50. The WBC fell exponentially with a HVD of 3.1 mcs.-destroyed, the lowest level being 14,000 on 2.10.50. The Hb rose to a maximum of 82% by 11.1.51, but by then the WBC had risen to 138,000. The spleen diminished considerably but never above the umbilicus, and indeed by January 1951, had again become large and uncomfortable. This fact and the rapid rise in WBC led to further treatment, in spite of the good Hb response and improved general health. The second treatment in this case was by splenic x-ray therapy, begun on 31.1.51 and terminated on 13.3.51. The WBC by this treatment was reduced to 6,000 per c.mm. by 15.3.51 though the Hb did not improve above the 80-85% level. The spleen also was reduced once more in size but again only to the umbilical

level, though it was more comfortable for the patient. The general condition remained good until 31.8.51 when the leukaemia deteriorated and the patient also developed recurrent skin nodules of breast cancer as well as lung metastases. A few weeks before her death on 25.10.51 an attempt was made to control her malignancy with chemotherapy (T.E.M.) but no improvement was noted. Unfortunately an autopsy was not permitted.

Case M 17.

Mrs. A.W., aged 64, weight 55 kilos, felt unwell and noted abdominal swelling in 1951. She saw her doctor regularly but was given tonics for her lassitude without examination until July 1952, when she was referred to Bolton Royal Infirmary. Leukaemia was diagnosed and she was sent to the Christie Hospital on 26.9.52. By then she was ill with a very large spleen and liver, and oedema of the ankles and lumbar region. There was no lymphadenopathy, no ecchymoses, petechiae or mucosal bleeding, the initial Hb was 58% and platelets were plentiful. The WBC was 510,000 of which 2% were blast cells and some 54% total immature cells, mainly metamyelocytes and myelocytes. 7.8 mcs. of P^{32} were given on 29.9.52, a further 3.6 mcs. on 24.10.52, 3.0 mcs. on 30.10.52, 5.0 mcs. on 7.11.52

and 3.0 mcs. on 18.11.52. The WBC fell exponentially with a HVD of 3.2 mcs.-destroyed, the lowest level being 14,000 on 28.11.52, when the Hb was 78%. The Hb rose to a maximum of 92% on 19.1.53, the WBC then having risen to 53,000. The liver became impalpable by 19.1.53 and the spleen just palpable on that date. The general condition improved very considerably but during September, 1953, she developed haematuria and deterioration was apparent both clinically and haematologically. The haematuria was intermittent at first but the patient died in uraemia on 6.11.53. Autopsy was not permitted.

Case M 18.

Mrs. F.M.H., aged 61, weight 40 kilos, attempted suicide on 3.6.51 without success. She was considered mentally normal but was found to have myeloid leukaemia. Her general health was fair, the spleen grossly enlarged, there was generalised small lymphadenopathy, but no haemorrhagic features. Platelets were slightly reduced and the initial Hb level was 80%. The WBC was 90,000 per c.mm., with 1% blast cells and 7.5% total primitive cells. The bone marrow and peripheral blood in this case suggested a leuko-erythroblastic disease, but all clinical and radiographic surveys, both initially and on many occasions before death, failed to reveal any malignancy or to support a

diagnosis of myelosclerosis. 4.0 mcs. of P³² were given on 10.8.51, followed by 2.0 mcs. on 16.8.51, on 27.8.51 and on 11.9.51. The WBC fell exponentially with a HVD of 3.2 mcs.- destroyed, the lowest level being 6,800 on 19.10.51. The Hb rose to 96% by 31.7.52 by which time the WBC had risen to 31,000 per c.mm. The spleen became much reduced in size by January, 1952, and the general condition vastly improved, though mental instability proved troublesome from time to time. The patient remained remarkably well but died, curiously, from a sudden uncontrolled haemorrhage from a varicose ulcer, on 18.2.53. Autopsy was not permitted.

Case M 19.

Mr. J.D.N., aged 56, weight 70 kilos, complained of lethargy in early 1949, followed by aching in the left side of the abdomen. He also noted an increasing tendency to bruising after trivial injuries. He was referred to the Christie Hospital by his family doctor on 30.6.49 and chronic myeloid leukaemia was diagnosed. The general condition was fair, the spleen was considerably enlarged but the liver was not, neither was there any lymphadenopathy, pyrexia or mucosal bleeding. Platelets were plentiful and the initial Hb was 62%. The WBC was 320,000 per c.mm., with 1% blast cells and 19% total primitive white cells. The sternal marrow was hyperplastic

and confirmed myelogenous leukaemia. On 27.7.49 a dose of 7.0 mcs. of P^{32} was given, followed by 3.0 mcs. on 11.8.49, 4.0 mcs. on 20.8.49 and 3.0 mcs. on 1.9.49. The WBC fell exponentially with a HVD of 3.5 mcs.-destroyed, the lowest level being 11,000 on 10.10.49. The Hb then was 82% but rose to 100% by May, 1950, when the WBC was 16,000. The spleen was not palpable by March, 1950, and the patient's general health had improved remarkably - indeed he played cricket as a fast bowler. He felt less well in August 1950, the WBC rose to 81,000, the Hb fell to 88%, then the spleen became moderately enlarged again. A second course of P^{32} was given - 5.0 mcs. on 23.8.50 and 2.5 mcs. on 7.9.50. Again the WBC fell exponentially though on this occasion with a HVD of only 2.4 mcs.-destroyed - a significantly more sensitive response. The lowest WBC following this treatment was 5,500 per c.mm. on 10.10.50, the Hb then being 92%. The spleen by that date was again impalpable and the general health improved to its former vigour. A third course of treatment became necessary by August, 1951, and he was given 5.0 mcs. of P^{32} on 3.8.51. It was decided however to continue with splenic irradiation in this case, mainly because the patient demanded out-patient treatment. Six weekly splenic treatments were given from 28.11.51 until 10.1.52 and again an excellent remission followed.

The WBC fell to a low level of 9,000 on 24.1.52, and the Hb rose to a maximum of 98% by 9.4.52. The spleen too became impalpable by that date and the general health was excellent. This was short-lived, however, and by 27.5.52 the spleen was again painful and down to the umbilicus, the general health was not good and the WBC rising rapidly (82,000). Chemotherapy was instituted on 25.6.52 using B.E.P. Maintenance doses were given from time to time and a good clinical and haematological remission was achieved. The spleen became smaller and more comfortable, the WBC remained below 20,000 per c.mm. and the Hb around 95 - 100% until April, 1953, when the drug was changed to Myeleran. The blood picture remained excellent thereafter though the patient had various complaints of abdominal pain of uncertain origin - apparently not splenic infarction. Investigations revealed a curious left-sided impairment of renal function, dye being poorly excreted, presumed to be due to pressure from the overlying spleen. Myeleran kept him going very well until December, 1953, when ecchymoses, not seen since his first treatment in 1949, reappeared and were then associated with thrombocytopenia. The Hb began to drop slowly and on 19.1.54 a course of 6-mercaptopurine was instituted, ending on 14.2.54. This drug, and Myeleran, were given on two further occasions without

significant improvement and the patient died, with gross anaemia and a huge tender spleen, on 24.6.54. Autopsy was not permitted.

It is of interest that the HVDs for the two completed courses of P³² were 3.5 and 2.4 mcs.-destroyed.

Case M 20.

Mrs. A.T., aged 25, weight 60 kilos, noted menstrual irregularity about December 1950, followed by lassitude in 1951. She noted swelling in the abdomen in July 1951, was referred to Blackburn Infirmary in September and thence to the Christie Hospital on 16.10.51 as myeloid leukaemia. The general health was excellent, the spleen was considerably enlarged though the liver and lymph nodes were not enlarged, there were no ecchymoses, petechiae or pyrexia. Platelets were plentiful and the Hb level on admission was 58%. The WBC was 260,000 per c.mm. with 1% blast cells and 37% total immature white cells. Sternal marrow confirmed the diagnosis. 5.5 mcs. of P³² were given on 30.10.51, 3.0 mcs. on 7.11.51, 12.11.51, 20.11.51, 27.11.51 and 4.12.51 with a final 5.0 mcs. on 11.12.51. The WBC fell exponentially with a HVD of 3.6 mcs.-destroyed, the lowest level being 5,500 on 21.12.51. The Hb at that date was 72% but it rose to a maximum of 92%

by 31.3.52. The spleen was no longer palpable by 28.4.52 and the general health of the patient improved considerably. In May, 1952, there was a short epistaxis, and in July a period of menorrhagia. The latter ceased after excision of a cervical erosion on 29.7.52. The spleen began to enlarge again, the WBC increased and the Hb fell so that a second course of treatment, by splenic x-ray therapy on this occasion, was given from 30.12.52 to 27.1.53. The Hb increased from 78% in December 1952, to 94% by August 1953, in spite of an unexpected leukopenia. The splenic radiation had stopped at a WBC level of 6,000 per c.mm. but the count continued to fall to a minimum of 1,700 on 23.2.53. This leukopenia persisted and was complicated by perineal infections on two occasions. By June 1953, the WBC was 12,000 and it continued to rise until further splenic radiation became necessary in January 1954. The WBC then was 110,000, the Hb was 74% and the spleen, which had resolved completely during the leukopenic phase, had again become large and tender. The WBC fell slowly in response to x-ray therapy but the Hb showed no corresponding rise. On 4.2.54 an increase in blast cells was noted in the peripheral blood, the general condition deteriorated, bleeding recurred from the nose and uterus, and in spite of chemotherapy with 6-mercaptopurine the patient died on 27.2.54. Autopsy was not permitted.

Case M 21.

Mrs. D.T., aged 58, weight 54 kilos, was troubled with gout since 1937. An exacerbation of her gout led to a medical review in Park Hospital, Manchester, in 1951 and myeloid leukaemia was discovered. The patient's general health had been deteriorating slowly though her main symptom was discomfort in her gouty hands (See Figure 8). The general condition on admission to the Christie Hospital was poor, the spleen was enormous and filled most of the abdomen, though the liver and lymph nodes were not enlarged, neither was there any bleeding tendency or pyrexia. Platelets were plentiful and the Hb level on admission was 65%. The WBC was 140,000 per c.mm. with 1.5% blast cells and 28% immature cells of all types. 5.4 mcs. of P^{32} were given on 18.3.52 and 2.7 mcs. on 25.3.52, 1.4.52, 8.4.52, 22.4.52 and 29.4.52. The WBC fell exponentially with a HVD of 4.5 mcs.-destroyed to a lowest level of 5,600 on 3.5.52. The haemoglobin on that date was 62% but it rose to a maximum of 82% on 15.9.52, the WBC then being 30,000 per c.mm. Though the spleen became significantly smaller it was never above the umbilicus. The general condition did in fact ultimately improve but it is interesting that this patient had an acute exacerbation of her gout during this first month after completing her P^{32} therapy. She was

confined to bed with acutely painful and swollen ankles and wrists, but this cleared up and she was able to lead an active life once more. Unfortunately this patient was admitted to another hospital for investigation of her gout in December 1952, and though some clinical data were obtained, these were incomplete. No further anti-leukaemic treatment was apparently given but the patient died on 17.7.54.

Case M 22.

Miss E.C., aged 31, weight 51 kilos, became lethargic in 1952 and after periods of improved health she finally had a blood examination which showed a leukaemic picture. After investigation at Westmorland County Hospital she was referred to the Christie Hospital on 25.3.54. The general condition was not good and the patient looked ill. The spleen was grossly enlarged to the iliac crest and the liver was also considerably enlarged. There were no haemorrhagic signs and no lymphadenopathy. The Hb on admission was 68%, platelets were plentiful, and the WBC was 200,000 per c.mm., 1.0% being blasts and 38% total primitive cells. 6.0 mcs. of P³² were given on 26.3.54, followed by 4.0 mcs. on 15.4.54, and 5.0 mcs. on 27.4.54 and 4.5.54. The WBC fell exponentially, with a HVD of 4.5 mcs.-destroyed, reaching its lowest level of 10,000 per c.mm. on 10.7.54. The Hb at that date had risen to its highest

level of 127% and the spleen was no longer palpable. The general health of the patient improved considerably and rapidly and was well-maintained until the summer of 1955. By June, 1955, the Hb had dropped to 80% and the WBC had risen to 141,000. On 27.6.55 a dose of 6.0 mcs. of P^{32} was given followed by 3.0 mcs. on 12.7.55. The WBC again fell exponentially though, with a HVD of 1.4 mcs.-destroyed, much more sensitively than on the first occasion. The WBC flattened out at a fairly high level (30,000) but the Hb rose to 100% on 10.9.55. The general health again improved sufficiently to return to work as a school teacher, but she was re-admitted to hospital on 24.1.56 gravely ill. Pyrexia and epistaxis suggested an acute leukaemic phase and the patient died on 8.2.56.

Autopsy showed pneumonia and a large recent infarction in the spleen. The bone marrow of the femur, sternum and vertebrae did not indicate aplasia but showed active leuko- and erythropoiesis. The plasma clearance-rate of radio iron on 26.1.56 had been rapid (20 minutes half-clearance time) but the patient was too ill to pursue detailed study.

The HVDs were 4.5 and 1.4 mcs.-destroyed.

Case M 23.

Mrs. S.P., aged 68, weight 51 kilos, first developed epistaxis in 1950. This recurred from time to time, and in March 1952, she noted a painful and tender swelling in the abdomen. Investigation at Wigan Infirmary disclosed leukaemia and she was admitted to the Christie Hospital on 21.8.52. The general condition was good, the spleen was enlarged well below the umbilicus, but the liver and lymph nodes were impalpable. There were no petechiae, ecchymoses or pyrexia. Platelets were plentiful and the Hb on admission was 63%. The initial WBC was only 31,000 per c.mm. but with 2.0% of myeloblasts and 11% of immature white cells of all types. The sternal marrow was hyperplastic with a shift to the left in leukopoiesis, and active erythropoiesis. On 26.8.52 a dose of 7.3 mcs. of P³² was given followed by 5.25 mcs. on 16.9.52. The WBC fell exponentially, with a HVD of 4.6 mcs.-destroyed, to a minimum level of 5,200 on 6.10.52. The haemoglobin then was 80% but it rose to a maximum of 126% on 6.8.53, the WBC at that date being 18,000 per c.mm. The spleen became just palpable by February, 1953, and the general health improved considerably. This excellent remission lasted until February 1955, and even then the Hb was still 92% and the WBC only 50,000, though the spleen was down to the pubis and most uncomfortable. Splenic

x-ray therapy was given from 8.2.55 to 28.2.55 in an effort to reduce the size of the organ. As often happens, the spleen showed little diminution in size yet much of the local discomfort and tenderness disappeared. The greatly enlarged spleen has persisted to date and though the patient is still alive she is now becoming progressively anaemic. Radio-iron studies have shown a rapid plasma clearance-rate and iron turnover, and since the sternal marrow has shown active erythropoietic and leukopoietic activity these findings suggest a haemolytic phase. Some response to steroids may be expected though the general condition of the patient justifies no optimism.

Case M 24.

Mr. J.W.C., aged 72, developed dyspnoea in April 1949, and investigation at Rochdale Infirmary revealed myeloid leukaemia. He was admitted to the Christie Hospital on 31.5.49, when the general condition of the patient was poor, the spleen was moderately enlarged, but the liver and lymph nodes were not palpable. There were no ecchymoses, petechiae, or pyrexia, but the scarcity of platelets and the very low haemoglobin level of 26% suggested a terminal leukaemia. This was one of the first leukaemic patients treated in this series and his poor response would not nowadays be surprising. The

WBC on admission was 100,000 per c.mm., with 1.0% blasts and 12% primitive cells of all types. A dose of 7.5 mcs. of P^{32} was given on 1.6.49, followed by 2.3 mcs. on 8.6.49 and 3.0 mcs. on 13.6.49. Though the WBC fell exponentially, with a HVD of 5.0 mcs.-destroyed, the Hb did not improve. After the last P^{32} dose a small blood transfusion was given but the patient suddenly deteriorated and died on 30.6.49. Autopsy showed once again the curious bright red and haemorrhagic marrow (sternal) described in several other cases. In addition Dr. Helen Russell commented on the heavy oedematous lungs.

Case M 25

Mr. W.M., aged 46, weight 60 kilos, developed undue lassitude about December 1951, followed by abdominal swelling which was investigated at Chorley Hospital in February 1952. Leukaemia was discovered and the patient was admitted to the Christie Hospital on 19.2.52. The general condition was poor, having deteriorated rapidly, the spleen was grossly enlarged into the right lower abdomen, and the liver too was grossly enlarged. There was no pyrexia or mucosal bleeding. The initial Hb level was 46%, the WBC 300,000 per c.mm., blast cells amounting to only 0.5%, with some 32% immature cells of all types. 6.0 mcs. of P^{32} were given on 26.2.52, followed by 3.0 mcs. each on 4.3.52, 11.3.52, 18.3.52, 25.3.52,

2.4.52, 8.4.52, and 22.4.52. The WBC fell slowly but exponentially, with a HVD of 5.2 mcs.-destroyed, the lowest level being 15,000 per c.mm. on 24.4.52. The Hb at that date was 77% and it rose to a maximum of 80% by 1.5.52, the WBC then being up to 32,000. At the end of that month the patient suddenly deteriorated with an acute myeloblastic leukaemia and died on 4.6.52. Unfortunately, autopsy was not permitted.

Case M 26.

Mrs. M.F., aged 41, weight 62 kilos, developed abdominal swelling, lassitude, loss of weight, and sweating in April 1949. Investigation at Wigan Infirmary revealed myeloid leukaemia and she was admitted to the Christie Hospital on 11.10.49. The general condition was quite good, the spleen was substantially enlarged but the liver and lymph nodes were not palpable. There was no bleeding tendency and no pyrexia, platelets were plentiful, and the initial Hb level was 62%. The WBC on admission was 460,000 per c.mm., 0.2% being blast cells, and all primitive cells amounting to only 5% of the total. 6.0 mcs. of P^{32} were given on 13.10.49, followed by 4.0 mcs. on 21.10.49 and 2.11.49, and 3.0 mcs. each on 5.11.49, 17.11.49, 28.12.49 and 25.1.50. The WBC fell slowly but exponentially, with a HVD of 5.5 mcs.-destroyed, to a minimum level of 36,000 per c.mm. on 28.11.49. The Hb at that date

was 78% but it rose to a maximum of 90% by 25.1.50, the WBC then being 102,000 per c.mm. The spleen became reduced to a few cms. below the costal margin, and the general health of the patient improved considerably. By April 1950 the WBC had risen to 160,000 and the Hb had dropped to 80%; the spleen was again moderately enlarged, and though the general health remained good a further course of radiotherapy was begun on 21.4.50 when 3.0 mcs. of P^{32} were given. A similar dose was given on 28.4.50 but with such a slowly falling count further treatment was continued by splenic x-ray therapy, starting on 8.5.50. The WBC fell to a minimum of 4,900 on 27.6.50, when the Hb was 91%, the spleen not palpable, and the general health excellent. The Hb rose to 98% by 14.9.50 but the spleen became large and tender and the WBC rose to 160,000 by the end of 1950. Further splenic irradiation was given from 20.2.51 to 24.3.51, and again the spleen disappeared behind the costal margin by 10.5.51 and the Hb on that date was 106%. Deterioration during the next few months called for chemotherapy with a mustard derivative, from 29.8.51 to 7.9.51. The WBC was controlled but the Hb showed little improvement, and though chemotherapy was repeated in November there was no real response. Small doses of splenic irradiation were tried again in view of previous responsiveness to this treatment but the patient died on

12.12.51.

Autopsy confirmed widespread myelogenous leukemic infiltration, but in addition the femoral marrow showed areas of fibrous tissue replacement, i.e. myelofibrosis, and the sternal marrow showed lesser similar changes. The spleen showed large infarcted areas but also areas of active haemopoiesis.

Case M 27.

Miss J.B., aged 12, developed symptomless abdominal swelling noted by her Mother rather than by the patient, in May 1950. Investigation in Accrington Hospital revealed myelogenous leukaemia and she was admitted to the Christie Hospital on 5.9.50. The general condition was fairly good, the spleen nearly filled the abdomen, and the liver also was moderately enlarged. There was no bleeding tendency or pyrexia, platelets were plentiful, and the initial Hb level was 44%. The WBC on admission was 590,000 per c.mm., 4.0% being blast cells and 78% immature cells of all stages. On 8.9.50 the first dose of 4.25 mcs. of P^{32} was given, followed by similar doses on 14.9.50 and 21.9.50. The WBC fell very slowly, and it was decided to avoid further P^{32} in this case and switch instead to splenic x-ray therapy. The latter began on 29.9.50 and ended on 6.10.50. The initial fall in the WBC

in response to P^{32} alone was sufficient to establish that the response was exponential with a HVD of 8.4 mcs.-destroyed. The WBC fell in response to P^{32} and x-ray therapy to a minimum level of 6,200 per c.mm. by 16.10.50, the Hb then being 64%. By 21.11.50 the Hb was 82% but the WBC had already risen to 24,000. The spleen never resolved as far as the umbilicus but the general health showed a distinct improvement. Re-treatment was necessary by February 1951, and splenic irradiation from 13.2.51 to 9.3.51 led to considerable improvement again. The spleen was barely palpable by April 1951, and by July the Hb was 108%. By December 1951, though the general condition remained excellent, the spleen was again huge and the WBC 300,000 per c.mm. From 14.12.51 to 2.1.52 another course of splenic x-ray therapy reduced the size of the spleen to a more comfortable level, it also reduced the WBC to 11,000 by 7.1.52, but as so often happens at this stage, it failed to improve the red cell count. By June, general deterioration had set in, and though B.E.P. was tried from 19.6.52 onwards, a myeloblastic phase ended in death on 7.8.52. Autopsy was not permitted.

Case L 1.

Mr. W. McC., aged 69, weight 63 kilos, noted lumps in the neck in December 1950. Investigation in Warrington Infirmary revealed chronic lymphatic leukaemia and he was referred to the Christie Hospital on 5.3.51. On admission he was slightly cyanosed and had inflammatory changes in the right lower lobe of his lung. The spleen was just palpable, the liver was not palpable but there were lymph nodes enlarged though small in all areas. The Hb was 66%, platelets were plentiful and there were no haemorrhagic features. The WBC was 56,000 per c.mm. with many large immature lymphocytes. A dose of 10.0 mcs. of P³² was given on 13.3.51 and the WBC fell exponentially, with a HVD of 0.9 mcs.-destroyed to a minimum level of 3,500 per c.mm. on 25.4.51. The Hb on that date was 72% but it rose to a maximum level of 80% on 15.6.51 when the WBC was 16,000 per c.mm. The spleen became impalpable by May 1951, and the general condition improved considerably though slowly, the opacity in the right base being completely cleared by June 1951. The blood picture deteriorated rapidly during January 1952, and the patient was re-admitted on 22.1.52 with symptoms and signs of coronary thrombosis. He had in fact a history of coronary thrombosis in 1946. He improved with bed rest and sedation and was allowed home on 3.3.52. The Hb then was

68% with 58,000 white cells, 48,000 of which were lymphoblasts. It was decided to avoid any positive anti-leukaemic treatment for the time being but the patient died suddenly in another hospital on 11.4.52.

Case L 2.

Mrs. F.R., aged 43, weight 45 kilos, developed malaise and lassitude when aged 40 and had a rather premature menopause. In June 1953, she noticed a lump in the left axilla and was referred to Oldham Royal Infirmary where blood examination revealed lymphatic leukaemia. She was admitted to the Christie Hospital on 15.7.53 when her Hb was 84%, platelets plentiful, and there were no haemorrhagic signs. The spleen was moderately enlarged, the liver was not palpable, but lymph nodes in all areas were slightly enlarged. The WBC was 144,000, 97% being lymphocytes with many smear cells. On 17.7.53 a single dose of 6.4 mcs. of P^{32} was given and proved adequate. The WBC fell exponentially with a HVD of 1.1 mcs.-destroyed to a minimum level of 9,600 per c.mm. on 14.8.53. The Hb on that date was 90% but it rose to 102% by 11.3.54 by which time the WBC had risen to 52,000 per c.mm. The spleen resolved significantly but incompletely, but the lymph nodes became quite impalpable by 24.12.53. The general condition of the patient was greatly improved but in October 1954, she

deteriorated quite rapidly. The Hb was still at 96%, but the WBC had risen to 102,000. In spite of the good Hb level and moderate WBC the patient's symptoms of anorexia, lassitude, dyspnoea, splenic discomfort, and occasional ecchymoses led to a further treatment with 6.0 mcs. of P^{32} on 14.10.54. The WBC again fell exponentially with a HVD of 1.2 mcs.-destroyed, reaching a lowest level of 6,400 on 24.11.54. The Hb on the latter date had dropped to 80% - not a good finding, but curiously enough the patient's general health had improved very considerably. By February, 1955, the spleen was impalpable and the Hb reached 100% by June 1955. Though she has had one or two bouts of pulmonary infection the patient remains active and well with no disturbing symptoms. On 24.4.57 her Hb was 96% and the WBC 64,000, the liver was not palpable, the spleen enlarged 3 cms. below the costal margin. Only one node was palpable, a small one in the left axilla. There were no petechiae or ecchymoses, and the appetite was excellent.

The two HVDs in this case were again remarkably similar - 1.1 and 1.2 mcs.-destroyed.

Case L 3.

Mrs.E.S., aged 51, weight 74 kilos, developed herpes zoster in the cervical region in June 1948, and thereafter discovered enlarged nodes in the neck. These subsided, but investigation in Oldham Royal Infirmary showed a blood picture suggesting early lymphatic leukaemia. No treatment was indicated at that time, but by June 1950, she had 50,000 white cells per c.mm., 77% being lymphocytes. On admission to the Christie Hospital in August 1950, the WBC was 70,000 with 92.5% lymphocytes, many being smear types. The spleen extended nearly to the umbilicus, the liver was not felt but lymph nodes in all areas were palpable though not greatly enlarged. The Hb level was 76%, platelets were plentiful, and no haemorrhagic signs were seen. An initial dose of 7.0 mcs. of P^{32} was given on 23.8.50 followed by 2.0 mcs. on 30.8.50 and 1.0 mc. on 7.9.50, 14.9.50 and 21.9.50. The WBC fell exponentially with a HVD of 1.3 mcs.-destroyed. The Hb rose only 8% to 84% on 2.10.50 when the WBC was 3,000 per c.mm. The lymph nodes showed no significant resolution, and particularly disappointing was the fact that ascites, present on admission, not only persisted but increased considerably. The general condition did not improve, the Hb and WBC both collapsed during October and the patient died on 28.10.50. The ascites in this case was an unusual feature, but unfortunately no autopsy was permitted.

Case L 4

Mr. J.H.D., aged 55, weight 56 kilos, noticed a swelling in the left neck in January 1951. Investigation at Manchester Royal Infirmary revealed chronic lymphatic leukaemia and he was referred to the Christie Hospital on 26.2.51. At that time the WBC was 33,000 and the Hb 86%. The patient felt well and no treatment was indicated. He was seen at short intervals until October by which time the Hb had fallen to 66% and the WBC had risen to 100,000 per c.mm. 97% of the white cells were lymphocytes with many smear types, platelets were plentiful, and the spleen and liver were not palpable. On 30.10.51 a dose of 5.5 mcs. of P^{32} was given followed by 3.0 mcs. on 7.11.51 and 12.11.51. The WBC fell exponentially with a HVD of 1.4 mcs.-destroyed, to a minimum level of 2,700 on 20.11.51. The Hb on the latter date was 62% but rose slowly to a maximum of 90% on 27.10.52. The WBC by that time was 17,500 per c.mm. The lymph nodes showed little resolution, but the general condition of the patient improved considerably. By October 1953, the first remission had clearly terminated both clinically and haematologically, the Hb being 55%, the WBC 120,000 per c.mm. and the general condition quite poor. Recent "influenza" had left him feeling ill. At this stage chemotherapy was employed out of interest, and not because of any contra-indication to radiation therapy. One of the

nitrogen mustard derivatives (C.B.9859) was given on 3.10.53 and produced a rapid drop of the WBC to about 1,000 cells per c.mm. by 14.10.53! The Hb also fell and 4 pints of blood were transfused during 20 and 21.10.53. The Hb then rose from 46% to 67% and continued to rise to 86% on 19.1.54. The lymph nodes had also shown a dramatic resolution and were scarcely palpable within 10 days of the chemotherapy. The platelets also dropped to between 40,000 and 50,000, but the patient's general health undoubtedly improved during the 4 months following this rather frightening chemotherapy. By April, 1954, further chemotherapy was indicated, T.E.M. being used on this occasion. Again worthwhile improvement followed, though a pneumonic attack in August 1954 spoiled the clinical value of this remission. By December 1954, the Hb was down again to 45%, the WBC 120,000 and platelets also reduced. Tentative doses of x-rays to the spleen were initiated on 2.12.54 with little real improvement. This was continued on a weekly out-patient basis from 29.3.55, but though the spleen became less uncomfortable for a time, the patient finally deteriorated and died on 12.10.55. The WBC was rising rapidly before death and the Hb was falling. No autopsy was permitted.

Case L 5.

Mr. W.H.B., aged 53, weight 59 kilos, noted swollen glands in the neck three years before being referred to Blackburn Infirmary where chronic lymphatic leukaemia was diagnosed. On admission to the Christie Hospital in February 1953, the Hb was 68%, platelets were plentiful and there were no haemorrhagic findings. The spleen was moderately enlarged, and lymph nodes were grossly enlarged in the neck, axillae and groin. The WBC was 500,000 per c.mm., with scarcely any polymorphs, but many smear cells, large lymphocytes, and lymphoblasts. On 27.2.53 a dose of 8.46 mcs. of P^{32} was given, followed by 3.0 mcs. on 13.3.53 and 23.3.53. The WBC fell exponentially, with a HVD of 1.4 mcs.-destroyed, to a minimum level of 5,200 on 31.3.53. The Hb at that date was 70% but it rose slowly to a maximum level of 102% in February, 1954, the WBC then being 108,000 per c.mm. In May 1954, this patient developed an attack of herpes zoster over the right shoulder region (See Figure 6) and this was followed by a widespread papular eruption (not vesicular) on the trunk. Biopsy of one of these papules showed "rather widespread but patchy infiltration of the sub-epithelial layers by lymphocytes, with an occasional clump of histiocytes". By July 1954, the WBC was 200,000 and the Hb 72%. A single dose of 6.0 mcs. of P^{32} was

given on 29.7.54 and again the WBC fell exponentially with a HVD of 0.9 mcs.-destroyed to a lowest level of 13,000 per c.mm. by 6.9.54. The Hb on that date was 83%, but this rose steadily to 98% by 28.9.54. The general condition also improved, the spleen and lymph nodes however showed little response. By February 1955, the Hb had fallen again to 68% and the WBC was 285,000 per c.mm. A single dose of 5.0 mcs. of P^{32} was given on 25.2.55 and again the WBC fell exponentially with a HVD of 1.1 mcs.-destroyed to a lowest level of 8,000 by 5.4.55. The Hb then was 70% but it rose to 88% in August 1955. However recurrent pulmonary infections led to progressive deterioration and by February 1956, the Hb had fallen to 40% and the WBC was up to 304,000. Tentative doses of x-rays to the spleen were given between 16.2.56 and 24.2.56, but in spite of blood transfusions and general supportive measures the patient died on 5.7.56. Autopsy was not permitted.

Note again the limited variation in the HVDs for three courses of P^{32} - 1.4, 0.9 and 1.1 mcs.-destroyed.

Case L 6

Mr. H.R., aged 66, developed pleurisy in July 1954, and swollen glands in the right neck in September 1954. He was admitted to the Christie Hospital on 19.10.54 and investigation revealed chronic lymphatic leukaemia. The spleen was

moderately enlarged, the liver was not palpable but lymph nodes were large and florid in the right neck, axillae and groins, and both tonsils were considerably enlarged. The Hb was 68%, platelets were reduced but no haemorrhagic features were noted. The WBC was 570,000 per c.mm., nearly all lymphocytes, with smear cells, large immature lymphocytes and lymphoblasts. On 29.10.54 a dose of 6.0 mcs. of P^{32} was given followed by a further 6.0 mcs. on 15.11.54. The WBC fell exponentially, with a HVD of 2.0 mcs.-destroyed, to a minimum of 19,000 per c.mm. on 21.12.54. The Hb on that date was 78% and it rose steadily to a maximum of 93% on 29.3.56, the WBC then being up to 40,000 per c.mm. The general condition of the patient improved, but the spleen showed no response, and the lymph nodes, especially the mass in the right neck, showed only moderate resolution. It is of interest that though additional resolution of the neck nodes did occur after x-ray therapy on 1.2.55 there was incomplete resolution even after 2,000r in 4 days through a field 10 x 12 cms. This dosage produced patchy moist desquamation, and might well have produced total if temporary resolution of squamous cell carcinoma, much less lymphosarcoma. The nodes of chronic lymphatic leukaemia are truly limited in their radio-sensitivity. By February 1956, further treatment was necessary. The Hb had fallen to 64%

and the WBC had risen to 180,000 per c.mm. On 13.2.56 a dose of 4.7 mcs. of P^{32} was given, followed by 3.1 mcs. on 28.2.56. The WBC again fell exponentially, with a HVD of 1.5 mcs.-destroyed, to a minimum level of 19,500 per c.mm. on 14.3.56. The Hb at that date was 68% but it rose slowly to a maximum of 72% by July 1956. The spleen and nodes showed no response, and though there was real subjective improvement until November, there was rapid deterioration in December 1956. On 18.12.56 a single dose of 5.0 mcs. of P^{32} was given and yet again the WBC fell exponentially with a HVD of 0.8 mcs.-destroyed from an initial level of 154,000 to a lowest level of 19,700 per c.mm. on 4.1.57. The general condition, however, did not improve and the Hb fell steadily from a pre-treatment level of 52% to 28% on 19.2.57. This might have been expected from the finding on 14.12.56 that the time for 50% plasma clearance of Fe59 was 141 minutes. (Marrow samples were at that time unsatisfactory). The patient is now moribund (June, 1957).

The three HVDs in this case were 2.0, 1.5 and 0.8 mcs.-destroyed.

Case L 7.

Mr. J.T.M., aged 49, weight 48 kilos, developed a generalised erythematous rash during December 1954. This became an exfoliative dermatitis and while in the North Lonsdale Hospital blood examination disclosed chronic lymphatic leukaemia, with 210,000 white cells, 96% of which were lymphocytes. The Hb level was 70%, platelets were reduced, the spleen was not palpable but the liver was just palpable. No lymph nodes were felt and there were no petechiae, ecchymoses or other haemorrhagic features. 5.0 mcs. of P^{32} were given on 27.1.55 and during the following 4 days blood counts showed an exponential fall in the WBC with a HVD of 2.0 mcs.-destroyed. The skin showed a rapid improvement during these first four days, but the patient suddenly collapsed and died on 1.2.55. At autopsy the leukaemia was confirmed, blood smears looked like acute lymphoblastic leukaemia, but the bone marrow was quite extraordinary. Dr. J.A. Shrigley reported "large areas of marrow are replaced by proliferating fibroblasts, reticulum cells, and intense eosinophilic leucodytic infiltration". The case was discussed with Dr. M.C.G. Israels who confirmed the leukaemia but could not explain the other curious marrow findings.

Case L 8.

Mr. H.B.S., aged 56, weight 71 kilos, gave a history of recurrent pyrexial attacks with pulmonary infections during ten years prior to his leukaemia diagnosis. In 1949 he became distinctly more weak than hitherto and was finally referred to a physician in November 1950, and thence to the Christie Hospital on 8.11.50 as chronic lymphatic leukaemia. The spleen was moderately enlarged, the liver was not palpable, nodes were slightly enlarged in all areas, there were no haemorrhagic signs, and the general health was only fair. The Hb was 84%, platelets were reduced, and the WBC was 165,000 per c.mm., 95.5% being lymphocytes, with many smear types and moderate numbers of lymphoblasts. On 17.11.50 a dose of 10.0 mcs. of P^{32} was given, followed by 5.0 mcs. on 24.11.50 and 1.12.50. The WBC fell exponentially, with a HVD of 2.3 mcs.-destroyed, to a minimum level of 4,500 per c.mm. on 13.12.50. The Hb on that date was 82% but it rose to a maximum of 102% by February 1951, by which time the WBC had also climbed to 21,000. The patient's general health improved during this remission, though he was troubled from time to time by a variety of vague symptoms - headaches, pains in the chest, diarrhoea, etc. - and was investigated extensively to exclude coronary thrombosis. He nevertheless maintained an active

business life until January 1953 by which time his Hb had fallen to 80% and the WBC was 132,000 per c.mm. A dose of 10.0 mcs. of P^{32} was given on 22.1.53 followed by 3.0 mcs. on 5.3.53. The WBC fell again exponentially, with a HVD of 2.5 mcs.-destroyed, reaching 6,100 per c.mm. on 18.2.53. The Hb on the latter date was only 72% but it rose to 90% by September 1953. The spleen became impalpable by 5.3.53, but the nodes behaved curiously in that where they were only just palpable before treatment they became distinctly larger in all areas about five days after the first injection of P^{32} and became almost impalpable again about six weeks after treatment. A single exposure of 600r x-rays to both sides of the neck on 24.9.53 (10 x 8 cm. fields, at 250 Kv.) produced no resolution whatever. By November 1953 the Hb had again fallen to 78%, the WBC was 72,000, platelets reduced, and the general condition of the patient was poor. On 13.11.53 a dose of 6.5 mcs. of P^{32} was given, but after an apparent response of the WBC and the Hb during December 1953, he deteriorated rapidly with marrow exhaustion and auto-antibodies. The patient died on 12.2.54, but autopsy was not permitted.

The HVDs for the two completed courses of P^{32} were 2.3 and 2.5 mcs.-destroyed.

Case L 9

Mr. J.W.D., aged 67, weight 49 kilos, had at least four attacks of bronchitis and pneumonia between 1946 and 1952. During an attack in February 1952 an enlarged spleen was found, and investigation at the Northern Hospital, Manchester, disclosed chronic lymphatic leukaemia. The spleen was grossly enlarged, the liver edge was four cms. below the right costal margin, lymph nodes were only slightly enlarged in the groins, and there were no haemorrhagic findings. The Hb was 60%, platelets moderately reduced, and the WBC was 100,000 per c.mm., with nearly 97% lymphocytes, many being smear types. On 1.4.52 a dose of 5.0 mcs. of P^{32} was given, followed by 2.5 mcs. each on 8.4.52, 16.4.52 and 22.4.52. The WBC fell exponentially, with a HVD of 2.3 mcs.-destroyed, to a lowest level of 5,200 by 1.5.52. The Hb at that date was 66% and it rose to a maximum level of 88% by 25.8.52, by which time the WBC was only 7,800 per c.mm. The liver became impalpable by 9.6.52 and the spleen was reduced to the umbilical level by the same date. The patient's general health improved considerably, but the whole picture began to deteriorate about November 1954, when the Hb had fallen to 66%, the WBC being up to 74,000 per c.mm. The patient, however, insisted that he felt fit in spite of the

haematological deterioration. He removed to the south of England during 1955 and Dr. Jan de Winter has since reported that the patient has shown worthwhile response to x-ray therapy until January 1957 when at last his health was showing signs of terminal deterioration.

Case L 10

Mr. V.D., aged 62, weight 68 kilos, complained of lassitude and loss of weight for two years. Backache in May 1953 led to a medical investigation at the North Lonsdale Hospital where chronic lymphatic leukaemia was found. On admission to the Christie Hospital on 22.5.53 the spleen was enlarged to the umbilicus, the liver edge was enlarged 3 cms. below the costal margin, but only two nodes were palpable in the left groin. There were no haemorrhagic signs, the Hb was 84% and platelets were moderately reduced. The WBC was 96,000 per c.mm., 99% being lymphocytes with many smear cells. 9.7 mcs. of P³² were given on 3.6.53, and the WBC fell exponentially, with a HVD of 2.5 mcs.-destroyed, to a minimum level of 12,400 on 23.6.53. The Hb on that date was 78% but it rose to a maximum of 106% by 8.1.54 when the WBC was up to 23,000 per c.mm. The spleen showed significant resolution within two months of treatment, but the nodes in the groin resolved more slowly. The general condition of the patient

also improved considerably within two months of treatment, and this remission lasted for two years. A second treatment of 5.0 mcs. of P^{32} was given on 16.8.55, the indications for this being clinical rather than haematological. The Hb was 82% and the WBC only 38,000. The spleen, however, was enlarging, the general health was poorer, and the patient had had several pyrexial attacks of pneumonitis. There was a rapid improvement in general well-being after this P^{32} , and although the WBC fell no lower than 18,500, the Hb rose to 93% by 23.11.55. The WBC on the latter date was 23,000 per c.mm. It should be noted that the WBC had again fallen exponentially with a HVD on this occasion of 4.0 mcs.-destroyed. This patient was last seen for review on 26.4.57 when his general health remained very good apart from old-standing arthritis. The spleen was still at the umbilicus but was not uncomfortable. The liver was not palpable and there were no substantial lymph nodes to be felt. The Hb was 80% and the WBC 8,800 per c.mm.

The HVDs for his two courses of P^{32} were 2.5 and 4.0 mcs.-destroyed.

Case L 11

Mr. J.S., aged 62, weight 57 kilos, complained of increasing lassitude and susceptibility to infections for 18 months before investigation at Barrow Hospital disclosed chronic

lymphatic leukaemia. On admission to the Christie Hospital on 23.3.53 the liver was just palpable, the spleen was moderately enlarged, and lymph nodes were also moderately enlarged in the left neck and both axillae. There were no haemorrhagic signs, the Hb was 58%, platelets were somewhat reduced, and the WBC was 266,000 per c.mm. with 97% lymphocytes and many smear cells. On 14.4.53 a dose of 8.1 mcs. of P^{32} was given, followed by 4.5 mcs., 1.5 mcs., and 3.0 mcs. respectively on 28.4.53, 5.5.53, and 6.5.53. The WBC fell exponentially, with a HVD of 2.7 mcs.-destroyed, but the Hb did not improve, and indeed in June the Hb fell to 46% and the WBC to 6,200 per c.mm. The patient felt weak and was re-admitted to hospital where he was given two pints of packed red cells. His improvement was immediate, and as so often happens, the Hb improvement was out of all proportion to the quantity of transfused blood. By September the Hb was 105% and by February 1954 was recorded at 128%, the WBC then being 23,000 per c.mm. The general condition had also improved enormously from the time of the small transfusion, the spleen was not palpable, and there were no nodes or haemorrhagic signs. In July, 1955, he deteriorated again, the Hb fell to 80% and the WBC rose to 41,000. A single dose of 6.0 mcs. was given on 4.8.55 and the WBC fell exponentially, with a HVD

of 2.0 mcs.-destroyed, to a lowest level of 7,000 per c.mm. by 28.10.55. The haemoglobin rose to 100% by December, 1955, and the patient felt "absolutely splendid". By December, 1956, he was again in need of treatment and had 5.3 mcs. of P^{32} on 28.12.56 followed by 2.0 mcs. on 11.1.57. The WBC fell from 66,000 to 11,000 on 8.2.57 and the Hb rose from 82% to 105% by the same date. The HVD on this occasion was 2.6 mcs.-destroyed. When last reviewed on 8.3.57 this remission was being well maintained.

The HVDs for these three courses of P^{32} were 2.7, 2.0 and 2.6 mcs.-destroyed.

Case L 12

Mr. W.F.H., aged 61, developed an acute respiratory infection in August, 1953. He had a further pneumonic episode in April, 1954, was referred to Oldham Royal Infirmary and thence to the Christie Hospital on 9.6.54. The general condition was good, the spleen just palpable, and lymph nodes in the neck, axillae and groins were florid. There was no pyrexia, no petechiae, ecchymoses or mucosal bleeding. The Hb was 66%, platelets were scarce, and the WBC was 934,000 per c.mm., with large lymphocytes and smear cells in small numbers. The first course of P^{32} consisted of 3 doses each of 6.0 mcs. on 17.6.54, 1.7.54 and 20.7.54. The WBC fell exponentially,

with a HVD of 2.7 mcs., the lowest level being 14,500 on 12.8.54. The Hb rose to a maximum of 94% on 14.4.54, the WBC at that date having climbed to 197,000 per c.mm. The spleen was not palpable by 28.10.54 and the large lymph nodes had become considerably smaller by September, 1954. The general condition also improved significantly, but began to deteriorate again by November, 1955. A second course of P^{32} began on 1.12.55 with 5.0 mcs. followed by 3.0 mcs. on 23.12.55. The WBC again fell exponentially but on this occasion more sensitively, the HVD being 0.9 mcs.-destroyed. The Hb at the start of this second course was only 60%, the WBC 500,000 and platelets 150,000 per c.mm. An Fe59 study indicated poor erythropoiesis and confirmed the sternal marrow findings of scanty nucleated red cells. The Hb did, however, appear to improve, as did the general condition, until 20.1.56 when purpura and mucosal bleeding heralded the fatal termination on 27.1.56. At autopsy the most striking feature was the generalised small haemorrhages in most organs, and a massive intracranial haemorrhage which had destroyed both internal capsules and most of the left posterior occipital lobe.

The two HVDs in this case were 2.7 and 0.9 mcs.-destroyed.

Case L 13

Mr. A.S.M., aged 46, weight 67 kilos, first complained of a lump in the left axilla about March, 1953. He felt well, but on examination at Park Hospital, Manchester, chronic lymphatic leukaemia was discovered and he was referred to the Christie Hospital on 29.6.53. At that time the spleen was enlarged to the umbilicus, the liver was not palpable, but he had large florid nodes in both axillae and neck as well as bilateral hilar nodes. There was a congenital absence of the right pectoralis major muscle. The initial Hb level was 90%, the WBC 196,000 with smear and blast cells in small numbers. An initial dose of 9.6 mcs. of P^{32} was given on 10.7.53 and the WBC fell exponentially with a HVD of 2.8 mcs.-destroyed. A second injection of 4.5 mcs. was given on 24.7.53 and the WBC fell to a lowest level of 12,000 on 10.8.53. The Hb rose to a maximum of 98% on 1.2.54. The WBC on the latter date was 53,000 per c.mm. It is interesting to note that after the first P^{32} injection the patient complained of transient discomfort in his enlarged lymph nodes and there was some discernible increase in their size. The nodes did, however, become significantly smaller after treatment and the spleen was not palpable by 7.12.53. By January, 1955, the Hb had fallen to 83%, the WBC had risen to 253,000, the spleen was just palpable, but the lymphadenopathy was again florid.

A second course of P^{32} therapy began with 5.0 mcs. on 13.1.55, repeated on 27.1.55, and with 3.0 mcs. on 10.2.55. Again the WBC fell exponentially with a HVD of 2.8 mcs.-destroyed. The WBC fell to a lowest level of 21,000 on 19.3.55, the highest recorded Hb being 94% on 23.5.55. The WBC on the latter date was 49,000 per c.mm. The spleen on this occasion never became quite impalpable and the liver was also palpable. Deterioration became obvious during January, 1956 - falling Hb, rising WBC, scarce platelets, increasing size of nodes and spleen. A further course of P^{32} began with 4.5 mcs. on 2.3.56, followed by 5.0 mcs. on 23.3.56. The WBC responded again exponentially, and again with a HVD of 2.8 mcs.-destroyed, falling to 18,000 per c.mm. by 11.4.56. The Hb rose from 74% to 86% on 16.4.56, the WBC then being 20,000. The spleen was not palpable on 9.7.56 but the nodes remained unresponsive.

This remission continues in June 1957.

The remarkably constant HVDs for three courses of P^{32} should be noted - 2.8, 2.8 and 2.8 mcs.-destroyed.

Case L 14

Mr. W.T.J., aged 27, weight 63 kilos, complained of pain in the left thigh for two years, but investigations were uninformative until November 1949, when he was found to have a

leukaemic blood picture. He was referred from Wrexham Hospital to the Christie Hospital on 30.11.49. The spleen then was just palpable, the liver was not palpable nor were there any enlarged lymph nodes. There were no haemorrhagic signs but platelets were scarce (90,000 per c.mm.), the Hb was 52% and the WBC only 17,000 with many smear cells, large lymphocytes, and lymphoblasts. A dose of 5.0 mcs. of P^{32} was given on 30.12.49 followed by a further 4.0 mcs. on 11.1.50. The WBC fell exponentially, with a HVD of 3.3 mcs.-destroyed, the lowest level being 5,000 per c.mm. on 19.1.50. The Hb on that date was 60% and it never increased above 62%. The spleen did not resolve and the general condition never really improved. Diarrhoea with blood in the stools, shortly after his treatment, raised the suspicion that the whole clinical picture might have been Brucellosis, but all serological tests were negative, as also was sigmoidoscopy. The patient became acutely ill in March 1950, with pyrexia, bleeding from the gums and rectum, with tenderness of the spleen, no lymphadenopathy but rapidly progressive anaemia. He died on 17.3.50. This was one of the first patients treated at this centre with P^{32} and in retrospect one cannot but think it was unwise to have treated such a dubious and probably acute leukaemia. Autopsy, unfortunately, was not permitted.

Case L 15

Miss S.S., aged 58, weight 59 kilos, complained of lack of energy for 2 years and lumps in both axillae for 15 months before being referred to the Manchester Jewish Hospital where chronic lymphatic leukaemia was diagnosed. On admission to the Christie Hospital on 25.12.52 the spleen was moderately enlarged, the liver was not palpable but lymph nodes were grossly enlarged in all areas. There were no haemorrhagic signs, platelets were moderately reduced, the Hb was 68% and the WBC was 167,000 per c.mm., 96% being lymphocytes with many smear cells. On 31.12.52 a dose of 8.46 mcs. of P^{32} was given, followed by 4.0 mcs. on 15.1.53 and 22.1.53. The WBC fell exponentially, with a HVD of 3.3 mcs.-destroyed, but it fell steadily to a minimum of 4,000 on 24.3.53 and the Hb also fell steadily to 24% on the same date. The peripheral blood and sternal marrow all suggested aplasia, though the complete failure of 4 pints of whole blood and 4 pints of packed red cells to prevent the progressive fall in the Hb level suggested a haemolytic factor. The patient died on 29.4.53 but autopsy was not permitted.

Case L 16

Miss D.R., aged 62, developed left-sided hemiplegia due to cerebral thrombosis in 1949. She was also troubled by rheumatoid arthritis, but in January 1954, she had acute broncho-pneumonia and was found in Oldham Royal Infirmary to have chronic lymphatic leukaemia. The Hb then was 86% and the WBC 267,000 per c.mm. She was kept under observation until December 1954, when she was referred to the Christie Hospital for treatment. On admission the general health was fairly good, the spleen was just palpable, the liver impalpable, but lymph nodes were generally enlarged. There were no haemorrhagic features, but the Hb was down to 60%, platelets were scarce and the WBC was 680,000, all but 0.5% being lymphocytes, including many smear cells and large lymphocytes. On 9.12.54 a dose of 5.0 mcs. of P^{32} was given and this produced a slow exponential response in the WBC with a HVD of 4.0 mcs.--destroyed. On 28.12.54 the predicted Minimum Effective Dose was in the region of 25 mcs. and in view of this slow response the treatment method was changed to splenic x-ray therapy. The WBC fell to a minimum of 9,900 on 3.2.55, the Hb then being 67%. The Hb continued to a maximum of 96% by May, 1955, the WBC by then being 45,000 per c.mm. The spleen became impalpable by March 1955, but the lymph nodes showed no significant resolution. The general health improved enormously, but in November 1955,

further splenic irradiation became necessary after a fall of Hb to 68% and a rise in WBC to 280,000 per c.mm. Again the general health improved, the WBC fell and the Hb rose to a maximum of 82% in March 1956. By July 1956 deterioration was rapidly increasing and another course of splenic x-ray therapy was begun on 19.7.56 and supplemented by a small blood transfusion. The platelets were now down to 50,000 and petechial haemorrhages appeared in showers. The patient removed to the Southport area in September 1956, and in January 1957 was reported to be just holding her own after blood transfusions and cortisone.

Case L 17

Mr. A.E.J., aged 52, weight 76 kilos, noticed swollen glands in his neck in July 1953, he was investigated at Wigan Infirmary, and referred to the Christie Hospital on 19.11.53. The general condition was good, the spleen just palpable, and he had florid enlargement of cervical, axillary, and mesenteric nodes. The liver was not enlarged, he was afebrile, with no petechiae, ecchymoses, or mucosal bleeding. The Hb was 98%, platelets slightly reduced, and the WBC was 178,000 with some smear cells. 5.7 mcs. of P³² were given on 1.12.53, 7.0 mcs. on 15.12.53 and 7.3 mcs. on 6.1.54. The WBC fell exponentially, with a HVD of 4.7 mcs.-destroyed, to a lowest level of 12,700

per c.mm. on 22.2.54. The Hb on the latter date was 104%, the highest level recorded during the first remission. The general condition improved considerably, the spleen was impalpable by 17.6.54, and the nodes had become significantly smaller. By May, 1955, the general condition had deteriorated, the Hb had fallen to 65%, the WBC was 300,000 and blast cells were making their appearance. A second course of P^{32} was given as follows:- 5.0 mcs. on 26.5.55, 6.4 mcs. on 9.6.55, 7.0 mcs. on 24.6.55 and 8.0 mcs. on 8.7.55. The WBC again fell exponentially, the HVD on this occasion being 5.2 mcs.-destroyed. The general condition undoubtedly improved, and the lymph nodes again became much smaller. The Hb however, did not significantly improve and by October 1955, he was again ill, with gross splenic enlargement, hepatomegaly, and florid lymph nodes. The rapid collapse of erythropoiesis was associated with a rapid Fe59 clearance rate which suggested haemolysis, though Coomb's test was negative. Deterioration continued in spite of supportive measures, (avoiding anti-mitotic agents) and the patient died on 3.3.56.

The two HVDs in this case were 4.7 and 5.2 mcs.-destroyed.

Case L 18

Mr. R.N., aged 55, weight 66 kilos, noted swelling of his neck glands in September 1952, saw his family doctor in May 1953, and was referred to Accrington Hospital in August 1953, when chronic lymphatic leukaemia was found. On admission to the Christie Hospital in September 1953, the spleen was just palpable, the liver impalpable, lymph nodes slightly enlarged in all areas but there were no haemorrhagic signs. The Hb was 72%, platelets moderate in number, and the WBC was 230,000 per c.mm., 98.5% being lymphocytes, with smear and blast cells. On 11.9.53 a dose of 9.4 mcs. of P³² was given, followed by 8.4 mcs. on 29.9.53. The WBC fell exponentially with a HVD of 6.4 mcs.-destroyed, but as the WBC fell so also did the haemoglobin and platelet levels and the general health deteriorated. The patient was troubled by septic lesions of the arms and face and he died with aplasia and pyrexia on 30.12.53. Unfortunately autopsy was not permitted.

Case L 19

Mr. A.E.L.F., aged 71, weight 68 kilos, developed herpes zoster in December 1952, and while in Crumpsall Hospital was found to have chronic lymphatic leukaemia. On admission to the Christie Hospital on 3.3.53, his spleen was moderately enlarged, the liver was impalpable, but lymph nodes were florid

in axillae and groins. There were no haemorrhagic features, the Hb level was 74%, platelets were plentiful, and the WBC was 260,000 per c.mm., 97% being lymphocytes, with many smear forms. On 13.3.53 a dose of 9.7 mcs. of P^{32} was given, followed by 4.85 mcs. on 31.3.53 and 5.5 mcs. on 10.4.53. Though the WBC fell exponentially with a HVD of 7.2 mcs.-destroyed, this was clearly a radio-resistant case and the WBC fell slowly to a minimum of 40,000 per c.mm. on 24.4.53. The spleen and lymph nodes showed significant resolution and the general health also improved greatly. The Hb however increased only by 10%, reaching 84% by January 1954, the WBC by that time being up to 182,000 per c.mm. The Hb level remained in the 70 - 80% range, however, for many months, and the patient remained active and free of symptoms until April 1955. The WBC was then 225,000 and the Hb 74%, but the spleen was uncomfortable and the patient felt generally unwell. On 16.5.55 a dose of 7.5 mcs. was given (approximately the HVD of the first course of P^{32}). By 2.6.55 it was obvious that the same slow exponential fall in the WBC was taking place. For this reason splenic x-ray therapy was instituted on that date, and the WBC was depressed down to a minimum level of 8,600 by 29.6.55 - a much more rapid effect than with P^{32} . The spleen became impalpable and the Hb rose to 90% by 27.9.55, but the

WBC was also already rising rapidly and this remission was short-lived. On 24.1.56 a course of C.B. 1348 was started and the Hb rose slowly from 63% to between 75 and 80%. When last reviewed on 16.4.57 the general health was good apart from dyspnoea (aged 75!). The lung fields were clear clinically and radiographically. Nodes were palpable only in the axillae, the spleen was enlarged to the umbilicus and the liver was just palpable. There were no haemorrhagic signs and the Hb was 76%, platelets were only 82,000 and the WBC 164,000 per c.mm. The low platelet count is the main deterrent to further treatment, but fortunately the patient is comfortable and happy.

Case L 20

Mr. G.R.A., aged 69, weight 63 kilos, noted lumps in the neck for 17 months and increasing fatigue for 9 months before admission to Withington Hospital in March 1950. Chronic lymphatic leukaemia was diagnosed and the patient admitted to the Christie Hospital on 26.4.50. On admission the spleen was grossly enlarged into the pelvis and across the mid-line, the liver was enlarged about 4.0 cms. below the costal margin, there were florid nodes in all areas, oedema of the ankles, but no haemorrhagic signs. The Hb was 52%, platelets were moderately reduced, and the WBC was 300,000 per c.mm. with 97.5%

lymphocytes including smear cells, large lymphocytes and lymphoblasts. On 3.5.50 a dose of 8.0 mcs. of P^{32} was given followed by 7.0 mcs. on 10.5.50, by 5.0 mcs. on 17.5.50, by 7.0 mcs. on 24.5.50, by 5.2 mcs. on 31.5.50, a further 7.0 mcs. on 7.6.50, and finally 1.4 mcs. on 17.6.50. This large dose of P^{32} reduced the WBC, Hb and platelet counts, though the WBC did fall quite exponentially with a HVD of 7.7 mcs.-destroyed. On 21.6.50 the Hb was down to 29%, the WBC was 50,000 and platelets were scarce. There were petechiae on the lower limbs. Four pints of packed cells were given and the improvement, though slow at first, continued until March 1952, when the Hb was 84%, the WBC was 6,500 and there was no palpable spleen, liver or lymph nodes. This astounding change from grave illness to near normality may have been assisted also by multi-vitamin therapy. In October 1952, he was described by me as "unrecognisable from his original state". He had continued to gain weight, was very fit, had no oedema, the Hb was still 84%, the WBC 6,900 with no palpable spleen, liver or nodes. In June 1953, he began to deteriorate and by September the Hb was 56%, the WBC 118,000, the spleen was again below the umbilicus, the liver 5.0 cms. enlarged, and lymph nodes were again palpable. A second course of P^{32} was begun on 16.10.53 with 9.6 mcs. repeating the same dose on 30.10.53.

Unfortunately there was no improvement on this occasion. The WBC and Hb fell progressively in spite of transfusions, vitamins, etc. There was evidence of auto-haemolysis terminally, and the patient died on 19.12.53.

Case L 21

Mr. I.S., aged 67, weight 70 kilos, developed a sore throat in October 1952, and was seen at Blackpool Victoria Hospital on account of enlarged tonsils. Examination disclosed chronic lymphatic leukaemia, but his Hb level was 98%, the total WBC only 49,000, and since his general health was good no active treatment was advised. He was referred to the Christie Hospital on 8.1.54 by which time he had many slightly enlarged lymph nodes in all areas, the spleen was just palpable but the liver was not enlarged and there were no haemorrhagic signs. The Hb was 96%, platelets moderately reduced, and the WBC was 127,000 per c.mm., 96.5% being lymphocytes, including smear cells and immature lymphocytes. The patient felt rather unwell and it was decided to treat with P^{32} - perhaps a little unwisely, in retrospect. On 19.1.54 a dose of 6.0 mcs. of P^{32} was given followed by another 6.0 mcs. on 9.2.54 and again on 23.2.54. The WBC fell very slowly but exponentially with a HVD of 15.0 mcs.-destroyed (the most resistant case I have seen). So slow

was this response that splenic x-ray therapy was instituted on 12.3.54. However, after only 2 small exposures it was decided not to pursue radiation therapy any further. In April 1954, the patient was feeling well and the Hb was up again to 95% while the WBC was 62,000 per c.mm. On 21.5.54 he was reviewed and found to be unchanged, but he died suddenly at his home on 25.5.54 and autopsy was not carried out. The presumptive cause of death was coronary thrombosis.

Case E 1

Mr. G.L., aged 49, weight 56 kilos, complained of increasing swelling of the abdomen for nine months before consulting his doctor in September 1949. He had no other symptoms, and was referred to the Christie Hospital on 3.10.49. The spleen was grossly enlarged into the left iliac fossa and across the midline. There were no enlarged lymph nodes, the liver was impalpable, there were no petechiae or other haemorrhagic features, and no pyrexia. The general health was poor, however, the Hb was 85%, platelets were plentiful, the WBC was 70,000 per c.mm., 10% being primitive cells of the myeloid series, and 1.0% myeloblasts. He was regarded as a case of chronic myeloid leukaemia, and on 13.10.49 a dose of 6.0 mcs. of P³² was given, followed by 4.0 mcs. on 21.10.49. The WBC had only just begun to show a significant depression (60,000) when the patient developed considerable splenic pain, collapsed and died on 5.11.49. Autopsy by Dr. R.M. Taylor confirmed the myeloid hyperplasia in the femoral marrow, with active erythropoiesis and normal megakaryocyte production. The marrow was described, however, as "almost plum-coloured". The spleen showed considerable congestion, and areas of old and one large recent infarction. The lungs were also congested and there was an area of haemorrhage in the left lower lobe.

The brain too was extremely congested. The adrenals were small and flat, and there was considerable haemorrhagic exudate in the peritoneal cavity. There was gross congestion of the entire intestinal tract, with small sub-mucosal haemorrhages, but no sub-serosal haemorrhages were found. Both kidneys were extremely congested. The significant histological features, apart from leukaemic infiltration of various organs, was the extensive interstitial oedema in the lungs, heart, lymph nodes, spleen, and kidneys. There was also portal cirrhosis of the liver, and signs of tubular damage in the kidneys. The post-mortem blood urea level was 490 mgms. per 100 mils.

Case E 2

Mr. E.H., aged 71, weight 66 kilos, complained of abdominal discomfort, headaches and lassitude, from January 1952, but consulted his doctor only in July 1952. Investigation at Wrexham Hospital disclosed chronic myeloid leukaemia, and he was admitted to the Christie Hospital on 5.8.52. The general condition of the patient was quite good, the spleen was enlarged to the umbilicus, the liver was impalpable, there was no lymphadenopathy, and no haemorrhagic signs or pyrexia. The Hb was 56%, platelets were plentiful, and the WBC was 300,000

per c.mm., 3.0% being myeloblasts, and 44% immature myeloid cells of all types. On 6.8.52 an initial dose of 10.0 mc. of P^{32} was given, followed by 3.0 mcs. on 26.8.52 and 5.75 mcs. on 10.9.52. The WBC fell erratically, with no regular exponential relationship to P^{32} dosage, reaching its lowest level of 7,800 per c.mm. by 17.9.52. The spleen was impalpable by 6.10.52 and the Hb rose to a maximum of 105% by 14.1.53. The general condition improved remarkably and he gained 14 kilos in weight. By April 1953, however, rapid deterioration had occurred. The spleen was again down to the umbilicus, and was tender and painful. The Hb fell to 56% and the WBC rose to 348,000 per c.mm. On 12.5.53 a dose of 10.0 mcs. of P^{32} was given, and 3.0 mcs. on 26.5.53. Again there was an irregular and fluctuating fall in the WBC when plotted against integral body dosage from the P^{32} . Nevertheless the WBC fell to 11,000 by 5.6.53, and the Hb rose to 88% by 30.9.53. Though the spleen had resolved behind the costal margin, the WBC by the latter date had risen rapidly to 270,000 per c.mm. On 16.10.53 a single dose of 10.0 mcs. of P^{32} was given and yet a third time there was no exponential fall in the WBC, though it did fall to 8,800 by 2.11.53 and the Hb rose to from 68% on 12.10.53 to a maximum of 94% on 29.1.54. The WBC on the latter date was already up to 112,000 and although the general

health had improved during this fourth remission further treatment was called for in March 1954. Splenic x-ray therapy began on 3.3.54 and continued for four weeks. The WBC fell to a minimum of 6,000 by 6.4.54, the spleen again became impalpable, the general condition improved remarkably, and the Hb rose from 58% to 84%. A sixth course of treatment, again by splenic irradiation began on 18.11.54, a seventh course a year later on 22.11.55, and his most recent treatment on 26.2.57. During 1955 the patient was found to have diabetes mellitus, easily controlled by diet.

This case clearly indicates that worthwhile, if short-lived remissions can be produced by P^{32} even when the relationship between the falling WBC and integral body dosage is not an exponential one. The reason for this is not apparent.

Case E 3

Mrs. M.E.T., aged 57, weight 45 kilos, felt off colour for many months, then developed persistent diarrhoea, and consulted her doctor in September 1952. Investigation at Wigan Infirmary disclosed chronic myeloid leukaemia, and after transfusion with packed cells she was transferred to the Christie Hospital on 7.10.52. The patient was then pale and ill-looking, with considerable enlargement of both the spleen and the liver, lymph nodes were not palpable and there were no haemorrhagic

signs or pyrexia. The Hb was 32%, platelets were plentiful, and the WBC was 146,000 per c.mm., 15% being blasts and 30% total primitive white cells. This patient was considered a rather sub-acute case of myeloid leukaemia, having regard to her relatively short illness, low haemoglobin level and significant number of myeloblasts. However, a dose of 7.95 mcs. of P^{32} was given on 14.10.52, followed by 3.0 mcs. on 30.10.52. The WBC did not fall exponentially, though it did fall to a minimum of 7,100 by 25.11.52. During the first week of November 1952 the patient complained of pain in the chest and dyspnoea, and had pneumonic signs which cleared up on antibiotics. This pneumonic episode may have influenced the relationship of the WBC to integral dosage, possibly by producing a mixed population of white cells - those of "leukaemic origin" and those of "inflammatory origin" - with perhaps different life spans. The spleen showed significant but incomplete resolution and the Hb rose from 32 to 50% before transfusion on 11.12.52. The patient's general health did not improve, however, and she died in another hospital on 2.1.53. Autopsy was not carried out.

Case E 4

Mr. R.E.D., aged 28, weight 68 kilos, developed epigastric pain, headaches and giddiness during August 1952. Investigation in Wrexham Infirmary revealed myeloid leukaemia and he was referred to the Christie Hospital on 8.10.52. He was pale and ill, had generalised small lymph nodes, the spleen was enlarged nearly to the umbilicus, the liver was not palpable, and there were no haemorrhagic features or pyrexia. The Hb was 46%, platelets were reduced, and the WBC was 74,000 per c.mm., 1.4% being myeloblasts, and 30% total primitive white cells. The rapid onset of the illness and the gross anaemia suggested a somewhat subacute rather than a truly chronic myeloid leukaemia, but P³² therapy was instituted on 24.10.52 with a dose of 10.0 mcs. This was followed by 5.0 mcs. on 18.11.52, but the WBC fell in an irregular non-exponential manner, and the Hb showed no response. A small transfusion of 2 pints of whole blood was given on 28.11.52 with significant improvement in the general condition. The spleen became impalpable on 9.12.52, there were no haemorrhagic signs or pyrexia, and on 10.12.52 the Hb was 68%. By February, 1953, the Hb had collapsed to 34%, the WBC was 10,800 and the general condition poor. In spite of transfusions, cytamene, and other supportive measures in another hospital, the patient developed

cerebral symptoms and died on 5.3.53. Autopsy was not permitted.

Case E 5

Miss M.J., aged 62, weight 42 kilos, found lumps in her neck about 1950. In 1952 she stopped working because of anginal pain and in January 1954, had an attack of coronary thrombosis. Investigation at the Manchester Jewish Hospital disclosed chronic lymphatic leukaemia. On admission to the Christie Hospital on 24.5.54 the patient's general condition was fair, there was generalised small lymphadenopathy, the spleen was just palpable, the liver impalpable, there were no haemorrhagic signs, but the patient looked dehydrated. The latter improved rapidly in hospital and on 1.6.54 a dose of 6.0 mcs. of P^{32} was given. The WBC showed no response whatever and remained between 320,000 and 370,000 per c.mm. There was some basal congestion at this time and the patient had coryza and some cough. This may have influenced her WBC, though I doubt this. The Hb had also remained stationary at 60%. On 29.6.54 splenic x-ray therapy was started and the WBC fell, but very slowly, to 20,000 on 5.8.54, and then rapidly to 3,200 by 13.9.54. At this latter date the platelets had also dropped to 70,000 per c.mm. and there were several large ecchymoses.

These disappeared, the general condition improved remarkably, the spleen became impalpable in September 1954, the Hb was 86% by November 1954, and apart from recurrent cardiac difficulties this remission lasted until August 1955. The leukaemic infiltration of the lungs raised the question of tuberculosis during 1955. This was excluded, however, by several negative cultures and guinea pig inoculation. The WBC rose to 84,000 and the Hb fell to 63% with general malaise. Splenic irradiation began again on 18.8.55, ending on 20.9.55. There was no real improvement, however, and the patient died with terminal haemorrhages into the skin, on 3.10.55.

Case E 6

Mr. H.B., aged 53, developed a submandibular swelling in 1947 but was reassured by his family doctor and the lump disappeared during an attack of pneumonia. In 1948 more glands appeared in the neck and he was investigated at Manchester Royal Infirmary early in 1949. On admission to the Christie Hospital on 23.9.49 the general condition was fair, there was florid enlargement of lymph nodes in all areas, including the hila and mediastinum. The spleen was enlarged 5.0 cms. below the costal margin, the liver was not palpable, but there were palpable mesenteric nodes in the abdomen.

There were no haemorrhagic signs or pyrexia. The Hb was 76%, platelets were reduced, and the WBC was 149,000 with many smear cells. 8.0 mcs. of P^{32} were given on 27.9.49, followed by 3.0 mcs. on 2.11.49. The WBC by the latter date had already fallen to 11,000 per c.mm., but not in an exponential fashion. The Hb had not improved, and though the spleen was a little smaller, the large nodes were still troublesome. Accordingly, single exposures of 500r were given to both sides of the neck and to both groins and axillae between 2.11.49 and 7.11.49. By January 1950, the spleen was no longer palpable, the nodes were somewhat smaller but still enlarged, the Hb was 78% and the WBC 7,900 per c.mm. By September 1950, further treatment was necessary because of clinical deterioration and a WBC up to 210,000 and Hb down to 68%. On 12.9.50 a dose of 5.0 mcs. of P^{32} was given but the whole blood picture collapsed and sternal marrow on 3.10.50 showed little sign of any haemopoietic activity. The patient died on 18.10.50.

Case E 7

Mr. W.R., aged 54, complained of lassitude, occasional vomiting, anorexia and loss of weight for 12 months. He had lumps on both sides of the neck for 4 weeks before he finally consulted his doctor, was referred to the Manchester

Royal Infirmary, and chronic lymphatic leukaemia was diagnosed in April 1952. He was admitted to the Christie Hospital on 1.5.52 when his general health was only fair, he had large florid nodes in all areas, the spleen and liver were just palpable, there were no petechiae or other haemorrhagic signs, and no pyrexia. The Hb was 56%, platelets were plentiful, and the WBC was 265,000 per c.mm. with a substantial number of smear cells. On 13.5.52 a dose of 9.5 mcs. of P³² was given, and the WBC fell rapidly, but not exponentially, to a low level of 5,000 per c.mm. by 9.6.52. Though the lymph nodes also regressed significantly the Hb showed no improvement and remained at the 50 - 55% level during June and July, 1952. The patient was re-admitted to hospital on 11.8.52 with a Hb of only 20% and in spite of blood transfusion she died on 4.11.52. Autopsy was not permitted.

Case E 8

Mr. J.T.M., aged 64, (a French polisher - of aetiological significance?) 'collapsed' in June, 1952, and was admitted to Blackburn Infirmary where lymphatic leukaemia was diagnosed. On admission to the Christie Hospital on 30.7.52 the Hb was only 34%, the WBC 155,000 with lymphoblasts and smear cells, the spleen just palpable, enlarged nodes in all areas, but no haemorrhagic signs. He was regarded as a

sub-acute case of leukaemia and before P^{32} was given he was transfused, with difficulty. On 5.8.52 a dose of 9.2 mcs. of P^{32} was given and the WBC fell irregularly and rapidly to 3,500 per c.mm. on 28.8.52. The Hb also fell rapidly to 18% and did not respond to transfusion. The patient died on 14.9.52. In retrospect, this case should not, of course, have been treated by a radiation method.

Autopsy by Dr. J.A. Shrigley showed considerable lymphocytic infiltration of the bone marrow as well as the kidneys, lungs and lymph nodes. Otherwise no special features were noted.

Case E 9

Mr. F.B., aged 37, felt unusually tired in October, 1951, and during the autumn of 1952 developed dyspnoea on effort. He was treated by his doctor, unsuccessfully, as pernicious anaemia, but was finally investigated in Blackpool Infirmary in November, 1952, when lymphatic leukaemia was discovered. On admission to the Christie Hospital on 9.12.52 his Hb was 82% but he had had 10 pints of blood transfused during the previous few weeks. The WBC was only 35,500 per c.mm. with many primitive white cells. The spleen and liver were just palpable and there was a generalised small

lymphadenopathy. Because of the satisfactory clinical and haematological condition active treatment was withheld, but the whole picture deteriorated rapidly early in January, 1953. The patient had epistaxis, the WBC rose to 60,000 and the Hb fell to 40% - all suggesting a subacute leukaemia. The patient was transfused again and on 15.1.53 a dose of 11.5 mcs. of P^{32} was given. The blood picture became aplastic, with the haemoglobin at about 20%, the WBC reaching 750 per c.mm. on 11.2.53. Packed-cell transfusions improved the patient enormously, but though he was kept going with repeated transfusions, he died with marrow failure on 23.4.53. This again was a patient for whom it would have been better to avoid radiation therapy, though probably any anti-mitotic agent would have been equally ineffective.

Case E 10

Mr. C.W.F., aged 65, developed sudden dyspnoea in August, 1953, after a short period of lassitude. He was admitted urgently to Burnley Hospital and acute lymphatic leukaemia was diagnosed. On admission to the Christie Hospital on 20.8.53 his general health was not good, there were generalised small lymph nodes, the spleen was just palpable but the liver was not so, the Hb was only 34%, and the WBC 130,000 with many lymphoblasts. 9.3 mcs. of P^{32} were given on 3.9.53,

followed by 3.0 mcs. on 18.9.53 and 4.0 mcs. on 25.9.53. The WBC fell irregularly to a low level of 8,300 by 2.10.53, but the Hb also fell in spite of transfusions. The patient became pyrexial, developed purpura, gross anaemia, thrombocytopenia, and died on 5.10.53.

Autopsy, by Dr. Helen Russell, confirmed lymphatic leukaemia, with much haemorrhage into many of the organs, including the brain. The marrow of the sternum and lumbar vertebrae was again a curious, purple-pink colour. Microscopy showed typical lymphatic leukaemic marrow with suppression of the red and granular series. There was also, throughout many of the organs examined, a notable capillary dilatation which Dr. Russell believes to be an effect of P^{32} . Incidentally, the patient had a congenital horse-shoe kidney.

Case E 11

Mr. R.M.P., aged 67, noted increasing lethargy for three years but did not respond to symptomatic treatment by his doctor. Investigation in Bury Hospital finally disclosed lymphatic leukaemia in October 1954, and on admission to the Christie Hospital on 19.11.54 the general condition was quite good. There was generalised lymphadenopathy, the spleen was moderately enlarged, the liver was impalpable, there were no haemorrhagic signs, and no pyrexia. The Hb was 69%, platelets

were scarce, and the WBC was 263,000 per c.mm. On 23.11.54 a single dose of 6.0 mcs. of P^{32} was given. The WBC fell, not exponentially, and never below 70,000 because the Hb, having remained static, suddenly collapsed to 30% on 13.12.54 and the patient died on 16.12.54.

Autopsy, by Dr. Helen Russell, disclosed an unusually extensive lymphocytic infiltration of all the organs examined, including even the tongue. Dr. Russell again commented on the unusual red colour of the bone marrow to the naked eye, and this was associated microscopically with capillary congestion. Groups of nucleated red cells were also seen in many areas. Again comment was made of the oedematous capillary congestion of the lower lobes of the lung, and the interstitial oedema of the liver.

Case E 12

Mrs. L.C.A., aged 50, weight 63 kilos, developed tonsillitis in April 1948, and noted swollen lymph nodes in the neck. The nodes persisted and biopsy in Ancoats Hospital, Manchester, on 19.1.49 was reported as lymphosarcoma. However, on admission to the Christie Hospital on 2.2.49 it was found that, though the total WBC was only 11,400 per c.mm., 9,500 of these were lymphocytes. The sternal and iliac marrow also showed a considerable preponderance of lymphocytes. The

spleen and liver were not palpable. Lymph nodes were enlarged in all areas, but there were no haemorrhagic features, the Hb was 86% and platelets were plentiful. Single x-ray exposures of 400r each were given to the nodes in the neck, axillae and groins, but the nodes showed little resolution. The patient remained well until February 1951, when the liver was enlarged 4 cms. and the spleen 6 cms. below the costal margin. The WBC on 19.2.51 was 46,000 and 42,000 of these were lymphocytes. The Hb was still 84% and no anti-leukaemic treatment was given. In May, 1951, the patient developed some proptosis and diplopia on lateral deviation of the eyes. I 131 tracer studies excluded thyrotoxicosis and a small dose of 400r to the right orbit on 31.5.51 was followed by a ten days' course of x-ray therapy to substantial lymph node masses in the upper abdomen during September, 1951. The WBC at that time was 102,000, with a Hb level of 80%. This settled to a WBC of 4,800 by 29.10.51, the Hb remaining static. The patient remained well but, by September 1953, the WBC had risen to 340,000 per c.mm. and the Hb had fallen to 40%. The spleen was not palpable. On 9.9.53 a dose of 8.0 mcs. of P^{32} was given followed by 5.0 mcs. on 24.9.53. The WBC fell, but not exponentially, to a

low level of 6,000 per c.mm. by 5.10.53, but the Hb had also fallen rapidly to 26%. In spite of repeated transfusions the general condition deteriorated and the Hb did not rise above 45%. By April, 1954, the patient was intolerant to closely cross-matched blood. She left hospital on 29.4.54 with a Hb of 14% and was considered beyond further help. However, when seen again on 13.7.54 the Hb was 80% - a remarkable improvement, clinically and haematologically, which seemed to be attributable to raw liver which the patient had been eating in large quantities. A spontaneous cessation of auto-haemolysis is another possible explanation. Unfortunately this improvement did not last, in spite of continued liver therapy, massive doses of Vitamin B 12 and cortisone. She died on 12.12.54 but autopsy was not permitted.

GENERAL CONCLUSIONS

1. In spite of more than a century of continuous study, the initiating, the sustaining, and the compensatory mechanisms at work in leukaemia are still not understood. A vast literature daily becomes more vast, and increasingly complex and subtle methodologies are being brought to bear on this many-faceted problem. A glance at one of the most recent publications on leukaemia (Rebuck, Bethell and Monto, 1957) underlines this point by describing, e.g. new approaches to the study of cell-structure by electron and phase-contrast microscopy; antigenic, environmental, and genetic studies; new leukopheretic techniques in the study of leukopoiesis; and ever more detailed biochemical probings into the intra-cellular metabolism of leukaemic and normal cells. All of this scientific subtlety, however, does not diminish the need for more bed-side observation and thought by the clinician.

2. With prevention of leukaemia in mind, the author is of the opinion that further aetiological studies are of urgent importance. As with other forms of malignant disease, new carcinogenic agents are constantly being discovered, and one of the great challenges of our time lies in the knowledge that many causative agents remain only to be unmasked.

3. So far as the management of the leukaemias is concerned, therapeutic eclecticism would seem to be the ideal. There is an obvious advantage for the patient to be managed in a hospital or institute where the entire armamentarium is available, the appropriate weapon being chosen according to individual requirements. An unforeseen but natural result of the introduction of chemotherapy has been that physicians throughout the country are now eager to treat their leukaemic patients by themselves. With a relatively rare disease, this means that no one worker or group of workers is now able to observe these patients in large numbers, and the opportunity to study and assess newer drugs is becoming increasingly limited. This is unfortunate, but perhaps organized therapeutic trials will overcome this difficulty.

4. The author's experience with P^{32} therapy for chronic leukaemia has demonstrated that remissions can be induced which are in every way comparable with those achieved with x-ray or chemo-therapy. The concept of the minimum effective dose for each individual patient is a new and practical approach to leukaemia therapy, and its theoretical advantages are also significant. This is now the routine treatment for suitable cases at the Christie Hospital in Manchester.

5. The reason for individual differences in the radio-sensitivity of leukaemic white cells is as elusive as the rest of the basic problems of leukaemia. Experiments with tissue cultures in vitro can demonstrate changes in radio-sensitivity dependent e.g. on the oxygen saturation of the culture medium, and many other sensitising and protective chemical agents are known. But this knowledge does not appear to explain the in vivo differences in sensitivity in humans.

6. What of the future? Bierman (1957) has rightly re-emphasised the error of focussing too much attention on the leukocytes in leukaemia, and he has called for a broader outlook on the disease than heretofore. Nevertheless, the exponential relationship between the falling white cell count and the integral dosage from P^{32} provides a unique opportunity, without detriment to the patient, to study and possibly to measure the effects of sensitising, protective, and adjuvant drugs. The author is particularly interested in the possibility also of measuring the life-spans of leukaemic white cells, and relating them, if possible, to the Half Value Dose of P^{32} . Unfortunately, as remarked above, untreated leukaemia is being seen less frequently at this centre.

It seems to be an innate human urge "to reduce the diverse to the identical", to seek a unifying comprehensive hypothesis, but the known facts about leukaemia still defy such a manipulation. At the moment we are like Plato's philosophers in their subterranean cave, aware only of the shadows, unable to explain or even to relate them, but conscious that by a "toilsome ascent up the steep slope" we shall ultimately see the reality.

SUMMARY

This thesis is concerned with the response to P^{32} of chronic leukaemia in humans.

Section I outlines the historical basis of classification of the leukaemias, preference being given for a simple working system. The common clinical syndromes are described, followed by a brief account of the main clinical pathological features. Aetiology is also considered here, including incidence, the relationship of leukaemia to other diseases, and the aetiological importance of various external factors, chemical and physical.

Section II is concerned with the principles of management of leukaemic patients, and outlines the evolution of modern therapeutic practice.

Section III discusses the pharmacology of radioactive phosphorus, the anti-leukaemic agent with which this thesis is primarily concerned. The biochemical and the physical features are described, its absorption, distribution, and excretion, and finally the biological effects which follow its administration.

Section IV describes the author's experience in treating 60

patients with P^{32} at the Christie Hospital and Holt Radium Institute in Manchester, England. The evolution of a dosage system is discussed, and it is shown that in more than 90% of selected cases of chronic leukaemia an exponential relationship exists between the falling white cell count and the Integral Body Dosage from P^{32} . The logarithms of the WBC plotted against the cumulative IBD (most conveniently expressed in millicuries-destroyed) gives a straight line graph. Such a straight line can be extrapolated at an early stage in treatment and permits a prediction to be made of the Minimum Effective Dose for each patient. This method of treatment has provided satisfactory remissions both clinically and haematologically.

This exponential relationship has held in all but 12 of the 60 treated patients, but in 7 of these there were obvious reasons for this non-exponential behaviour.

Following recurrence of symptoms, 15 patients have received a second course of P^{32} , seven of these have had a third, and 1 a fourth course. The pattern of response has been remarkably similar to the first, but with a curious tendency to increasing sensitivity.

Section V describes one of several possible applications of

the exponential fall in the WBC - a quantitative study of white cell sensitivity. The HVD is a quantitative expression of leukopoietic sensitivity for each individual. Twenty seven cases of chronic myeloid and twenty one of chronic lymphatic leukaemia were tabulated in order of their white cell sensitivity, and various haematological and clinical data were similarly tabulated, but with none of these has any clear correlation been demonstrated.

Section VI provides summaries of the case histories of the sixty patients treated by P^{32} .

It is concluded that in addition to and in spite of much detailed and complex research, there is need for more clinical study of leukaemia, and especially for aetiological investigation. Management of patients is advocated in centres possessing all modern therapeutic techniques, and regret is expressed at the dilution of experience that has followed the introduction of chemotherapy. Therapeutic trials might be organised on a national scale to offset this loss of clinical material. The prediction method of P^{32} dosimetry is advocated when this isotopic treatment is appropriate. Much more work is seen to be necessary if even small questions are to be answered in this vast problem.

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