# LEUKAEMIA IN KENYA

DR. EDWARD GEORGE KASILI,

M.B., Ch.B. (E.A.) M.R.C.Path.

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## D E C L A R A T I O N

This is a thesis of original research work carried out by me in the department of pathology, Faculty of Medicine, University of Nairobi and the Kenyatta National Hospital from 1975 to 1979. This work has not been presented to any other institution for purposes of obtaining a degree.

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EDWARD GEORGE KASILI.

## A C K N O W L E D G E M E N T S.

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## A B S T R A C T.

The main objective of the study was to show that leukaemia was more common in Kenyan Africans than has been the belief from impressions. Literature review revealed that there have been sporadic case reports of leukaemia in Kenyan Africans since 1924. However, increasing leukaemia documentation has only featured in the seventies because of the progressively developing awareness and interest in the disease (Table 3, page 20).

This retrospective and prospective study covered 456 cases of all types of leukaemia diagnosed at the Kenyatta National Hospital between 1971 and 1977. Those cases admitted to this hospital were further fully investigated and treated if they did not die immediately. Then several clinicopathological variables and biodata were analysed in all the cases.

The overall national crude incidence is 0.5 cases per 100,000, with a maximum tribe-specific incidence being 1.2 cases per 100,000. Childhood (below 15 age group) leukaemia accounted for 28% of all types of leukaemia, giving an incidence of 0.3 cases per 100,000, in contrast to the adult incidence of 0.7 cases per 100,000. However, 48% of all acute leukaemias occurred in childhood as compared with only 4.7% of the chronic types. There is a peak occurrence of all types of leukaemia in the first decade of life, with a minor secondary peak in the sixth decade. The nadir appears in the 4th and 5th decades. There is an apparent deficit of acute lymphocytic leukaemia in the 0-4 year age-group but acute myelogenous presents with a peak in the second decade of life. Chronic granulocytic has the highest prevalence in the 20-40 year age-group and chronic lymphocytic in the 40-70 year period. There is an overall male to female ratio of 1.47:1, but the childhood ratio is 1.7:1. Tribal distribution correlates with proximity of various tribes to medical services and there is no obvious geographical pattern.

Leukaemia typing shows that the myeloid leukaemias are twice as frequent as the lymphocytic types, with the following distribution: AML (including myelomonocytic) - 31.6%; ALL (including acute prolymphocytic) -14.9%; ALSCL - 5.5%; AMoL - 3.3%; AUL - 0.9%; CGL - 28.5%; CLL - 15.3%; ALSCL emerges as an important entity, which occurs maximally in the 5-9 year age-group.

The general behaviour of leukaemia shows no gross difference from what is known about leukaemia from elsewhere. However, subtle but important features stand out. The majority of patients present with advanced disease, most often in terminal stages, as is evidenced by the high mortality rate within the first month after diagnosis, frequent gross organomegaly, severe anaemia and thrombocytopenia, hyperleucocytosis (37% over $200 \times 10^9/l$; 42% over $30 \times 10^9/l$,) or marked blastaemia with the generally poor clinical performance. There is a high frequency (23%) of facial chloromatous presentation in childhood AML and AM-ML, which often simulates Burkitt's lymphoma. Cases of acute leukaemia masquerading as rheumatoid arthritis or aplastic anaemia are not uncommon.

There were remission induction rates of 69% for all the acute leukaemias, in which ALL had 85% and AML - 54%. None of the patients with AMoL or AUL attained remission. Sixty three percent of AML, patients died within one month and almost all were dead within 12 months after diagnosis. Only 32% of ALL patients died within one month, and 37% survived for more than 12 months (Fig. 20). In childhood acute leukaemia, about 90% of ALL attained remission status, only 10% died within one month and all had a median survival of 15 months. Similarly, 60% of children with AML went in to remission and all had a median survival of only 8 months. The chronic leukaemias showed orthodox features although CLL appeared to have a poorer outlook than CGL (Fig. 20).

The quality of survival, even if reasonable, was interrupted by a diversity of infections which often caused death. Autopsy in 76 cases confirmed that death was due to haemorrhage in 24%; infection - 20%; multiple causes - 16%; other causes, including organ failure - 30%. No disseminated fungal infection was encountered.

The problems of diagnosis with consequent underdiagnosis of leukaemia in Kenya are highlighted. Effective management of this disease, in Kenya, is beset with problems of ignorance by the public, patients, as well as the lack of medical team work and the prohibitive socio-economic factors.

Thus, leukaemia is a common disease in Kenya, as it also accounts for 4% of medical and paediatric admissions. Its behaviour is, in general, the same as is known about it elsewhere, although it appears to be more aggressive, probably due to the late presentation of patients. There is urgent need for establishing its precise incidence by community surveys and also for a thorough study of associated aetiological factors. For the present, acute awareness of its existence is mandatory if early diagnosis, which is a prerequisite to successful management, has to be made.

# CHAPTER ONE

## INTRODUCTION

Preamble.

One to two decades ago, leukaemia, and in particular acute leukaemia, was considered uncommon in Africans (1-5) and consequently featured very little in the health statistics as a cause of morbidity and mortality. However, with the changing pattern in disease structure, due to improving health care and successful control of communicable diseases, the importance of chronic degenerative problems and cancer, leukaemia included (6) has emerged. With the ubiquitous application of agricultural chemicals for weed and insect killing, widespread use of x-rays for radiodiagnosis, the stupendous proliferation of drugs whose leukaemogenic potential is unknown and improved diagnostic facilities, leukaemia is on the undoubted increase in developing countries, Kenya being no exception. Since leukaemia is therefore going to increasingly feature as a great cause of morbidity and mortality among other cancers, studies of its incidence, epidemiology and biological behaviour are essential for health care planning and delivery.

The main objective of this study is to attempt to show that leukaemia is more common in Kenya than has been previously believed, by delineating its incidence and epidemiology. An appraisal of its biological behaviour, aetiological factors and response to treatment is included. The study therefore covers a historical review of the concepts in the evolution and definition of leukaemia as a disease; its pattern in tropical Africa as can be ascertained from the

literature review of the last two decades; the problem as it was seen in Kenya from 1920-1977 from documentary evidence, and leukaemia as seen from my personal retrospective and prospective work covering seven years, 1971-1977 inclusive.

## Historical note.

Although leukaemia could have existed as a disease during the era people like Hippocrates practised medicine, it was not until Velpeau (7), gave the first accurate account of it in 1827. His patient, a 63-year-old-male, presented with prominent abdominal swelling, fever, weakness and urinary stones. He died soon after admission and at autopsy, the liver and spleen were enormously enlarged. The blood in the vessels was described as "looking like gruel, resembling, in colour and consistency, the yeast of red wine; -- more like laudable pus mixed with blackish colouring matter". It was also during the period 1836 to 1845, with use of clinical information and microscopic technique, that workers in several countries attempted to delineate the picture of leukaemia (8-11).

Virchow, in 1845, published a description of a 50-year-old-female who had died after a year's illness that was characterized by wasting, abdominal swelling and diarrhoea. At autopsy, she had gross enlargement of the liver and spleen. The blood vessels are described as having contained "yellowish-white, almost greenish mass" in which there were very few red blood corpuscles. The white blood cells were greatly increased in number. He, however, found no evidence of suppurative infection. Unlike Craigie and Bennett (10,11), he did not think that his patient suffered from pyaemia (12).

He therefore introduced the term "leukaemia (13) two years later. This term literally means "white blood", a phrase "Weiss Blut" which he had used to describe the blood of his patient in the German language.

All along, the patients described had been diagnosed at autopsy, until Fuller in 1846 (14), reported the first case of leukaemia diagnosed during life and confirmed at post-mortem. In subsequent years, increasing numbers of patients diagnosed during life were reported. Bennett (15) described 37 patients with the disease, and seventeen of them had been diagnosed during life. The characteristic features described in all patients up-to-date had consisted of chronic ill-health with loss of weight, abdominal swelling, fever and weakness; post-mortem findings were those of enormously enlarged spleen and liver, and lymph node enlargement. The blood vessels contained what looked like pus, described severally as "yellowish-white, almost greenish-mass". The microscopy of the blood vessel contents revealed large numbers of abnormal, granular and colourless corpuscles. From these descriptions, the disease that was recognized appears to be what we identify today as chronic granulocytic leukaemia.

Virchow, (16) summarising his findings in his publications of 1856 and 1858, pointed out that reactive transitory leucocytosis, which was commonly seen in inflammatory diseases, had to be distinguished from the progressive disease that he had given the name "leukaemia". In leukaemia, the white blood cells were not only increased but there was a reduction in the red cells and changes were also noted in other organs.

He therefore classified the disease into two types: "splenic leukaemia", which was characterized by splenic enlargement; "lymphatic leukaemia", which was featured by general lymph node enlargement. He further distinguished the two classes of leukaemia by use of cytology, where he found that in lymphatic leukaemia there were smaller cells than in splenic leukaemia, and that the smaller cells contained only one nucleus. He also suggested that the lesions in the spleen and lymph nodes resulted from hyperplasia of the normal elements whereas organs such as the liver and the kidney were infiltrated by abnormal cells present in the blood. Following the description of the two chief varieties of chronic leukaemia, Freidreich in 1857 (17), identified an acute form of the disease and soon afterwards, Biermer (18) reported leukaemia in a child for the first time.

Bone marrow involvement in the leukaemic process was first pointed out by Neumann (19) in the period 1870 to 1878. His initial observations were made at an autopsy of a man who had died of "splenic" leukaemia. He was impressed by the abnormal appearance of the bone marrow which was not red like that of a normal individual but appeared "dirty, greenish-yellow-like-pus". In referring to the evolutionary concepts and terminology in leukaemia, he championed the view that there was "a myelogenous" type in addition to the recognized splenic and lymphatic forms. Inspite of Freidreich's account of the acute form (17), leukaemia was generally regarded as chronic until the late 19th century when Ebstein (20) reported a patient with acute leukaemia and reviewed sixteen other cases collected from the literature. Thereafter, there was a spate of confirmatory

reports.

However, a major step forward in the evolution of haematology which also led to an enormous increase in knowledge about normal blood, haemopoiesis in general and leukaemia, was the introduction of differential stains by Ehrlich (21). He identified all the varieties of normal peripheral blood leucocytes that we today recognize in the various types of leukaemia. He also introduced new staining procedures which helped to clarify the nomenclature difficulties in leukaemia. By these techniques, he showed that both the "splenic" and"myelogenous" types of leukaemia were characterized by a proliferation of granulocytes. The entity we know today as erythro-leukaemia was first alluded to by Hirschfeld in 1898 (22), who believed that many cases of acute granulocytic leukaemia had red cell precursors in the leukaemic process as well.

When Naegeli in 1900 (23) used the term "myeloblast" for the first time, to refer to the non-granular cell from which myelocytes were derived, he was unable to distinguish it from lymphocyte precursors. This finding provided some explanation for what had been called "mixed" leukaemia and acute transformation in the late stages of chronic leukaemia. In 1913, Reschard and Schilling (24) described an acute leukaemia of "splenocytes" or "monocytes", the type we know today as the "pure monocytic" leukaemia. Only a further six cases of it were reported in the next fifteen years; although, from 1930 onwards, an increasing number of reports indicated a general agreement on the occurrence of this type of leukaemia. It was then further subclassified into the "Schilling type" (pure monocytic) and the "Naegeli" type or the "myelomonocytic" type.

"Leukaemia", became increasingly recognized, not as a single clear-cut entity, but a group of disorders that featured an abnormal proliferation and maturation in the bone marrow and then release of leucocytes into the peripheral blood and lymphoreticular tissues. These abnormal cells eventually infiltrated many organs. However, once the nomenclature difficulty was overcome, it was clearly demonstrated that there were two chief types of leukaemia according to their behavioural nature, i.e. acute and chronic. Further subtyping was determined by the nature of the cells participating in the proliferative process. Hence leukaemia, whether acute or chronic, could be typed as granulocytic (or myelogenous), lymphocytic (or lymphatic) and lastly monocytic.

The introduction of the sternal puncture aspiration in 1929 (25), permitted the recognition, for the first time, of "aleukaemic" leukaemia. At this time, multiple myeloma was identified as a "subleukaemia" of plasma cell leukaemia. More new types of leukaemia were identified as time went by. Di Guglielmo (26), described the first case of acute "erythraemic myelosis", a disorder that carries his name up to today, and what had probably been alluded to earlier by Hirschfeld (22). This represented a generalised proliferation of abnormal erythroblasts in the bone marrow, analogous to the leucocytic proliferation that was seen in acute leukaemia. The term "leucosarcoma", first used by Sternberg (27), denoted those cases of "lymphosarcoma" which had a leukaemic blood picture. This was further confirmed by Isaacs (28) when he demonstrated lymphosarcoma cells in circulating blood from a patient with lymphoma, thereby introducing the term "lymphosarcoma cell leukaemia". An increasing number of cytological

variants of leukaemia were subsequently described. Without considering the chronological order in which they first appeared in the literature, they included undifferentiated leukaemia, chronic monocytic leukaemia, leukaemic reticuloendotheliosis (29), eosinophilic leukaemia, acute promyelocytic leukaemia (30), basophilic or mast cell leukaemia (31), prolymphocytic leukaemia and so on. Most of these are rare, but they can be typed fairly accurately by use of physical features, cytological appearances and cytochemical characteristics. The first description of a "preleukaemic" state appeared in the early fifties, when Block (32), reported cases of "preleukaemic acute human leukaemia". This is an ill-defined process which is characterized by bizarre clinical symptomatology and haematological findings which may precede an overt leukaemic process after a varying period of time.

In summary, leukaemia is, today, considered as a neoplastic process which is characterized by generalized, purposeless and self-perpetuating abnormal proliferation or accumulation (33) of any of the leucocytic series. The process is associated with quantitative and qualitative abnormality of white blood cells in circulation and almost always leads to the tetrad of anaemia, thrombocytopenia, infections and organomegaly; and eventually, death. The nature of the abnormality in the human is ill-understood, although the various types of leukaemia, as we know them today, are classified in Table 1.

Table 1. Classification of leukaemia (Kasili 1975)

| I: ACUTE FORMS. | II: CHRONIC FORMS. |
|---|---|
| A) MYELOGENOUS:<br>1. Myeloblastic. (AML)<br>2. Myelomonocytic. (AM-ML)<br>3. Promyelocytic. (AP-ML)<br>4. Erythroleukaemia. (EL)<br>5. Others. | A) GRANULOCYTIC: (CGL)<br>1. Myeloid. (CML)<br>2. Eosinophilic.<br>3. Basophilic.<br>4. Myelomonocytic. |
| B) MONOCYTIC:<br>1. Monoblastic. AMoL)<br>2. Histiomonocytic. | B) MONOCYTIC: |
| C) LYMPHOCYTIC:<br>1. Lymphoblastic. (ALL)<br>2. Prolymphocytic. (APLL)<br>3. Lymphosarcoma cell. (ALSCL) | C) LYMPHOCYTIC:<br>1. Lymphatic. (CLL)<br>2. Prolymphocytic. (CPLL)<br>3. Lymphosarcoma cell. (CLSCL)<br>4. "Hairy" cell (L.R.E.) |
| D) UNDIFFERENTIATED:<br>Stem cell. (AUL) | D) ERYTHROLEUKAEMIA: |
| E) PLASMA CELL: | E) SMOULDERING:<br>Subacute ) Oligoleukaemia or low blast cell count leukaemia.<br>Preleukaemia) |

Aetiology.

As it is for the majority of human cancers, the aetiology of human leukaemia is mainly speculative and largely unknown. Human leukaemogenesis is, however, probably a function of a multiplicity of factors in the host and environment which intricately interact to cause leukaemia as an end product (34). In contrast, animal leukaemia is known to be induced by several leukaemogens, both in natural and experimental situations. Apart from genetic predisposition to leukaemia in the $AK_3R$ mice, avian myeloblastosis, feline, murine and bovine leukaemia are of viral aetiology and can be induced by chemical carcinogens as well. Chemical carcinogens, particularly the cyclic hydrocarbons can induce leukaemia in experimental animals, either by activating potentially oncogenic viruses or causing chromosomal damage. The incompetence of the immune mechanism is known to be a major predisposing factor in the development of leukaemia in mice and the role of radiation as a leukaemogenic agent in animals is also well established (35).

The precise role of these factors in human leukaemogenesis is uncertain because the information available is mainly based on epidemiological and cummulative data. The insurmountable problem of lack of confirmatory evidence is due to the fact that it is against ethical principles and regulations of human experimentation to culpably induce leukaemia in an individual for experimental sake. Nevertheless, a brief review of the circumstantial role played by each of the leukaemogenic factors is outlined in the following paragraphs.

a. Genetic predisposition.

Studies of human leukaemia occurring in families indicates that siblings of a leukaemic child have a $2\frac{1}{2}$ times risk or 8.1% concordance of developing leukaemia when compared with unrelated members of the population. This suggests the presence of an operative leukaemogenic gene. This becomes more obvious in consanguineous marriages (36) and implicates an autosomal recessive pattern of inheritance. The role of genetic predisposition is clearly evident in monozygotic twins, who have about 20-25% concordance rate of developing leukaemia, when it is negligible in fraternal twins. It should however be realised that familial leukaemia occurs in a setting where extrinsic leukaemogenic factors are also operative. For instance, most of the leukaemia reported in monozygotic twins occurs in the first year of life, an observation which incriminates a prenatal leukaemogenic agent (37). It is well known that most congenital constitutional disorders are associated with chromosomal aberrations, which are also linked with a high risk of acute leukaemia (38). These chromosomal aberrations include G22 trisomy in Down's syndrome in which the risk of leukaemia is 20 times that of the general population (38). The increased frequency of chromosomal breakage in cultures in Bloom's and Fanconi's syndromes is associated with a relatively high risk of acute myelogenous leukaemia. Conversely, relatives of patients with familial leukaemia have been demonstrated to carry chromosomal aberrations. The sex chromosome trisomy in the Klinefelter's syndrome and the D-trisomy of Pattau's syndrome have been reported to have an increased susceptibility to leukaemia (38). The missing Y in chronic granulocytic leukaemia, the C abnormalities in myeloproliferative disorders (39) and the aneuploidy encountered in the acute leukaemias, whether "passengers"

or "drivers" are additional pieces of information that corroborate the genetic role in leukaemogenesis. More recently, however, HLA-A2 and B5 types have been found to be significantly frequent in individuals with acute lymphocytic leukaemia, whereas HLA-A/B12 show a deficit in acute myelogenous leukaemia (40).

b. Viral leukaemogens.

As stated above, there is a good deal of confirmatory evidence to incriminate viruses in the aetiology of animal leukaemia, but the information available in human leukaemia is purely circumstantial. Virus-like particles have been found in leukaemic cells, serum and urine of patients suffering from leukaemia (41). Type C-oncorna virus of the simian type has been isolated and purified from human myelogenous leukaemia cells (42). The significance of this finding is still questionable. Another piece of evidence comes from the clustering of leukaemia cases in time and space being, evidence of an infectious agent, probably, a virus playing a role in the causal transmission of leukaemia (43).

c. Chemical leukaemogens.

Epidemiological data suggest that chemical carcinogens play an important role as leukaemogenic agents in human leukaemia, either as activators of potentially oncogenic viruses, suppressors of the immune surveillance or de novo inducers of leukaemia. Benzene was the first agent to be causally associated with leukaemia (44). Studies of benzene handlers in industries from many parts of the world have revealed excess of leukaemia in the risk group as compared with the general population.

As well as suffering a high risk of aplastic anaemia, benzene workers have an excess of chromosomal aberrations. An increased risk of acute non-lymphocytic leukaemia has been reported in patients treated for cancer with cytotoxic drugs, especially alkylating agents (45). The leukaemogenic potential is probably related to their clastogenic capacity. The risk increases with the intensity of chemotherapy and duration of survival, reaching a peak of 5-10% of the treated patients in ten years. Other agents that have been blamed for being leukaemogens are azathioprine and chloramphenicol when used for treating non-neoplastic conditions.

d. Radiation leukaemogenesis.

There is solid data to indicate that irradiation, be it accidental, therapeutic or diagnostic is associated with a definitely increased risk of leukaemia in the exposed populations. The latent period between exposure and development of leukaemia is of the order of $1\frac{1}{2}$ years with a peak at 7 years. Although there may be linear radiation dosage relationship and the incidence of acute leukaemia induced, 400 rads appear to be a limiting dose below which the relationship becomes ill defined. The best data for accidental exposure are those from the Japanese populations of the Nagasaki and Hiroshima cities who suffered the effects of atomic bomb explosions in 1945. The incidence of acute and chronic granulocytic leukaemia increased over and above that expected for the general population, attaining a peak at seven years, and was still demonstrable at 14 years (46). The incidence was highest at the epicentre and progressively diminished away from it.

It has been clearly shown that patients who receive radiotherapy for ankylosing spondylitis; 32P, for

polycythaemia rubra vera, and $^{131}I$ for thyroid cancer have shown an increased risk of developing leukaemia (47). Diagnostic radiation in the prenatal periods is another facet of radiation that has been associated with increased incidence of acute leukaemia of childhood in the offspring of the irradiated mothers (48). Lastly, United States radiologists, followed up for a long time, have shown evidence of increased susceptibility to leukaemia (49).

e. Immunocompetence and leukaemogenesis.

The role the deficient immune apparatus plays in leukaemogenesis should not be underestimated. There is increased frequency of malignancy, leukaemia not excepted, in people who, whether due to age, disease or therapeutic immuno-suppression have reduced immunocompetence (50). Elevated frequency of acute leukaemia has been reported in immunodeficiencies such as Wiskott-Aldrich syndrome, ataxic telangiectasia, congenital agammaglobulinaemia and autoimmune disorders (37). Immunological deficits complicating treated Hodgkin's disease and multiple myeloma in the long survivors may offer part of the explanation for the increased occurrence of, predominantly, acute myelogenous leukaemia as a terminal event in these conditions. Finally, the fact that immunotherapy tends to prolong remmission times in acute myelogenous leukaemia serves as additional indirect evidence for the role of immune incompetence being a cofactor in leukaemogenesis.

Incidence.

The occurrence of leukaemia is world wide, although the figures available strongly suggest that there is considerable variation (51) in its incidence with regard

to geographical, racial, social, sex, age, and type distribution. It is, for example, alleged that leukaemia has a lower predilection for the black race than the whites. The American white children below 15 years have an incidence of 3.15 in 100,000 and black American children 1.42 in 100,000 of acute leukaemia (52). Females have, generally, a lower leukaemia incidence than males with ratios varying from 1:1.3 to 1:1.6 for all types of leukaemia. Whereas the Japanese suffer the lowest rate of chronic lymphocytic leukaemia in the whole world, African children have much higher rates of acute myelogenous leukaemia than the caucasians. Similarly, the myeloproliferative syndromes, except for chronic granulocytic leukaemia are relatively uncommon in Africans. The variation in age-type distribution becomes manifestly clear when it is realized that the chronic leukaemias are diseases of the adult and the aged, but rare in childhood. There is a peak occurrence for acute leukaemia in the first and for the chronic leukaemias after the fifth decade. Both the acute and chronic forms occur in almost equal proportions, although chronic granulocytic leukaemia is more common than chronic lymphocytic. The frequencies of the major forms of acute leukaemia vary tremendously from age to age, one geographical locality to another and series to series (Table 2).

It is a general consensus of many workers that the world incidence of leukaemia is on the increase. However, some believe that this is, relative, due to improved diagnostic facilities but others advance evidence for a genuine increase. If there is real increase, then the enhanced use of associated causal factors such as radiation and drugs could be a possible explanation.

Table 2: Geographical variation in the frequency of various types of acute leukaemia in series reported from Africa.

| SOURCE OF INFORMATION | AML | ALL | AMoL | OTHERS | TOTAL |
|---|---|---|---|---|---|
| 1. Uganda (64) | 22 | 16 | 1 | 7(1 EL) | 46 |
| 2. Congo (63) | 5 | - | - | 12 (2 EL) | 17 |
| 3. Kenya (66) | 28 | 15 | 2 | 10(1 EL) | 55 |
| 4. Kenya (78) | 25 | 17 | 0 | (1 (1 EL) | 43 |
| 5. Nigeria (77) | 34 | 27 | 16 | 12(1 EL | 89 |
| 6. Rhodesia (84) | 11 | 15 | - | - | 26 |
| 7. Present series (Kenya) | 142 | 93 (25 ALSCL) | 15 | 6(2 EL) | 256 |

## Leukaemia documentation in tropical Africa during the last two decades.

The paucity of literature, on leukaemia in tropical Africa, in the years preceding 1960 is striking. This is probably because leukaemia was assumed to be indeed rare in Africa (53-54) as it was further stipulated that the acute forms and childhood leukaemia were even much rarer (55-57). Hence, any information available on leukaemia in tropical Africa, before the sixties, is barely scanty. This information can be divided into three forms: sporadic case reports, such as that by de Boer and Allen (58); reports based on the analysis of cancer cases from cancer registries (59-61); analysis based on causes for ward admissions in hospitals (54). The majority of these reports mentioned nothing about the epidemiology or behaviour of leukaemia in Africans and also made no attempt to document the clinico-pathological picture of the disease. They, however, indicate that during this period, leukaemia formed between 1-2% of all the cancers reported from the various countries of tropical Africa. The figures showed a preponderance of the chronic leukaemias with only a few acute and childhood forms.

Interest which was developed in the pattern of leukaemia in tropical Africa from the early sixties is evident from the sudden increase in reports on the specific retrospective and prospective surveys of the disease from various countries in Africa (2-5; 62-67). These, fairly comprehensive, studies not only, documented the incidence of leukaemia in Africans, but also its clinicopathological pattern. Some of the reports (3-5; 68) have claimed that there is a clear deficiency of childhood leukaemia in Africans. This contention was corroborated by broader cancer surveys (69).

Nevertheless, others (63-66) report substantial numbers of childhood leukaemia in their series. The latter reports suggest that the concept of the rarity of childhood leukaemia in Africans has been overemphasized, even if there appears to be a deficit of leukaemia in children in the 0-4-year age group. There is further indication that the apparent deficit of childhood leukaemia in tropical Africa is accounted for by gross underdiagnosis (64-67). However, all the series seem to be unanimous on the fact that the incidence of adult leukaemia in Africans is probably the same as that in Europeans or Americans. Apart from claims, by Haddock (4), that chronic lymphatic leukaemia was the most common in Africans, the rest of the series report the distribution of the various types of leukaemia as fairly similar to that seen in the Western countries, as given by Wintrobe (70). All the reports have documented undoubtable male preponderance. The clinical presentation, except for the high frequency of chloromatous tumours in acute myelogenous leukaemia in children (71), show no extra-ordinary features.

The sixties also saw a limited number of reports on leukaemia in tropical Africa, based on studies of anaemia in hospital in-patients (72-74), on cancer surveys (75), as well as on studies of malignant lymphoreticular neoplasms (1; 76). These studies tend to give an erroneous picture which suggests that leukaemia is an extremely rare disease in Africans. Some of them do not even mention the disease at all (73). No rationalised specific treatment, except with supportive blood transfusions, is reported in any of these series.

Reports of leukaemia in tropical Africa in the seventies are more extensive, and also concentrate on particular aspects of the disease. For instance, the studies of acute leukaemia in Nigeria (77) and Kenya (78),

childhood leukaemia in the Sudan (79), Tanzania (80), and Kenya (81); then chronic leukaemia as seen in Nigerians (82); prolymphocytic leukaemia in Uganda (83) and leukaemia in general (84). Case reports of rare presentations have occasionally been documented; for example, leukaemia in pregnancy (85), congenital leukaemia (86) and acute leukaemia with mastocytosis (87).

Conclusion drawn from these reports are: leukaemia should not be considered uncommon in Africans; the clinicopathological pattern of leukaemia in tropical Africa is similar to that experienced in temperate countries except for minor variations; there is a deficit of leukaemia in the 0-4-year age group; the acute myelogenous leukaemia is more common than acute lymphocytic leukaemia; there is still some amount of under-diagnosis which makes the knowledge of the true incidence of leukaemia in tropical Africa difficult; the response of leukaemia, in the African, to treatment has yet to be evaluated from carefully planned therapeutic protocols and lastly, aetiological factors should be sought by help of examining the epidemiological patterns of the disease.

Leukaemia reports in Kenyan Africans between 1924 and 1977.

Well authenticated cases of leukaemia have been documented in Kenya since 1924; infact, since the inauguration of a local medical journal (the present East African Medical Journal). There were three case reports in the twenties (58; 88-89) but none from 1930 until the sixties, (Table 3).

Table 3: Leukaemia cases reported in Kenya since 1924.

| Year | Number of cases reported. |
|---|---|
| 1924 | 1 ALL (58) |
| 1925 | 1 CGL (88) |
| 1929 | 1 CGL (89) |
| 1930 - 1960 | - None reported. |
| 1962 | Number not specified (59). |
| 1968 | 3 cases, acute leukaemia (72). |
| 1968 | 7 cases, leukaemia (74). |
| 1970 | 105 cases: 55 acute leukaemia<br>44 chronic leukaemia (66) |
| 1972 | 43 cases, acute leukaemia (78) |
| 1972 | 1 case, acute leukaemia with Mastocytosis (87) |
| 1975 | 1 case, congenital leukaemia (86) |
| 1976 | 10 cases, acute leukaemia (91) |
| 1976 | 1 case, acute leukaemia in pregnancy (85) |
| 1977 | 56 cases, childhood leukaemia (81). |
| 1978 | Present series. |

However, it is only during the last one decade that leukaemia reports from Kenya, have featured in the East African literature, documenting it not as an important cause of morbidity and mortality in the country, but as a mere curiosity. It was even popular teaching up to the late sixties that it was a rare disease in Kenya. Nevertheless, during this period, there were several categories of reports, not directed at documenting leukaemia specifically, but, as part of either cancer surveys in general (59), analysis of causes of medical ward admissions (73) or analysis of causes of severe anaemia in in-patients (72). Nothing was therefore known about the prevalence or pattern of leukaemia in this country until Taylor (90) started an organized bone marrow interpretation service and the keeping of statistics on leukaemia at the then Medical Research Laboratory in Nairobi. On the other hand, the seventies have seen more comprehensive reports, focused on leukaemia, with a view of establishing its incidence, epidemiology, biological behaviour and response to treatment. Both prospective and retrospective surveys were employed (66, 78, 81,91). These studies have indicated that leukaemia is not as uncommon in Kenya as it had been previously contented. They have further shown that leukaemia of childhood is prevalent, albeit with an apparent deficit in the 0-4-year age group. However, the type distribution analysis has revealed the higher incidence of the non-lymphocytic acute leukaemias than is reported from the western world. Acute lymphosarcoma cell leukaemia has been given prominence as an entity in one of the series (81).

Treatment, using modern chemotherapeutic agents has been used, with good results (81,91) although definitely inferior to the results achieved in more specialised centres in America or Europe.

The figures obtained from the literature, particularly before 1960, obviously give a wrong impression of the incidence of leukaemia in the Kenyan Africans as the medical services, leave alone the diagnostic aspects, were largely undeveloped. Hence, with the long cherished misconception that leukaemia was rare in the African, the index of diagnostic suspicion was low or even lacking. For instance, the cases reported as agranulocytosis (92) and Haemophilia (93) could have well been leukaemia. Furthermore, a great majority of leukaemic patients die at home and this inevitably accounts for the alleged rarity of the disease. Acute leukaemia, mainly of childhood being a "fast killer", further explains the deficit of not only adult acute leukaemia but also the childhood leukaemia that has so frequently been reported as absent in tropical Africa.

The classification of the diagnosed cases is so confusing that it is only the chronic granulocytic leukaemia, with its simplicity of clinical and morphological presentation, that has been labelled with any certainty of accuracy. This similarly accounts for the paucity of acute leukaemia reports, not only, from Kenya but tropical Africa at large. With improving haematological services, leukaemia as a diagnosis has become common, and there is no wonder that a week never passes without two or more cases being seen at the Kenyatta National Hospital. Nevertheless, the main hurdle is to establish the precise incidence of leukaemia in the country and then plan for a future strategy. <u>This is our present and future task!</u>

# CHAPTER TWO

## MATERIALS AND METHODS

Sources and materials.

The scope of this work is covered in two parts. The first part consists of a retrospective data collection and evaluation of all the cases diagnosed as leukaemia, from the Kenyatta National Hospital and peripheral hospitals of Kenya, for the years 1971-1974 inclusive. The second part comprises a prospective study of all the cases of leukaemia diagnosed at the Kenyatta National Hospital and a statistical documentation of those cases of leukaemia diagnosed on the material from the peripheral hospitals for the years 1975-1977 inclusive.

For the first part, all bone marrow reports, in the haematology laboratory in the department of Pathology and from the department of Medicine, for the period under study were examined. Those which had leukaemia as a diagnosis were scrutinized for vital statistical data, clinical information and any haematological data. These details were extracted and transferred on to information cards, a sample of which is illustrated in appendix 1. The data were then subjected to statistical analysis. The corresponding bone marrow slides and peripheral blood films which were May-Grunwald-Giemsa stained were reviewed. Unsatisfactory smears, which were either too thick, poorly stained, faded or inadequate were excluded. The final review diagnoses were then documented.

In the second part of the study, all the cases diagnosed from 1975 to 1977 had all the data mentioned above recorded on to the information cards as the bone marrow diagnoses were made. Those cases attending or admitted at the Kenyatta National Hospital, particularly children, were further evaluated clinically, investigated, and managed as detailed below.

## Methods.

### Clinical evaluation.

The following clinical parameters were elicited and documented for every patient during the physical work up:

(i) Age and sex;

(ii) Duration of illness;

(iii) Clinical features of anaemia, fever, haemorrhagic tendency, infection and organomegaly;

(iv) Other clinical features such as bone pain, gum hypertrophy, soft tissue swellings, arthritis, chloromas, neurological signs and jaundice.

### Initial laboratory evaluation.

(a) Peripheral blood examination consisted of the following tests:-

(i) Haemogram using the Electronic Coulter Counter (Model S).

(ii) Blood film morphology was studied with the aid of May-Grunwald-Giemsa staining; cytochemistry, using Sudan Black, P.A.S., Feulgen and leucocyte alkaline phosphatase stains (the details of the techniques are outlined in appendix I), was done where possible.

(iii) Chromosome analysis was carried out on a few cases of chronic granulocytic leukaemia. This was done in the department of Genetics, University of Helsinki by Dr. U. Gripenberg.

(iv) Platelet count was accomplished by the use of the Coulter Electronics thrombocounter.

(b) Bone marrow examination was performed on aspirates, from either the sternum in adults or iliac crest in children.

(i) Both smears and squashes were prepared.

(ii) Cytological and cytochemical procedures applied were the same as for the peripheral blood film.

(c) Due to the asynchronous nucleo-cytoplasmic maturation in primitive cells, they have less easily recognizable cytological features of differentiation. The final diagnosis of the various types of acute leukaemia was therefore arrived at by considering the following morphological criteria (Table 4):

(i) Cell company: presence of myelocytes, lymphocytes, monocytes or normoblasts.

(ii) Cell size - uniformity, variability, and presence of micromyeloblasts.

(iii) Cell outline - regularity.

(iv) Cytoplasmic staining and appearance with size of granules.

(v) Vacuoles, Auer rods and nuclear fragments.

(vi) Nuclear features - outline, Reider forms chromatin pattern an nuclear membrane.

(vii) Nucleoli - number and texture of the margin.

The chronic leukaemias, in most cases posed no diagnostic problem morphologically. However, all the diagnoses were based on the classification outlined in Table 1.

(d) Coagulation screening, consisting of the prothrombin time, Kaolin cephalin clotting time, thrombin time and fibrinolytic tests were done in acute promyelocytic leukaemia either after the diagnosis had been made or suspected.

(e) The following radiological examinations were done.

(i) Chest x-ray (PA and lateral).

(ii) Skeletal survey, where it was indicated, such as in bone pain. The bone suspected of being the seat of pain was always x-rayed.

Table 4: Differential cytological features in acute leukaemia.

| FEATURE | AML | ALL | AMoL & AM-ML | EL | ALSCL |
|---|---|---|---|---|---|
| Cell size variability | +++ | + | ++++ | ++++ | ++++ |
| Cell outline irregular | + | ++ | +++ | ++++ | +++ |
| Nuclear folding and indentation | ++ | ± | ++++ | ++ | ++ |
| More than two nucleoli | +++ | + | +++ | +++ | ++ |
| Chromatin pattern | fine | coarse | lacy | fine to coarse | spongy |
| Nuclear/cyto-plasmic ratio | variable | high | low to variable | varia-ble | varia-ble |
| Auer rods | ++++ | 0 | ++ | +++ | 0 |
| Reider forms | + | +++ | ± | 0 | ± |
| Cell company | granulo-cytic series | lymphoid series | monocy-tic & granu-locy-tic seri-es | ery-thro-id seri-es | lympho-id series |
| Abnormal granulocytes & eosinophils | + | 0 | + | ± | ± |
| Numerous platelets | + | 0 | + | ± | + |

Key to signs.

= Not a feature
= Rare feature
= Uncommon feature.
++ to +++ = Common feature.
++++ = Almost invariably present.

(f) Biochemical evaluation of renal and liver function included the following tests:-

(i) Liver function tests - serum proteins, alkaline phosphatase, the transaminases and bilirubin levels including serum immuno-electrophoresis whenever it was indicated.

(ii) Serum electrolytes, urea, calcium and uric acid determinations.

(g) Bacteriological investigations which were done comprised cultures of pus and throat swabs, stool, sputum and blood. Standard biochemical and bacteriological techniques were used all the time.

Patient management programme.

All the paediatric patients admitted to the K.N.H. (1975-77) were clinicopathologically evaluated as already described and were managed as described below. There was no such planned management for adults.

Specific therapy.

The standard practice of REMISSION INDUCTION, CYTO-REDUCTION AND MAINTENANCE PHASES of specific therapy was followed. But in view of the observed facts about acute leukaemia, that African patients tend to have advanced disease at presentation, with poorer prognosis and that they tolerate cytotoxic drugs well, the dosages were accordingly modified. Similarly, due to poor and irregular supply of drugs, protocols had to be changed or modified often until those detailed below were finally designed in January 1976. The protocol for ALL was based on the Acute Leukaemia Group B 6801 protocol (94) which was modified by adding a consolidation phase. The regimen for AML, was modelled after the Bart's III protocol (95).

After the first phase treatment, the patients were further followed up in the haematology clinic at K.N.H. at intervals depending on the individual patient's needs.

Adult acute myelogenous leukaemia, due to poor availability of drugs, was treated according to the Bart's III protocol (95).

Supportive therapy.

The format that was used for supportive care of the patients is given in appendix II.

Cytotoxic therapy protocols.

a) Acute lymphocytic leukaemia (including ALL, APLL, ALSCL and AUL). This consisted of:-

(i) Remission induction:

- Vincristine - 2 mg/$m^2$, I.V. weekly x 4.
- Prednisone - 40 mg/$m^2$, P.O in 3 doses, daily, tailing off in week 6.
- Daunorubicin - 40 mg/$m^2$, I.V., 2 doses given between the second and third doses of vincristine.

A bone marrow was done at the end of week 4 to assess the remission status, and if not in remission a further dose of vincristine was given.

(ii) Cytoreduction:

- Cyclophosphamide - 1200 mg/$m^2$, I.V., given in saline infusion on day 1.
- Cytosine arabinoside - 100 mg/$m^2$, I.V., twice daily as I.V. push on day 1-4.
- 6-Mercaptopurine - 100 mg/$m^2$, P.O., day 1-4.

The course is repeated after three days' rest.

(iii) Maintenance:

To start after one week's rest from the end of cytoreduction, and to continue indefinitely or until relapse occurs.

- 6-Mercaptopurine - 75 mg/$m^2$, P.O., daily.
- Methotrexate - 15 mg/$m^2$, P.O., weekly.
- Vincristine - 1 mg., I.V., monthly.
- Prednisone - 40 mg/$m^2$, P.O., in 3 doses daily x 7 days, monthly.
- Cyclophosphamide - 400 mg/$m^2$, I.V., every 3 months.

(iv) C.N.S. Prophylaxis:

This started after complete remission, at the beginning of maintenance therapy, on week 8, following a diagnostic lumbar puncture. Cranial radiation (2500 rads) was given over a period of three weeks using the cobalt unit. Intrathecal methotrexate was used in 5 cases.

(b) Non-lymphocytic acute leukaemia (including AML, APML, AM-ML, AMoL and EL and accelerated CGL with Juvenile C.G.L.).

(i) Remission induction and cytoreduction:

This consisted of the following schedule:-

- Daunorubicin - 40 mg/$m^2$, I.V., day 1.
- Cytosine arabinoside - 100 mg/$m^2$, I.V., twice daily, day 1-4 as infusion in normal saline.
- 6-Mercaptopurine - 100 mg/$m^2$, P.O., day 1-4.
- Prednisone 40 mg/$m^2$, P.O., in 3 doses, day 1-4.
- Cyclophosphamide - 1200 mg/$m^2$, I.V. in normal saline infusion, day 5 only.

This pulse therapy was repeated after a rest period of 5-9 days, until complete remission was achieved.

(ii) Maintenance:

This comprised monthly pulses of:-

- Daunorubicin - 40 mg/$m^2$, I.V., day 1.
- Cytosine-arabinoside - 100 mg/$m^2$, I.V. or S.C., day 1.
- 6-Mercaptopurine - 100 mg/$m^2$, P.O., day 1-4.

(c) Chronic leukaemia. These were treated along conventional lines (70) as described below.

(i) Chronic granulocytic leukaemia was treated with busulphan until the leucocyte counts dropped to less than $10x10^9/1$ and all the clinical signs regressed. Then maintenance therapy was monitored against the the total white cell counts. If these rose above $20x20^9/1$, therapy was reinstituted.

(ii) Chronic lymphocytic leukaemia was treated with chlorambucil or cyclophosphamide with or without prednisone, if the disease stage was II and above (Table 31). Stage I disease was not treated.

Follow up

Bone marrows were done on all the patients before they were discharged to the haematology clinic for follow up. Bone marrow examination was repeated as often as was indicated by the peripheral blood picture, such as in unexplained cytopenias and reappearance of blast cells. Reinduction therapy was instituted as soon as there was any evidence of relapse. The effectiveness of treatment and patient survival were finally assessed at the end of the study period.

Post mortem study.

Autopsies were performed on all patients who died in hospital and for whom consent for the post mortem was given. This was done in an attempt to ascertain the cause of death and study the pattern of organ involvement. Both gross and histological findings were documented and subsequently analysed.

# CHAPTER THREE

## RESULTS

## Vital statistical data.

### Incidence and type distribution.

A total of 456 cases of leukaemia, giving an annual mean of 65, were diagnosed over a period of seven years (1971-1977). This gives a crude national incidence of 0.5 cases per 100,000 per year. A calculated age incidence for leukaemia was 0.3 per 100,000 per year in children below 15 years and 0.73 per 100,000 in adults.

Leukaemia typing according to Table 1 showed the following distribution.

| | Numbers | % |
|---|---|---|
| Acute myelogenous | 144 | 31.6 |
| Acute lymphocytic | 68 | 14.9 |
| Acute monocytic | 15 | 3.3 |
| Acute lymphosarcoma cell | 25 | 5.5 |
| Acute undifferentiated | 4 | 0.9 |
| Chronic granulocytic | 130 | 28.5 |
| Chronic lymphocytic | 70 | 15.3 |
| | 456 | 100 |

About 60% of all the leukaemias are myeloid in origin. Acute and chronic granulocytic leukaemia occurred twice as often as acute and chronic lymphocytic leukaemia, respectively. Acute leukaemia accounted for 56.2% of the total. There was higher proportion of myelogenous and acute leukaemia in this series than is expected from established data (70). Of the 144 cases of acute myelogenous leukaemia, there were 76 acute myeloblastic, 27 acute myelomonocytic, 16 acute promyelocytic, two erythro-leukaemia (Di Guglielmo's disease), one eosinophilic and

22 unspecified. All the fifteen cases of acute monocytic leukaemia were monoblastic or pure monocytic (the Schilling type (24)). Ninety three cases of acute leukaemia of lymphoid origin, recorded for all ages, showed the following composition: 27% ALSCL; 3% acute prolymphocytic and 70% lymphoblastic. The distribution took a different pattern in children; i.e. acute lymphoblastic - 50%; ALSCL - 40% and acute prolymphocytic-10%. ALSCL, though a subspecies of acute lymphocytic leukaemia, is fully recognized as a clinicopathological entity in this series and it occurred as a complication of poorly differentiated lymphocytic lymphomas and two cases of Burkitt's lymphoma.

Out of 130 cases of chronic granulocytic leukaemia, only four were of the juvenile variant, showing negative $Ph_1$ chromosome studies, although 9 of them occurred in childhood. No attempt was made to subclassify the chronic lymphocytic leukaemias into chronic lymphosarcoma cell leukaemia (CLSCL) or chronic prolymphocytic leukaemia although one of them had been documented as "hairy cell" leukaemia. No definite cases of preleukaemia were identified.

Tribal distribution. (Tables 5a and b)

The frequency of leukaemia among the major and minor tribes correlated fairly well with the population frequencies of the respective tribes and also followed, closely, the tribal admission rates to the KNH (Table 5a and Fig. 1). The Kikuyu show an apparent excess of all types of leukaemia with the following contributions:-

Table 5a: Leukaemia frequencies according to tribes correlated with tribal population rates and admission rates to K.N.H.

| Tribe | Leukaemia rates % | Population rates % | KNH Admission rates % |
|---|---|---|---|
| Kikuyu | 39.7 | 20.1 | 33.9 |
| Kamba | 16.0 | 10.9 | 19.8 |
| Luyia | 7.0 | 13.3 | 9.2 |
| Luo | 10.1 | 13.9 | 17.2 |
| Meru | 5.9 | 5.6 | 3.9 |
| Masai | 4.4 | 1.9 | 3.3 |
| Kalenjin | 4.2 | 10.9 | 1.0 |
| Mijikenda | 0.7 | 4.8 | 1.5 |
| Embu | 1.1 | 1.1 | 1.7 |
| Kisii | 1.5 | 6.4 | 2.2 |
| Somali | 1.1 | 2.6 | 4.9 |
| Other | 4.4 | 6.8 | 1.4 |
| Unknown | 3.9 | - | - |

Table 5b: Tribal distribution of various leukaemia types.

| Tribe | AML | ALL | CGL | CLL | ALSCL | AMoL | AUL | TOTAL | PERCENT |
|---|---|---|---|---|---|---|---|---|---|
| Kikuyu | 63 | 40 | 50 | 19 | 4 | 3 | 2 | 181 | 39.7 |
| Kamba | 21 | 10 | 20 | 11 | 2 | 8 | 1 | 73 | 16.0 |
| Luyia | 13 | 4 | 10 | 4 | 0 | 1 | 0 | 32 | 7.0 |
| Luo | 8 | 4 | 14 | 15 | 4 | 0 | 1 | 46 | 10.1 |
| Meru | 9 | 3 | 10 | 1 | 3 | 1 | 0 | 27 | 5.9 |
| Kalenjin | 7 | 0 | 7 | 5 | 0 | 0 | 0 | 19 | 4.2 |
| Masai | 5 | 2 | 7 | 4 | 1 | 1 | 0 | 20 | 4.4 |
| Embu | 3 | 0 | 1 | 0 | 1 | 0 | 0 | 5 | 1.1 |
| Kisii | 0 | 1 | 2 | 4 | 0 | 0 | 0 | 7 | 1.5 |
| Mijikenda | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 | 0.7 |
| Somali | 1 | 0 | 2 | 2 | 0 | 0 | 0 | 5 | 1.1 |
| Other | 7 | 2 | 5 | 3 | 2 | 1 | 0 | 20 | 4.4 |
| Unknown | 7 | 2 | 1 | 1 | 7 | 0 | 0 | 18 | 3.9 |
| Total | 144 | 68 | 130 | 70 | 25 | 15 | 4 | 456 | 100 |

CLL - 28%; ALL - 59%; AML - 44%; and CGL - 38.5%; as compared with their population rate of 20.1% of the total country's population. They predominate in the tribal distribution because of their proximity to good hospital services in and around Nairobi, coupled with good communication and easy access to hospitals (66). This was reflected in their high admission rate to the KNH, and corroborated by the overall tribal incidence of leukaemia of 1.2 per 100,000. The Kamba on the other hand show figures of leukaemia frequency as follows: all types of leukaemia - 16% of all the tribes; AML - 14.6%; ALL - 14.7%; CGL - 15.4%; CLL - 15.7%; with an overall incidence of 0.9 per 100,000. This closely correlates with their population rate of 10.1% and KNH admission frequency of 16%. The Luo constituted an overall of 10% of all types of leukaemia, but showed a genuine excess of CLL, accounting for 21% of all the cases of CLL. They had lower than expected rates of AML - 5.6% and ALL - 5.9%. However, CGL frequency (10.8%) tallied with their population size which is 13.9% of Kenya population. The Luyia showed the expected overall content of 9.2% of AML as compared with their population of 13.3%. They however showed a deficit in ALL and CLL, forming 5.9% and 5.7% of the total of each respectively. The Kalenjin, with a population frequency of 10.9% of the overall Kenyan population showed a deficit in all types of leukaemia, except CLL - 7.1%, which showed an intermediate frequency. The Meru exhibited an expected pattern for AML, ALL, CGL and a deficit of CLL. The Masai showed higher figures of leukaemia rates, particularly CLL and CGL with an overall distribution of 4.4% for all types of leukaemia, than is expected from their population frequency of 1.9%. All the minor tribal groups showed rates which correlate relatively well with their population frequencies and geographical location in relation to health services.

Age and sex distribution.

Sixty percent of all the leukaemia cases (Fig. 2; Table 6) occurred in the first three decades of life; 45% in the first and second; 25% during the first decade while 28% below fifteen years. Forty eight percent of the acute forms of leukaemia occurred in childhood, below 15 years of age. There is a primary peak in the first decade of life. This is mainly due to a male predominance in acute leukaemia. A secondary peak, seen in the sixth decade (Fig. 2), is again due to a male predominance, although a mild female peak also appears at this time (Fig. 3). A female preponderance is present during the second decade of life. The nadir, for both sexes, occurs in the fourth and fifth decades. The overall male to female ratio is 1.47:1, and it approaches 2:1 in the first decade of life, while it is almost 1:1 in the second decade. It is about equal in the 4th and 5th decades, but sharply rises in favour of males in the 6th decade.

Sixty five percent of acute leukaemia occurs in the first two decades of life and AML occurs more often than ALL during this period (Table 7). There is a peak frequency for all types of acute leukaemia in the 5-9 year age group. For childhood leukaemia, ALL has a peak occurrence in the first decade of life. Almost all cases of ALL are seen in the first three decades of life. The peak that is seen in the first decade is followed by a fairly uniform spread across childhood and it becomes a rare disease after the age of thirty. The youngest patient documented was 4 months old. The male to female ratio of 1.3:1 for ALL is uniform for all age groups. The male dominance is thus significantly less than is seen in AML. Acute myelogenous leukaemia increases in prevalence to a peak presentation in the second decade during which period the male to female ratio is 1:2 (Tables 8 and 7). However, males form a greater majority

Table 6: Age and sex distribution in all leukaemias correlated with KNH medical admissions and age frequency in the Kenyan population.

| Age in years | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Age unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 54 | 38 | 35 | 19 | 18 | 28 | 17 | 3 | 59 | 271 |
| F | 27 | 37 | 18 | 14 | 14 | 16 | 11 | 3 | 45 | 185 |
| Total | 81 | 75 | 53 | 33 | 32 | 44 | 28 | 6 | 104 | 456 |
| % of total of all types of leukaemia | 17.8 | 16.4 | 11.6 | 7.2 | 7.1 | 9.6 | 6.2 | 1.3 | 22.8 | 100 |
| % of total medical admissions | 14.6 | 16.3 | 16.0 | 10.7 | 6.2 | 8.0 | 4.8 | 1.8 | 21.6 | 100 |
| % of total Kenya population | 35.3 | 33.0 | 15.7 | 10.5 | 6.9 | 4.4 | 2.7 | 1.5 | - | 100 |

Table 7: Age distribution in acute leukaemias.

| Type of leukaemia | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Total |
|---|---|---|---|---|---|---|---|---|---|
| AML | 29 | 35 | 21 | 10 | 7 | 7 | 8 | 2 | 119 |
| ALL | 31 | 17 | 6 | - | 1 | 2 | 1 | - | 58 |
| AMoL | 4 | 3 | 2 | 1 | - | 1 | - | - | 11 |
| ALSCL | 11 | 6 | 1 | 1 | 1 | 1 | - | - | 21 |
| Total | 75 | 61 | 30 | 12 | 9 | 11 | 9 | 2 | 209 |
| % of total | 35.9 | 29.1 | 14.4 | 5.7 | 4.3 | 5.3 | 4.3 | 1.0 | 100 |

Table 8: Age and sex distribution in acute myelogenous leukaemia.

| Age | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 23 | 12 | 15 | 5 | 2 | 3 | 4 | 2 | 12 | 78 |
| F | 6 | 23 | 6 | 5 | 5 | 4 | 4 | 0 | 13 | 66 |
| Total | 29 | 35 | 21 | 10 | 7 | 7 | 8 | 2 | 25 | 144 |

Table 9: Age and sex distribution in acute lymphocytic leukaemia.

| Age | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 18 | 10 | 3 | - | - | - | 1 | - | 6 | 38 |
| F | 13 | 7 | 3 | - | 1 | 2 | - | - | 4 | 30 |
| Total | 31 | 17 | 6 | - | 1 | 2 | 1 | - | 10 | 68 |

Table 10: Age and sex distribution in acute monocytic leukaemia.

| Age | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 3 | 1 | 2 | - | - | - | - | - | - | 6 |
| F | 1 | 2 | - | 1 | - | 1 | - | - | 4 | 9 |
| Total | 4 | 3 | 2 | 1 | - | 1 | - | - | 4 | 15 |

Table 11: Age and sex distribution in acute lymphosarcoma cell leukaemia.

| Age | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 7 | 6 | - | 1 | 1 | 1 | - | - | 3 | 19 |
| F | 4 | - | 1 | - | - | - | - | - | 1 | 6 |
| Total | 11 | 6 | 1 | 1 | 1 | 1 | - | - | 4 | 25 |

(3.8:1) during the first decade. The male predominance (2.5:1) is again obvious in the third decade, but sex distribution evens out from the fourth decade onwards.

The figures for AMoL, ALSCL and AUL (Table 10 and 11) are too small for any accurate generalizations. Nevertheless, the majority of cases with AMoL and ALSCL were seen in the first two decades of life. There is a prominent sex bias (3.2:1) in ALSCL which has a maximum expression in the 5-9 years age group.

For childhood acute leukaemia, there is a male predominance of about 2:1, which is maintained in the 0-4 and 5-9 age groups (Fig. 4 and Table 12) and it disappears in the 10-14 age group where the ratio approaches 1:1, due to a progressive increase in the female cases. Whereas just over 50% of the AM-ML occurred below 15 years of age and a third of them in the first decade of life, only one case of the 16 AP-ML was seen in childhood and none in the first decade of life (Table 13). It had peak occurrence in the third decade. Most of the AM-ML occurring in children appeared between the ages of 5 and 14 years.

Chronic granulocytic leukaemia (Tables 14 and 15) shows a mild peak in the 25-35 years age group, inspite of a fairly even age scatter from 10 to 70 years. It is not uncommon in childhood as 7 % of the cases in this series presented before the 14th birthday (Table 16) and the youngest patient diagnosed was 11 months old. The average male to female ratio is 1.9:1, although the male predilection clearly emerges after the age of forty. The peak occurrence for CLL (Table 17) is between 40 and 70 years. The cases that were reported within the age group of 15-30 years were probably not classical CLL but they could have been either chronic prolymphocytic leukaemia or chronic lymphosarcoma cell leukaemia. No case of CLL was diagnosed below the age of 15, and the youngest patient was 17 years old. The male to female ratio was fairly uniform at 1.6:1 throughout all the age groups.

Table 12: Age and sex breakdown of all the leukaemias in childhood.

| Age | 0-4 | 5-9 | 10-14 | Total |
|---|---|---|---|---|
| M | 22 | 32 | 24 | 78 |
| F | 12 | 15 | 22 | 49 |
| Total | 34 | 47 | 46 | 127 |

Table 13: Age distribution of AM-ML and APML.

| Leukaemia | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | Total |
|---|---|---|---|---|---|---|---|
| AP-ML | 0 | 3 | 5 | 2 | 3 | 3 | 16 |
| AM-ML | 9 | 8 | 2 | 2 | 3 | 3 | 27 |

Table 14: Age and sex distribution in chronic granulocytic leukaemia.

| Age | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 2 | 7 | 13 | 11 | 8 | 13 | 5 | - | 26 | 85 |
| F | 2 | 5 | 7 | 7 | 3 | 3 | 2 | 2 | 14 | 45 |
| tal | 4 | 12 | 20 | 18 | 11 | 16 | 7 | 2 | 40 | 130 |

Table 15: Age distribution in chronic leukaemia.

| Age | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Total |
|---|---|---|---|---|---|---|---|---|---|
| CGL | 4 | 12 | 20 | 18 | 11 | 16 | 7 | 2 | 90 |
| CLL | - | 2 | 2 | 2 | 12 | 17 | 12 | 2 | 49 |
| Total | 4 | 14 | 22 | 20 | 23 | 33 | 19 | 4 | 139 |
| % of total | 2.9 | 10.1 | 15.8 | 14.4 | 16.5 | 23.7 | 13.7 | 2.9 | 100 |

Table 16: The distribution of various childhood leukaemias according to age and sex.

| Age | 0-4 | 5-9 | 10-14 | Total |
|---|---|---|---|---|
| AML | 9 | 20 | 23 | 52 |
| ALL | 16 | 15 | 12 | 43 |
| AMoL | 2 | 2 | 3 | 7 |
| ALSCL | 2 | 9 | 3 | 14 |
| AUL | 2 | - | - | 2 |
| CGL | 3 | 1 | 5 | 9 |
| CLL | - | - | - | - |
| Total | 34 | 47 | 46 | 127 |

Table 17: Age and sex distribution in chronic lymphocytic leukaemia.

| Age | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | Over 70 | Unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 0 | 2 | 2 | 1 | 7 | 11 | 7 | 1 | 12 | 43 |
| F | - | - | - | 1 | 5 | 6 | 5 | 1 | 9 | 27 |
| Total | 0 | 2 | 2 | 2 | 12 | 17 | 12 | 2 | 21 | 70 |

## Clinical manifestations at presentation (Fig. 5 and Tables 18-21).

### Fever.

Fifty percent of all the cases had fever at presentation, but it was generally more frequent and severe in acute leukaemia than in the chronic type. The common pattern was that of persistent fever. Eighty percent of the cases with fever had demonstrable infection.

### Pallor.

Pallor of the mucous membranes was recorded in 224 cases (86%) out of 262 in which it was looked for. Forty five percent had moderate to severe pallor. It was of greater severity in acute than chronic leukaemia, but much more marked in AML than ALL. Cases of AMoL, AM-ML and ALSCL tended to exhibit less pallor than acute myeloblastic or acute lymphocytic leukaemia (Table 19), which had 42% and 39% of moderate to severe pallor respectively. CLL, interestingly, had more than 70% of the cases with moderate to severe pallor.

### Haemorrhagic manifestations.

These varied from the consequential, such as bruises at puncture sites, to spontaneous petechiae, bruises, haematoma and persistent bleeding from orifices. Epistaxis (Fig. 6) was the most common form of bleeding from the mucous membranes followed by bleeding from the gums. Petechial haemorrhages were often widespread, although they appeared most frequently over the trunk. Bruises predominated at pressure areas. Intraocular and subconjunctival haemorrhages were seen in two cases each.

On the average, bleeding tendencies were recorded in approximately 40% (80 out of 212) of all the leukaemias but, as expected, they were more frequent in acute (Fig. 5) than

Table 18: Frequency of occurrence of certain clinical manifestations in leukaemia at presentation.

| | AML | ALL | AMoL | ALSCL | AUL | CGL | CLL | Mean of all leukaemias. |
|---|---|---|---|---|---|---|---|---|
| Fever | 0.63 | 0.53 | 0.60 | 0.33 | 0.50 | 0.38 | 0.25 | 0.49 |
| Pallor | 0.91 | 0.83 | 0.82 | 0.80 | 1.00 | 0.76 | 0.89 | 0.86 |
| Bleeding | 0.57 | 0.40 | 0.50 | 0.67 | 0.25 | 0.18 | 0.06 | 0.38 |
| Lymph node enlargement | 0.55 | 0.80 | 0.89 | 1.00 | 1.00 | 0.54 | 0.91 | 0.70 |
| Splenomegaly | 0.36 | 0.65 | 0.60 | 1.00 | 0.75 | 0.94 | 0.89 | 0.72 |
| Hepatomegaly | 0.59 | 0.69 | 0.63 | 0.83 | 0.50 | 0.76 | 0.69 | 0.68 |
| Bone pain | 0.41 | 0.42 | 0.00 | 1.00 | 0.50 | 0.26 | 0.18 | 0.34 |
| Wasting | 0.33 | 0.33 | 0.43 | 0.33 | 0.25 | 0.43 | 0.41 | 0.39 |

chronic leukaemia. AML had the highest number of cases presenting with bleeding and was most severe in acute promyelocytic leukaemia. Where coagulation studies were carried out, in the latter, features of disseminated intravascular coagulation were demonstrated.

Organomegaly.

On the average, 70% of all leukaemic cases had lymph node enlargement, splenomegaly or hepatomegaly (Table 18). ALSCL had the highest frequency of lymphadenopathy; this feature was present in all cases in which it was looked for. CLL and AMoL were the runners up with about 90% frequency of lymph node enlargement. Just over 50% of both AML and CGL presented with lymphadenopathy. Lymphadenopathy was often generalised, although cervical involvement was present in 65-70% of the cases. Mediastinal lymph node enlargement was recorded in 50% of the cases with ALL. Massive cervical, axillary and inguinal lymphadenopathy (Fig. 7) occurred in four cases of CGL; the enlargement was otherwise of mild to moderate degree in most cases. Rarely were the lymph nodes painful but they were always rubbery. Large mediastinal lymph node masses caused a superior vena caval syndrome in two cases of AMoL (Fig. 8) and one of CGL.

Splenomegaly occurred in over 70% of all the leukaemias (Table 20). It was least frequent in AML, 36%; it was present in 67% each of ALL and AMoL and in 94% and 89% of CGL and CLL respectively. It was recorded in all cases of ALSCL. Splenic enlargement was assessed as mild (0-5 cm), moderate (6-10 cm), marked (11-15 cm), and massive if it was more than 15 cm below the costal margin in the midclavicular line. About 72% of CGL and 45% of CLL cases presented with marked to massive enlargement of the spleen (Table 20). This, on occasion, raised the possibility of kala-azar as a diagnosis. Massive splenomegaly was also seen in three cases of AML, but the three cases of AUL with

Table 19: Pallor as a presenting feature in various leukaemias expressed according to severity as 0-4*.

| Type of leukaemia | Total number reported | Number of cases at various degrees of severity. | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 1+ | 2+ | 3+ | 4+ |
| AML | 88 | 8 | 43 | 14 | 14 | 9 |
| ALL | 49 | 8 | 22 | 13 | 5 | 1 |
| AMoL | 11 | 2 | 6 | 3 | 0 | 0 |
| ALSCL | 5 | 1 | 4 | 0 | 0 | 0 |
| AUL | 4 | 0 | 3 | 1 | 0 | 0 |
| CGL | 58 | 14 | 36 | 3 | 2 | 3 |
| CLL | 47 | 5 | 9 | 14 | 11 | 8 |
| Total | 262 | 38 | 123 | 48 | 32 | 21 |

* 0-No pallor; 1+ - Mild pallor; 2-3+ - Moderate pallor; 4+ - Marked pallor.

Table 20: Leukaemia cases with splenomegaly at presentation, expressed according to size.

| Type of leukaemia | Total number reported | Number at various sizes | | | | |
|---|---|---|---|---|---|---|
| | | 0 cm | 0-5 cm | 6-10 cm | 11-15 cm | 15+ |
| AML | 76 | 49 | 17 | 4 | 3 | 3 |
| ALL | 46 | 16 | 16 | 12 | 2 | 0 |
| AMoL | 10 | 4 | 5 | 1 | 0 | 0 |
| ALSCL | 10 | 0 | 8 | 1 | 1 | 0 |
| AUL | 4 | 1 | 3 | 0 | 0 | 0 |
| CGL | 86 | 5 | 8 | 15 | 23 | 35 |
| CLL | 47 | 5 | 9 | 14 | 11 | 8 |
| Total | 279 | 80 | 66 | 47 | 40 | 46 |

splenomegaly had only mild enlargement. The splenic consistency in chronic leukaemia and AMoL was firm whereas it was often soft in acute leukaemia.

Liver enlargement was a presenting feature in about 70% of the cases (Table 18). It was more frequent in ALSCL, CGL and CLL than in the other forms of leukaemia (Fig. 5). Although the enlarged liver was often of soft consistency in acute leukaemia, probably suggesting that it was consequent to congestive cardiac failure due to anaemia, it was firm in the majority of AMoL cases. This latter feature probably indicated neoplastic infiltration, and hence was of diagnostic significance clinically.

Infections.

There was an infection rate of 37% on initial presentation (Table 21). Respiratory infection accounted for 42% of all the infections, giving an incidence of 16% in the series. These varied from minor ear, nose and throat (ENT) infections, such as otitis media and pharyngitis, to pulmonary tuberculosis which complicated four cases of chronic granulocytic leukaemia. However, bronchopneumonia accounted for the majority. Acute and chronic lymphocytic leukaemia were complicated by 58% of the respiratory infections altogether and they were frequently recurrent in nature. Skin infections, accounting for 19.4%, were the next most frequent. They consisted of superficial fungal infections scabies, furunculosis, episodes of cellulitis, and staphylococcal skin abscesses. The most commonly documented type of infection in the 27 cases of gastrointestinal infection was oral candidiasis, followed by Vincent's angina and dental alveolitis. Salmonella typhimurium enteritis occurred in six cases. The majority of the cases with septicaemia (13 of 22) occurred in AML. Salmonellosis and gram-negative organisms accounted for most of these. Urinary tract infection

Table 21: Infection as a presenting feature in leukaemia.

| Type of leukaemia | Site of infection: Respiratory system | GIT* | Skin | Bones | UGT* | CNS* | Septicaemia | Site not given | Total |
|---|---|---|---|---|---|---|---|---|---|
| AML | 11 | 8 | 10 | 0 | 3 | 1 | 13 | 0 | 46 |
| ALL | 23 | 4 | 13 | 1 | 0 | 1 | 4 | 2 | 48 |
| AMoL | 4 | 2 | 0 | 1 | 0 | 0 | 3 | 0 | 10 |
| AUL | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| ALSCL | 3 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 7 |
| CGL | 10 | 5 | 4 | 3 | 3 | 0 | 2 | 0 | 27 |
| CLL | 18 | 5 | 5 | 1 | 0 | 0 | 0 | 1 | 30 |
| Total | 71 | 27 | 33 | 6 | 6 | 2 | 22 | 3 | 170 |

*GIT - Gastrointestinal tract; UGT - Urogenital tract;
CNS - Central nervous system.

osteomyelitis and meningitis were reported in 14 cases. Crippling disseminated Salmonella typhimurium osteomyelitis was seen in one case of ALL (Fig. 9).

Other clinical features.

Bone pain was recorded in 34% of the cases (Table 18). It was a significant finding in some cases of AML and ALL in which the main presenting symptom was either bone pain or severe arthritis, with anaemia as an incidental finding. A few cases had typical features of rheumatic arthritis which were migratory and severe enough to limit ambulation. The severity of bone pain correlated with the skeletal radiological changes which were present in about 50% of the cases. These varied from periosteal infiltration to marked osteolytic changes (Fig. 10). Wasting appeared to reflect the chronicity of the disease and it was prominent in chronic leukaemia and a few cases of AM-ML.

Chloromatous tumours (granulosarcoma) were documented in 14 cases of acute myeloblastic and myelomonocytic leukaemia altogether and in two of chronic granulocytic leukaemia. This gives a frequency of 10% of chloroma in acute myelogenous leukaemia. Thirteen were orbital tumours and commonly presented with asymmetrical bilateral ocular proptosis (Fig.11a and b); four of them had corneal destruction, due to exposure xerosis, with attendant blindness. Only one case occurred in an adult, a female aged 25 years; the rest were in childhood, giving a frequency of 23% of chloromatous tumours in children with AML. Four of these cases presented variously to ophthalmology, neurosurgery and ENT units where two were diagnosed as Burkitt's lymphoma, one as intracranial hydatidosis and the other as recurrent retinoblastoma, previously enucleated. Two of the cases had no leukaemic picture at presentation.

Neurological deficits such as cranial nerve palsies and paraparesis, being complications of cerebromeningeal infiltration, were not uncommon in variants of AML, particularly AM-ML, at presentation. These features only occurred in

ALL or ALSCL after remission induction. Sudden blindness and partial loss of vision due to optic atrophy and intraocular haemorrhage, respectively, were among the presenting features in two cases of chronic granulocytic leukaemia (Fig. 12). One of them had typical Roath's spots.

Occasional cases of AM-ML and AMoL presented with gum hypertrophy (Fig. 13), non-specific abdominal pain and tenderness, periorbital oedema, muscle infiltration, non-specific dermatoses and the superior vena caval syndrome. Another notable symptom was jaundice. Skin infiltration was seen in two cases of ALL and one of CLL. Patients suffering from acute myeloblastic leukaemia and ALL were frequently robust and had non-specific complaints related to anaemia at presentation.

Four female patients had leukaemia in pregnancy: one acute undifferentiated, one acute myeloblastic and two chronic granulocytic. One of them has been fully documented (85). For the two CGL cases, the diagnosis was made in the post-partum period because the patients suffered postpartum haemorrhage. One of the cases also developed a malignant lymphoma, poorly differentiated, six months after the diagnosis of CGL. She died three months after the clinical onset of the lymphoma.

## Initial haematological findings.

### Haemoglobin levels.

Anaemia was documented in 89% of acute leukaemia but it was present in only 50% of chronic leukaemia at diagnosis. There was a significantly higher incidence of severe anaemia in AML than ALL at presentation. Whereas 82% of AML had severe anaemia (Hb below 8 g/dl), this occurred in 70% of ALL (Table 22 and Fig. 14 A). This might be a reflection of the speculated erythroid stem cell inhibition defect in AML (96) and a probably direct marrow infiltration in ALL. The other subspecies of acute leukaemia also often presented with severe anaemia. It was of greater severity in chronic

Table 22: Haemoglobin levels in 325 leukaemia cases at presentation.

g/dl

| Type of leukaemia | Below 5 | 5-8 | 8-10 | Over 10 | Total |
|---|---|---|---|---|---|
| AML | 45 | 48 | 12 | 8 | 113 |
| ALL | 16 | 19 | 8 | 7 | 50 |
| AUL | 2 | 2 | 0 | 0 | 4 |
| AMoL | 5 | 5 | 3 | 0 | 13 |
| ALSCL | 2 | 6 | 1 | 4 | 13 |
| CGL | 3 | 14 | 24 | 42 | 83 |
| CLL | 7 | 8 | 10 | 24 | 49 |
| Total | 80 | 102 | 58 | 85 | 325 |

Table 23: Total white blood cell counts in acute leukaemia at presentation.

Counts x $10^9$ / l

| Type of leukaemia | Below 4 | 4-10 | 10-30 | 30-50 | 50-100 | Over 100 | Tota |
|---|---|---|---|---|---|---|---|
| AML | 22 | 20 | 31 | 15 | 17 | 13 | 118 |
| ALL | 8 | 11 | 14 | 6 | 10 | 8 | 57 |
| ALSCL | 2 | 2 | 4 | 1 | 2 | 3 | 14 |
| AUL | 0 | 1 | 0 | 0 | 0 | 3 | 4 |
| AMoL | 0 | 5 | 1 | 1 | 3 | 2 | 12 |
| Total | 32 | 39 | 50 | 23 | 32 | 29 | 205 |

lymphocytic leukaemia than chronic granulocytic leukaemia, as 14% of CLL presented with Hb level below 5 g/dl, whereas only 4% CGL cases had Hb level below this limit (Table 22 and Fig. 15 A). Twenty percent of CGL and 30% of CLL had Hb levels below 8 g/dl respectively. This finding correlates closely with the frequency of pallor (Table 19).

Total white cell counts.

Whereas 42% of AMoL were subleukaemic (WBC counts less than $10x10^9/1$), 28.6% ALSCL were subleukaemic (Table 23), but 3 of 4 of AUL cases had a total white cell count above $100x10^9/1$. AML and ALL had 30-35% of the cases with either aleukaemic or subleukaemic pictures (Table 23 and Fig. 14B); the distribution between aleukaemic and subleukaemic cases was the same in both instances. Whereas only 21% of CGL, presented with a total WBC count of less than $100x10^9/1$, 65% of CLL cases had total WBC counts of $50-100x10^9/1$ (Table 24 and Fig. 15B). The majority of CGL cases (60%) had WBC counts within the range of $100-500x10^9/1$, and 18% had counts above $500x10^9/1$. Three cases had counts of over $1000x10^9/1$. Only 5% of CLL cases had counts above $500x10^9/1$. None of the chronic forms had aleukaemic or subleukaemic pictures.

Platelet counts.

The prevalence of thrombocytopenia (platelet counts less than $100x10^9/1$) was 81% in AML, but only 64% in ALL (Table 25 and Fig. 14C). In other words, 36% of ALL and only 19% of AML cases were not thrombocytopenic at presentation. Sixty three percent and 55% of AML and ALL, respectively, were severely thrombocytopenic with platelet counts of less than $50x10^9/1$. The implications of these findings are discussed below. The majority of the patients with AMoL and ALSCL in whom platelet counts were performed were thrombocytopenic and all cases of AUL had platelet counts less than $20x10^9/1$.

Table 24: Total white blood cell counts in chronic leukaemia at presentation.

| Type of leukaemia | Counts x $10^9$ / 1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | Below 10 | 10-50 | 50-100 | 100-200 | 200-500 | Over 500 | Total |
| CGL | 0 | 10 | 11 | 32 | 29 | 19 | 101 |
| CLL | 0 | 26 | 17 | 5 | 8 | 3 | 59 |
| Total | 0 | 36 | 28 | 37 | 37 | 22 | 160 |

Table 25: Platelet counts in 231 leukaemia cases at presentation.

| Type of leukaemia | Counts x $10^9$ / 1 | | | | |
|---|---|---|---|---|---|
| | Below 20 | 20-50 | 50-100 | Over 100 | Total |
| AML | 29 | 24 | 15 | 16 | 84 |
| ALL | 18 | 5 | 4 | 15 | 42 |
| AMoL | 2 | 2 | 3 | 2 | 9 |
| ALSCL | 4 | 4 | 0 | 2 | 10 |
| AUL | 4 | 0 | 0 | 0 | 4 |
| CGL | 0 | 2 | 3 | 40 | 45 |
| CLL | 4 | 5 | 7 | 21 | 37 |
| Total | 61 | 42 | 32 | 96 | 231 |

Forty three percent of CLL cases had thrombocytopenia; 24% of them had severe thrombocytopenia with counts below $50x10^9/1$ (Table 25 and Fig. 15C). Only 10% of CGL cases presented with thrombocytopenia; 4% had platelet counts below $50x10^9/1$ and none had a platelet count below $20x10^9/1$. Thus about 90% of CGL cases had normal or increased platelet counts.

Differential white cell counts.

Most cases in the study had no differential white cell counts; i.e. 81% of ALSCL, 71% of AML, 59% of ALL and 51% of CLL had no differential counts. This is a probable indication of lack of confidence by the observers who made the initial diagnosis in performing differential counts on abnormal films. However, differential counts in CGL, particularly when the counts are markedly raised, are time consuming and often inaccurate. The differential counts in ALL are also often inaccurate because the blast cells are often mistaken for lymphocytes and therefore counted as such. This could be the reason for only 35% of acute lymphocytic leukaemia cases having been recorded as having a differential blast count of more than 20% (Table 26B) and 60% of them as having a lymphocyte count of over 50%. In 79 cases of AML (Table 26A), 89% had over 20% blasts, 53% over 50% and 47% had a neutrophil count of less than 20%. Out of 45 cases of CLL, 44 had lymphocyte counts of more than 50% (Table 26F) and 21 cases had neutrophil counts of less than 20%. Blood films of most of the cases of chronic granulocytic leukaemia were reported as having "cells at all shades of maturation from blast cells to mature forms, with a preponderance of myelocytes (Fig. 16).

Cytological and cytochemical features.

The cytological features applied in the differential diagnosis of various acute leukaemias are illustrated in Table 4.

able 26 (A-F): Differential counts.

. Acute myelogenous leukaemia.

| Cell type % | 0-20 | 21-50 | 51-100 |
|---|---|---|---|
| Neutrophils | 37 | 7 | 3 |
| Lymphocytes | 24 | 6 | 12 |
| Monocytes | 15 | 9 | 2 |
| Blasts | 9 | 28 | 42 |

B. Acute lymphocytic leukaemia.

| Cell type % | 0-20 | 21-50 | 51-100 |
|---|---|---|---|
| Neutrophils | 25 | 10 | 3 |
| Lymphocytes | 5 | 11 | 23 |
| Blasts | 10 | 8 | 9 |
| Eosinophils | 8 | 0 | 0 |

C. Acute monocytic leukaemia.

| Cell type % | 0-20 | 21-50 | 51-10 |
|---|---|---|---|
| Neutrophils | 4 | 0 | 0 |
| Lymphocytes | 3 | 0 | 0 |
| Monocytes | 2 | 0 | 3 |
| Blasts | 2 | 2 | 3 |

. Acute lymphosarcoma cell leukaemia.

| Cell type % | 0-20 | 21-50 | 51-100 |
|---|---|---|---|
| Neutrophils | 3 | 1 | 0 |
| Lymphocytes | 0 | 1 | 2 |
| Blasts | 2 | 3 | 2 |

E. Acute undifferentiated leukaemia.

| Cell type % | 0-20 | 21-50 | 51-100 |
|---|---|---|---|
| Neutrophils | 0 | 1 | 1 |
| Lymphocytes | 1 | 1 | 0 |
| Blasts | 1 | 0 | 2 |

F. Chronic lymphocytic leukaemia.

| Cell type % | 0-20 | 21-50 | 51-1 |
|---|---|---|---|
| Neutrophils | 21 | 2 | 0 |
| Lymphocytes | 1 | 0 | 44 |

Acute myeloblastic leukaemia exhibits pleomorphic cellular features, but acute lymphoblastic tends to be monomorphic (Fig. 17A and B). Microblastic variants were not uncommon. Cases of AM-ML exhibited the most pleomorphic and polymorphic cytological features which also varied from case to case. A variable blending of monocytoid and myeloid appearances was however always present. Dysmyelopoietic changes resulting into bizarre nuclear shapes and nuclear fragments were commonly seen, in both AM-ML and acute promyelocytic leukaemia (APML). Reider forms were as common in ALL as AML, but Auer rods occurred in about 20% of non-lymphocytic acute leukaemia (ANLL) and most abundantly in APML (Fig. 17C). There are remarkable cytological similarities between AM-ML and APML with regard to the presence of myelomonocytoid cells. Acute undifferentiated leukaemia showed no features of differentiatic towards either the myeloid or lymphoid lines. The peripheral blood picture of one of the cases consisted of large, multinucleated cells with copious vacuolated cytoplasm, rather reminiscent of the appearances seen in malignant histiocytosis (Fig. 17D). The appearances of cells in ALSCL span those mature lymphocytes and the primitive cells of ALL. The lymphosarcoma cells vary in size and shape from small, through medium sized mononuclear cells, to large irregular malignant cells that have characteristically folded nuclei with coarse reticular chromatin pattern with one or two prominent nucleoli and moderately copious or sparse dark bluish cytoplasm (Fig. 17E). Smear cells are a striking feature.

Chronic lymphocytic leukaemia was almost always of the small celled type (Fig. 17F) although, occasionally, large celled variants having abundant cytoplasm were encountered. The presence of basket cells is a constant feature. One case of CLL followed up for years converted into a typical picture of CGL (Case 1, appendix III). Most of the CGL cases exhibited a leucoerythroblastic picture and a few of them had circulating megakaryoblasts.

The bone marrow invariably showed total replacement by the leukaemic process in all cases. It was hypercellular in all bu three cases of ALL (see case 6 appendix III) and one of AM-ML which presented with hypoplastic features. More than 50% of

AML, AM-ML and AMoL cases showed megaloblastoid features in the residual erythroid activity. Although this was minimal, the two cases of erythroleukaemia had florid megaloblastic changes. Reticulum cell hyperplasia and increased plasma cell population were frequent in AM-ML and AMoL. Vacuolation of leukaemic cells was an invariable feature in Burkitt's cell leukaemia and was seen in two other cases of acute leukaemia. At presentation, megakaryocytes were often normal or increased in numbers in AM-ML and CGL respectively. They were markedly reduced or, less often, absent in the other forms of leukaemia.

Cytochemical characteristics in 72 cases of acute leukaemia showed definite patterns (Table 27). There was strong Sudan Black positivity in the majority of acute myeloblastic and promyelocytic leukaemias; only two myeloblastics were negative. On the other hand only two acute myeloblastic cases were weakly positive for PAS and the rest were negative. However, APML showed weakly to strongly positive PAS patterns. All ANLL, apart from two cases each of AML, AM-ML and AMoL, were either moderately or strongly positive for Sudan Black. Only a few were strongly positive. AM-ML cases exhibited a twin population of strongly staining myeloblasts and poorly or negative staining monoblasts (Fig. 18A). Similarly AMoL cases, except one, were weakly to moderately PAS positive. All cases of ALL and ALSCL were negative for Sudan Black staining, and all except three (ALL-1; ALSCL-2) showed variable PAS positivity (weak to moderate). Feulgen staining revealed distinct features among acute leukaemias. AML and AM-ML exhibited 2 to 3 medium-sized pale grey to brown nucleoli in most blast cells and most of AMoL blasts had one to two large pale grey nucleoli. All cases of ALL had one to two small, dusty grey, indistinct nucleoli with prominent perinucleolar rim. Most of the ALSCL cells contained one to two nucleoli which were distinct, dusty grey but variable in size from small to large (Fig. 18B).

The leucocyte alkaline phosphatase (LAP) was done in 30 cases of chronic granulocytic leukaemia. The results showed the following pattern of activity:- score 0 (9 cases); score 1-10 (11 cases); score - over 10 (10 cases). There were 4 cases with

Table 27: Cytochemical characteristics in 72 cases of acute leukaemia.

| Type of leukaemia and number of cases ( ) | Stains used: Sudan Black (*Positivity) | | | | PAS (*Positivity) | | | | Feulgen (Number of nucleoli) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | 1-2 | 2-3 | 3+ |
| AML (18) | 2 | 2 | 5 | 9 | 16 | 2 | 0 | 0 | 1 | 11 | 0 |
| AP-ML (6) | 0 | 0 | 1 | 5 | 0 | 2 | 2 | 1 | 1 | 1 | 0 |
| AM-ML (17) | 0 | 2 | 12 | 3 | 1 | 7 | 9 | 0 | 1 | 9 | 2 |
| AMoL (5) | 2 | 0 | 2 | 1 | 0 | 3 | 2 | 0 | 1 | 3 | 0 |
| ALL (17) | 17 | 0 | 0 | 0 | 1 | 4 | 12 | 0 | 8 | 0 | 1 |
| ALSCL (9) | 9 | 0 | 0 | 0 | 2 | 4 | 3 | 0 | 9 | 0 | 0 |

* Degree of positivity.

0 - Negative.

1 - Weakly positive (± to +)

2 - Moderately positive (++ to +++)

3 - Strongly positive (++++ to +++++)

LAP of over 20; 2 of them were after therapy and had scores of 40 and 70 respectively.

## Results of other investigations.

### Biochemical:

Serum electrolytes and blood urea, determined on initial presentation, were normal in all cases. Uric acid was however elevated in some cases of CGL, CLL and cases of acute leukaemia with markedly raised leucocyte counts. The highest recorded was 9 mg/100 ml in a case of CGL. No cases of secondary gout were recorded. Liver function tests were normal in all cases prior to treatment.

### Radiological:

Chest x-rays showed mediastinal and hilar lymphadenopathy in all cases of ALSCL; all cases of AM-ML, AMoL or CGL which exhibited features of the superior vena caval syndrome; 50% of ALL and in all cases of CGL which had massive generalised lymphadenopathy.

### Cytogenetics:

The few cases of CGL in which the Philadelphia chromosome studies were done showed the acrocentric G22 chromosome in all except one. This exception was a case of juvenile chronic granulocytic leukaemia in an 11-month-old-infant.

## Treatment results.

Only 146 (32.0%) out of 456 cases collected are known to have received any form of therapy and most of them were treated during the 1974-1977 period. Fifty percent of the ALL were treated but only 25.7% of AML and a third of the chronic leukaemias respectively underwent treatment (Table 28 and Fig. 19).

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Table 28: Number of leukaemia cases that received treatment.

| Type of leukaemia | Total | Number treated | Percent |
|---|---|---|---|
| AML | 144 | 37 | 25.7 |
| ALL | 68 | 34 | 50.0 |
| AMoL | 15 | 2 | 13.3 |
| ALSCL | 25 | 6 | 24.0 |
| AUL | 4 | 2 | 50.0 |
| CGL | 130 | 41 | 31.5 |
| CLL | 70 | 24 | 34.3 |
| Total | 456 | 146 | 32.0 |

Table 29: Treatment results in 146 cases.

| Type of leukaemia | Number treated | Complete remission | Partial remission | No response | Not evaluable |
|---|---|---|---|---|---|
| AML | 37 | 12 | 8 | 14 | 3 |
| ALL | 34 | 23 | 6 | 2 | 3 |
| AMoL | 2 | 0 | 0 | 1 | 1 |
| ALSCL | 6 | 2 | 3 | 1 | 0 |
| AUL | 2 | 0 | 1 | 0 | 1 |
| CGL | 41 | 9 | 27 | 2 | 3 |
| CLL | 24 | 0 | 17 | 4 | 3 |
| Total | 146 | 46 | 62 | 24 | 14 |

For all cases that were treated (Table 29 and Fig. 19), complete remission was achieved in 27.4% and partial response in 46.6%, giving a total response rate of 74.0%. There was a failure rate of 16.0%. Ten percent of the cases were not evaluable because the treatment given was inadequate. The good partial response results falsely inflate the success rate which was, mainly realised in chronic leukaemia. Thus, 49.3% of acute leukaemia patients attained complete and only 19.7% partial remission respectively, giving an overall response rate of 69%. However, 67.6% of ALL and only 32.4% of AML attained complete remission. There was a remission induction failure rate of 38% in AML and only 6% in ALL. This gives a total response rate of 85% and 54% for ALL and AML respectively. None of the patients with AMoL and AUL went into complete remission, although one of AUL had a partial response. Only 2 out of 6 patients having ALSCL went into complete remission. Chronic granulocytic leukaemia, on the average, gave better results than CLL (Table 29), indicating that the latter was a more difficult disease to deal with.

The patients who achieved complete remission, generally, enjoyed a fairly good quality life before relapse. Retrospective records on patient survival are extremely inadequate, and in only 128 patients was there any indication of survival period (Table 30 and Fig. 20). Whereas 63% of AML patients were dead within the first month after diagnosis and almost all within 12 months, only 32% of ALL patients died within one month and 37% survived for more than 12 months. Analysis of paediatric cases seen from 1975-78 (Fig. 21) revealed that 35-40% of AML patients die within one month of diagnosis and those who achieve remission have a median survival of 8 months. Similarly, 10% of ALL and 20% of ALSCL die within one month with a median survival of 15 and 9 months respectively for those who attain remission. The longest surviving patient with ALL (APLL) had lived more than 40 months after

Table 30: Duration of survival from diagnosis to death in 128 cases.

| Type of leukaemia | Total number | Period of survival in months: Less than 1 | 1-3 | 3-6 | 6-12 | 12-24 | 24-60 | Over 60 |
|---|---|---|---|---|---|---|---|---|
| AML | 32 | 20 | 4 | 3 | 4 | 1 | - | - |
| ALL | 19 | 6 | 1 | 2 | 3 | 3 | 4 | - |
| AMoL | 3 | 2 | 1 | - | - | - | - | - |
| ALSCL | 6 | 1 | 1 | - | 4 | - | - | - |
| AUL | 4 | 2 | 1 | 1 | - | - | - | - |
| CGL | 43 | 3 | 2 | 3 | 9 | 6 | 11 | 9 |
| CLL | 21 | 1 | 1 | 1 | 1 | 4 | 10 | 3 |
| Total | 128 | 35 | 11 | 10 | 21 | 14 | 25 | 12 |

diagnosis at the time of data analysis. Acute monocytic leukaemia exhibits the worst survival time as most of the patients were dead within the first month of diagnosis. Chronic leukaemia patients show the most favourable survival as 19% of them, both CGL and CLL, are still alive and 60 months and only 33% were dead within 12 months. However, most of those dying within the first year are CGL, although the longest CGL survival died after 8 years of follow up.

Clinical course and behaviour of the various types of leukaemia.

The clinical course of the disease appeared to be influenced by a number of factors: the nature of leukaemia, i.e. whether acute or chronic; leukaemia type; nature of treatment; response to treatment; complications of the disease and therapy, such as infections and bleeding, and initial patient disability.

Acute leukaemia.

Acute leukaemia, and in particular acute myeloblastic, acute promyelocytic, acute monocytic and acute undifferentiated types, tended to take an aggressive course, killing the patients within a short time after diagnosis. Prompt commencement of treatment, in the acute non-lymphocytic leukaemias, only altered the course of the disease in a small proportion of patients, some of whom responded to therapy and attained remission. The majority of the patients got to hospital with a Karnofsky performance status (Table 31) of less than 40% (97). Patients with AM-ML often presented with significant wasting and some disability, which indicated a protracted or subacute course of the disease. APML, on the other hand, pursued a decisively short course, attended by severe haemorrhagic complications. Acute lymphocytic leukaemia appeared to steer an elusively benign but relentless course, attended by recurrent anaemia (case 6, appendix III). Respiratory infections took the toll in both AML and ALL.

Table 31: Karnofsky performance status.

| Criteria | % | Status of patient. |
|---|---|---|
| Able to carry on normal activity; no special care is needed. | 100 | Normal; no complaints; no evidence of disease. |
| | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| | 80 | Normal activity with effort; some signs or symptoms of disease. |
| Unable to work; able to live at home; cares for most personal needs; a varying amount of assistance is needed. | 70 | Cares for self; unable to carry on normal activity or to do active work. |
| | 60 | Requires occasional assistance but is able to care for most of his needs. |
| | 50 | Requires considerable assistance and frequent medical care. |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | 40 | Disabled; requires special medical care and assistance. |
| | 30 | Severely disabled; hospitalization is is indicated, although death not imminent. |
| | 20 | Very sick; hospitalization necessary; active supportive treatment necessary. |
| | 10 | Moribund; fatal processes progressing rapidly. |
| | 0 | Dead. |

Remission induction took an average of 6-8 weeks in ALL but 8-12 weeks or occasionally longer in the acute non-lymphocytic leukaemias. This period is critical because AML cases must pass through an aplastic phase, which was sometimes very prolonged, before remission was achieved. It was during this period that ALL patients went through a severe thrombocytopenic and leucopenic phase. Features of remission in the acute lymphocytic leukaemia included regression of organomegaly, and disappearance of pallor. If the platelet counts were within normal limits, they precipitously dropped by the second week of remission induction therapy. Modest polychromasia and normoblastaemia, indicating bone marrow regeneration, was superseded by increase in haemoglobin levels and decrease in transfusion requirements. A gradual rise in peripheral leucocyte counts due to a neutrophil response or due to eosinophilia in 10-20% of the cases followed. A platelet response came as the last parameter to improve during the 6th week of induction. Successful remission induction in AML and AM-ML was always heralded by thrombocytosis, which sometimes exceeded 600 x $10^9$/l, in the presence of a reticulocytopenia, during the second or third course of treatment. This was followed by a haemoglobin rise and finally, a neutrophil response. Persistence of thrombocytopenia and blast cells after the third course of induction therapy augured failure of remission induction. The haemoglobin of such patients rapidly dropped in spite of transfusion. Bone marrows done at the end of remission induction period showed hyperplasia and a prolific normoblastic response in ALL, but hypoplasia and increased reticulum cell and megakaryocyte activity in AML and AM-ML.

Relapses were clinically preceded by general ill-health and an increased rate of infections. Cytological stigmata of early relapse included isolated or multiple cytopenias, leucoerythroblastic response in ALL or ALSCL and pseudo-pelger forms in AML. Two cases, one of ALL and the other of ALSCL, exhibited features of florid microangiopathic haemolytic anaemia with severe red cell fragmentation before blast cells

were noticed in the peripheral blood film. Cytology of the relapsed acute leukaemia was characterized by the emergence of more primitive lymphoblasts (prolymphoblasts or macro-lymphoblasts) in ALL and an apparent shift of AML to AM-ML in the non-ALL types. On the average, relapse in acute lymphocytic leukaemia occurred after 12 months but it was manifest within 12 months in the acute non-lymphocytic types. Acute non-lymphocytic types were noticed to be universally resistant to reinduction therapy and killed the patient within a few weeks. However, about 50% of ALL were successfully reinduced. The rest responded partially or failed, but they nevertheless followed a less aggressive course than the non-ALL forms.

Post radiation somnolence was seen in 75% of ALL cases that received CNS radiation for prophylaxis against meningeal leukaemia, and it was very severe in four patients who had received intrathecal methotrexate at the same time. Progressive neuropathy and paresis, being due to cerebro-meningeal infiltration, were common terminal features of ALSCL and AM-ML. Two cases of ALL (case 6, appendix III) suffered acute blindness due to acute optic atrophy consequent on meningeal leukaemia while they were in haematological remission.

Chronic leukaemia:

The majority of chronic leukaemics presented with a Karnofsky performance status of about 60% (Table 31). Those cases of CGL which were in the accelerated phase at presentation died within weeks after admission, in spite of therapy. Most of those in the chronic phase at presentation responded to busulphan, some of them less satisfactorily than others. 6-mercaptopurine was occasionally used in cases that showed evidence of slow response to busulphan or in those having total white cell counts of more than $500 \times 10^9/1$. Response to therapy was accompanied by clinical regression of the spleen within 3-6 weeks. Total white cell counts dropped to less than $20 \times 10^9/1$ within four weeks. At this time the peripheral blood film showed thrombocytosis and increased polychromasia with a rise in haemoglobin level, if it was

initially low. Residual stigmata of the disease included vacuolated neutrophils which showed either poor or toxic granulation with odd looking hypersgmented neutrophils; pathological myelocytes or metamyelocytes; presence of normoblasts, monocytosis, basophilia or eosinophilia. Bone marrow examination often showed granulocytic hyperplasia.

Patients with chronic leukaemia generally enjoyed good quality life and often followed their professions normally while in remission. CGL patients maintained on busulphan developed skin hyperpigmentation, particularly of the flanks; but also of the palms, soles and oral mucosa, giving an Addison-like picture. These patients frequently suffered a troublesome, non-productive and irritative chronic cough. One case had chronic diarrhoea. Clinical changes that preceded acute transformation comprised the reappearance of splenomegaly; bleeding into the soft tissues in the presence of a normal or raised platelet count; rapid enlargement of the lymph nodes (case 5, appendix III), development of extramedullary granulosarcoma (muscular and CNS); and bone pain due to osteolytic bone involvement. These changes were followed by either rapidly mounting total white cell counts, in spite of treatment, appearance of blast cells in peripheral blood, pancytopenia or rarely a monocytosis, basophilia or eosinophilia. One case converted into thrombocythaemia with erythroblastosis terminally and the other developed a picture similar to polycythaemia rubra vera (case 5 appendix III): Pancytopenia in the course of CGL occasionally created problems in determining whether it was due to busulphan toxicity or impending acute transformation. Once an acute transformation was established, the patients died within 6-12 weeks, during which period their clinical condition deteriorated extremely rapidly.

Most of the patients with chronic lymphocytic leukaemia presented in stage III and IV (98) of the disease (Table 32). Their disease was often in a terminal state with complications of haemolytic anaemia, severe chest infections and bleeding tendencies. Although the course could have been previously insidious, rapid progression after admission to hospital was notable and it was accompanied by an acute transformation-like picture. Four cases are recorded to have had

Table 32: Clinical staging of chronic lymphocytic leukaemia (98).

| Staging | Features |
|---|---|
| 0 | Bone marrow and peripheral blood - lymphocytosis. |
| I | Lymphocytosis + enlarged nodes. |
| II | Lymphocytosis + splenomegaly ± hepatomegaly. |
| III | Lymphocytosis + anaemia. |
| IV | Lymphocytosis + thrombocytopenia. |

exfoliative dermatitis and two, herpes zoster. All the patients who had treatment attained partial remission only. Thus, the majority of CLL cases encountered were in the terminal stages and patients gave histories of long duration, mainly of fatiguability and ill-health, recurrent pulmonary infections or, rarely, easy bruising.

Complicating infections during therapy.

Disseminated deep mycoses were not documented in any of the cases. However, the incidence of bacterial infections during the induction period closely correlated with the degree of neutropenia, as has been shown by other workers (99). Respiratory infections accounted for over 70% of the causes of pyrexia, and either streptococcal or pneumococcal organisms were the most commonly isolated. Such infections were easily controlled by a combination of intravenous gentamicin and crystalline penicillin (appendix II, 3). Gram-negative septicaemia due to coliforms was commonly reported. Where a combination of gentamicin with penicillin was ineffective, as in Bacterioides septicaemia, clindamycin (Dalacin C, Upjohn International Ltd.) was very efficacious. In most cases, temperature settled within 24 hours of starting clindamycin. This experience was obviously noticeable in 8 cases of acute leukaemia that had failed to respond to first line antibiotic therapy. Salmonella septicaemia was recorded in one case of ALL, one of ALSCL and four of AM-ML. Two of the cases responded to chloramphenicol only. One patient who had AM-ML died from Acenitobacter septicaemia.

Viral infections documented during remission included chickenpox, measles, viral hepatitis B and herpes zoster. The severity of chickenpox and measles was significantly modified by the administration of immunoglobulins (appendix II, 4). Severe herpes zoster (Fig. 22) occurred in three children who were in remission from ALL and a milder form in five other patients.

Dermatophytes and generalized scabies in children with ALL or AML were often a nuisance and complicated over 50% of the cases. Lesions of tinea corporis cum capitis due to Microsporum were by far the most common fungal infections. Ulcerative and haemorrhagic oral candidiasis, mimicking methotrexate lesions, (Fig. 23) was not an uncommon complication during reinduction.

Complications of cytotoxic agents.

Drug intolerance and direct toxicity was notable by its rarity because vomiting and myelosuppression were recorded in a very small proportion of patients. Methotrexate intolerance and dermatoses were seen in three cases and one case, in children, respectively; cyclophosphamide haemorrhagic cystitis occurred in one case. Fatal myelosuppression was not encountered. This was so in spite of large doses of cytotoxic drugs being used, as has been reported before (81, 100). Nevertheless, alopecia was almost universal during the remission induction and cytoreduction phases of acute leukaemia. Regrowing hair appeared brittle and silky. Vincristine neuropathy was suspected but not established in two children.

Macrocytosis was common during therapy with S-active, phase specific, drugs such as cytosine arabinoside, but overt megaloblastosis was seen in only 15-20% of cases of acute leukaemia. Red cell fragmentation and features of micro-angiopathic haemolytic anaemia were often observed during remission induction. Reactive lymphocytes and atypical mononuclear cells were occasionally seen at the start of maintenance therapy. This feature often raised suspicion of relapse.

Organ failure such as due to drug hepatoxicity or cardiotoxicity and methotrexate neurotoxicity was not documented.

Autopsy findings.

Autopsies were done on 76 cases of confirmed leukaemia admitted to KNH in the period of 1971 to 1977. Of these, 43 were males and 33 females, giving a male to female ratio of 1.3:1, which was in keeping with the general sex distribution of leukaemic patients. This sex differential was however absent in children. There were more children going to autopsy than adults, as 40% of the leukaemia autopsies were in children. Although this compares well with 39.6% of Owor and Madda (101), only 28% of all the cases of leukaemia in the study occurred in children. This probably indicated that children with leukaemia suffered a higher mortality than adults. This is not surprising because childhood acute leukaemia accounted for 48% of all acute leukaemias in the series. Thus, more children than

adults died of leukaemia, mainly acute. This fact is manifestly clear when it is realised that cases of chronic leukaemia comprised 44% of all the leukaemias. This implies that either too few chronic leukaemia patients were autopsied or chronic leukaemias accounted for relatively much less mortality than acute leukaemia in this series. The latter is the most likely explanation as the duration of survival was generally longer and better in chronic than acute leukaemia (Table 29 and 30).

It seemed as if a relatively large number of acute lymphocytic leukaemia cases was autopsied in comparison with the rest of the leukaemia types (Table 33). Although this finding appears to be at variance with experience elsewhere (101), it suggests three factors: that children are likely to be more easily autopsied than adults as the majority of ALL occurred in children (Table 9); patients having other leukaemia types are most likely to die at home, or patients with ALL live longer and are more likely to die in hospital while under follow up. All these factors probably played some role if the chronic leukaemics are excluded.

General necropsy appearances.

All cases of acute leukaemia, unless they were in remission, showed profound pallor of all the viscera and serosal surfaces. This was less marked in the chronic leukaemics, who instead were often characterized by enlargement of the spleen, liver and lymph nodes. Para-aortic, paratracheal and mesenteric nodes were often most markedly enlarged, not only in chronic lymphocytic leukaemia, but also in some acute monocytic, acute myelomonocytic and terminal cases of chronic granulocytic leukaemia; three of the latter had massive lymph nodes. All the enlarged organs exhibited marked leukaemic infiltrate at histology. Lymphoreticular organ infiltration in acute monocytic leukaemia was reminiscent of histiocytic medullary reticulosis and not histiocytic lymphoma. Generalized nodular infiltration and ulceration of the colon was seen in four cases of acute myelomonocytic leukaemia. Generalized petechiae were present in all cases of acute leukaemia, but they were most notable in acute promyelocytic leukaemia. Rarely was it a feature in the chronic leukaemias. Pulmonary oedema, although incriminated as the major cause of death in two cases, was

Table 33: Leukaemia type distribution at autopsy.

| Type | Number |
|---|---|
| AML | 16 |
| ALL | 17 |
| AMoL | 2 |
| ALSCL | 6 |
| AUL | 2 |
| CGL | 11 |
| CLL | 5 |
| Acute - Not typed. | 17 |
| Total | 76 |

Table 34: Major causes of death in 76 cases.

| Causes of death | Number of cases | % |
|---|---|---|
| Haemorrhage | 18 | 23.7 |
| Infection | 16 | 21.0 |
| Both haemorrhage and infection | 7 | 9.2 |
| Organ failure | 18 | 23.7 |
| Multiple causes | 12 | 15.8 |
| Miscellaneous causes | 5 | 6.6 |
| Total | 76 | 100 |

also an accomplice in all cases dying of congestive cardiac failure due to anaemia, bronchopneumonia and multiple organ failure.

Bone marrow hyperplasia, as evidenced by whole length femoral marrow activity, was almost an invariable finding, apart from two cases, one of ALL and the other of AML, which showed hypoplasia. Green colouration of the bone marrow was not an uncommon feature in acute myelogenous leukaemia.

Causes of death.

Haemorrhage was an undoubted cause of death in 18 cases; infection, 16 cases; both infection and haemorrhage, 7 cases and specific organ failure, 18 (Table 34). Multiple organ failure was responsible for 12 cases and there was no obvious cause of death in one case. In the remaining four cases, death was caused by raised intracranial pressure due to chloroma (Fig. 24) and cerebromeningeal leukaemic infiltration in 2 cases (Fig. 25), gangrene of the bowel due to obstruction in one, and a liver abscess in the other. Some of the major findings recorded were: massive lymph node enlargement pressing on vital organs - 5; pyelonephritis - 1; chloroma - 3; lymphoma as a complicating neoplasm in two cases. The presence of three cases of chloroma out of 18 cases of AML (including AM-ML) gives a falsely high frequency of 19% as compared to 10% clinical frequency.

Haemorrhage and infection accounted for 54% of the deaths; other definite causes including organ failure, 30% and undefined, but probably multiple, causes 16%. This is in keeping with the clinical findings whereby patients presented in advanced stages of their disease with a consequently prominent element of organomegaly and organ failure but comparatively low haemorrhage and infection rates (Fig. 5; Table 21). This finding is corroborated by the extensiveness and frequency of leukaemic infiltration of various organs at histology (Table 35). The lymphoreticular organs were the most extensively and frequently infiltrated, followed by the kidneys and the central nervous system (CNS). The CNS showed leukaemic infiltrate in two cases which were in bone marrow remission. Hepatic infiltration was similarly most prominent in patients who had received no therapy. Hepatic fatty change was seen in some cases which had undergone treatment for acute leukaemia.

Table 35: Frequency of leukaemic infiltration in various organs.

| Organ | Liver | Spleen | Lungs | CNS | Bone Marrow | Lymph nodes | Kidneys | Ovaries | Testes |
|---|---|---|---|---|---|---|---|---|---|
| Number recorded | 39 | 35 | 38 | 22 | 16 | 20 | 26 | 2 | 5 |
| Infiltration present and (%) | 31 (79) | 25 (71) | 14 (37) | 15 (68) | 14 (88) | 19 (95) | 20 (77) | 1 (-) | 3 (-) |
| Not present | 8 | 10 | 24 | 8 | 2 | 1 | 6 | 1 | 2 |

Haemorrhage.

Haemorrhage was identified as the major cause of death in 23.7% of the cases. According to the site of haemorrhage, intracranial accounted for 5 cases, pulmonary - 2, gastro-intestinal - 5 and generalized -6. Intracranial haemorrhage was mainly intracerebral. Haemorrhagic necrosis of the spleen and lungs was occasionally documented. Generalized petechiae of the serosal surfaces occurred more extensively in acute myelogenous, and more so in acute promyelocytic leukaemia, than acute lymphocytic leukaemia. No haemorrhage into the nodes was documented. The kidneys and liver were also often reported as the seat of haemorrhage. Although haemorrhage featured mainly in acute leukaemia, it was the cause of death in two cases of chronic granulocytic leukaemia - one massive gastrointestinal and the other into the soft tissues of the neck.

Infections.

Bronchopneumonia accounted for 12 deaths out of the 16 attributed to infection as the major cause. This was most often confluent pneumonia, attended by marked pulmonary congestion. One of these was due to a staphylococcal infection Tuberculosis was the cause of death in one case, thus making a total of 13 cases dying of pulmonary infection. Septicaemia due to Salmonella typhimurium infection caused death in two cases and pyogenic liver abscess was the immediate cause of death in one. Pyelonephritis and fungal oesophagitis were found as complications in one case each. Schistosomiasis of the liver, colon and lungs was an incidental finding in two cases.

In summary, haemorrhage, followed by organ failure, then infection were the leading causes of death. Organ failure was attributed to anoxia due to anaemia and tissue destruction due to leukaemic infiltration.

# CHAPTER FOUR

## DISCUSSION

## CONCLUSION

## Epidemiological pattern.

### Prevalence and incidence.

It is not possible to ascertain the prevalence and incidence of leukaemia in the Kenyan population from the present study, which was hospital based. Moreover, the calculated rates would not wholly reflect the true picture of the disease unless the study was countrywide and wholly prospective. However, the yearly numbers of the cases diagnosed have increased from an average annual rate of about 40 cases per year in 1969 (66) to over 120 in 1977. This is not an increase in the incidence of leukaemia in Kenya, but a reflection of increased awareness that the disease is not uncommon, improved clinical suspicion, improved diagnostic facilities and presence of interested personnel. There is no doubt that with the growth in numbers and quality of medical centres and more determined effort from medical workers, more cases of leukaemia will come to light. Infact, what is seen could only be "one tenth of the iceberg"; the latter being a large pool of undiagnosed cases of leukaemia.

Availability of service as a big determinant of the number of cases diagnosed is further confirmed by the pattern of tribal distribution of not only leukaemia but most other diseases (102, 103). Thus, the Kikuyu accounted for about 40% of all the cases of leukaemia in the series (Table 5a) when they form only 20% of Kenya's population. This is due to their close proximity to hospitals, particularly K.N.H.; their easy accessibility to Nairobi (Fig. 26) where there is a high density of doctors with relatively well developed diagnostic services, better than in the rural areas. The same reasoning obtains for the Kambas, in whom 16% of all leukaemias were diagnosed.

This fact is further corroborated by the admission rates to K.N.H in that the higher the tribal admission rates, the higher the percentage of cases of leukaemia in the tribe. Leukaemia prevalence in other tribes correlated fairly well with the K.N.H. admission rates for them. This indicates a gross underdiagnosis of leukaemia in tribes other than the Kikuyu. There is therefore no clear geographical pattern independent of hospital services. Moreover, leukaemia is less likely to be diagnosed in a rural setting and hence less likely to be referred for treatment.

The true incidence of leukaemia in Kenya will remain uncertain fo sometime. However, the calculated incidence of 1.2 in 100,000 for the Kikuyu(page 38) is probably nearer the true national

incidence than the overall 0.5 in 100,000 calculated in this series. Hence, the amount of leukaemia seen currently is likely to be less than 20% of the expected.

Various underlying factors may be postulated to account for this deficiency. In spite of what has been said by Davies (68, 104), leukaemia is still severely underdiagnosed, not only in Kenya but in developing countries at large. Vast numbers of people in the tropics are exposed to a whole range of vicious and potentially fatal tropical infections. This has shifted the stress to infectious diseases during the training of all cadres of health personnel and the role of cancer, leukaemia not excepted, has therefore taken a secondary position. The diagnosis is only left for haematologists or to those interested in the problem, who in most cases are few. Thus, what the general physician or the occasional haematologist see in form of leukaemia is just but a discernible portion of what is otherwise a submerged iceberg. Most cases of acute leukaemia present with severe anaemia and the number of cases of anaemia admitted to a hospital is large. The majority are discharged soon after transfusion, either undiagnosed or incompletely investigated. This is mainly due to lack of adequate laboratory facilities or knowledgeable laboratory personnel and partly due to lack of awareness on the side of the attending doctors. Rarely, patients may present looking too well for a diagnosis of leukaemia to be entertained.

It is also known that queues at Government hospitals are long and on occasions intolerable. Patients therefore go back home and either die undiagnosed or go to private doctors who may not have facilities to investigate them. The few lucky ones who return to the hospital may have their leukaemia diagnosed but too late. The remainder are treated with iron or other haematinics with fatal consequences. A greater majority of patients with non-myelogenous leukaemia present with lymphadenopathy and splenomegaly (Table 18) and where a lymph node biopsy is done, the diagnosis of malignant lymphoma is made. The patient is documented and treated as such without further haematological evaluation. This partly explains the high incidence of malignant lymphoma and the paucity of leukaemia of childhood, thus superficially supporting Davies' theory (68) of biological equivalent. This may also be a sound explanation for the lower incidence of ALL in the 0-4 age group than is expected and high incidence of ALSCL in the 5-9 age group.

Most publications, documenting leukaemia incidence in tropical Africa, have depended on cancer registries for their figures. It is, however, true that cancer registries tend to be biased in gathering data because they mainly or wholly document histologically proven diagnoses, thus leaving out the majority of leukaemias.

Symptomatic manifestations of leukaemia are non-specific and without a leading symptom, the patients are unlikely to seek medical attention. As previously pointed out (66), and because of its protean nature, acute leukaemia is often missed in the clinical differential diagnosis. This factor is frequently magnified by lack of interested clinicians, incompetence at doing bone marrows and the inadequacy of the laboratory personnel in the rural areas. Diseases, such as rheumatic arthritis are often diagnosed instead of acute leukaemia if there is involvement of the skeletal system, as it happened in about 15% of childhood leukaemia in this series. Acute leukaemia is therefore likely to kill patients before diagnosis. Chronic leukaemia on the other hand presents after months of illness. The elusive nature of symptoms, coupled with prohibitive distances to the nearest hospital further make the patients not to report for medical attention, and so to seek non-medical advice. Such patients die at home without ever being diagnosed. The majority of chloromas have been mistaken for Burkitt's lymphoma, both clinically and histologically. Dry or bloody bone marrow aspirates are often mistakenly interpreted as aplastic anaemia (case 6 appendix III) and patients are managed as such without further haematological evaluation.

All the above information supports the contention of leukaemia undereporting in the Kenyan population, even if the childhood incidence of 0.3 in 100,000 is still higher than has been reported from Nigeria (77) where it is 0.19 per 100,000, but much lower than the Danish figure of 4.4 per 100,000 in boys (105). Nevertheless, in spite of its low incidence, leukaemia is an important cause of mortality in Kenya, as it accounts for 3.7% and 3.8% of deaths in children and adults, (Tables 36 and 37) respectively, at K.N.H.

Table 36: Causes of death according to sex in a paediatric in-patient population at KNH 1976-77.

| Cause | Male | Female | Total | % |
|---|---|---|---|---|
| All infections | 165 | 138 | 303 | 37.7 |
| Malnutrition | 40 | 42 | 82 | 10.2 |
| Cardiovascular disease | 26 | 24 | 50 | 6.2 |
| Malignancies | | | | |
| - Leukaemia | 18 | 12 | 30 | 3.7 |
| - Wilm's tumour | 10 | 5 | 15 | 1.9 |
| - Lymphoma | 8 | 5 | 13 | 1.6 |
| - Neuroblastoma | 2 | 2 | 4 | 0.5 |
| - Other | 4 | 3 | 7 | 0.9 |
| Total | 42 | 27 | 69 | 8.6 |
| Anaemia (other than due to leukaemia) | 20 | 10 | 30 | 3.7 |
| Neonatal (non-infective) | 69 | 51 | 120 | 14,9 |
| Gastroenteritis (non-infective) | 9 | 7 | 16 | 2.0 |
| Liver disease | 8 | 5 | 13 | 1.6 |
| Renal disease | 8 | 3 | 11 | 1.4 |
| CNS disease (including hydrocephalus) | 28 | 18 | 46 | 5.7 |
| Miscellaneous | 35 | 29 | 64 | 8.0 |
| Total | 450 | 354 | 804 | 100 |

Table 37: Medical causes of death according to sex in an adult in-patient population at KNH 1976-77.

| Cause | Male | Female | Total | % |
|---|---|---|---|---|
| Infections | 94 | 79 | 173 | 18.9 |
| Cardiovascular disease | 99 | 98 | 197 | 21.5 |
| Malignancies | | | | |
| - Liver carcinoma | 30 | 23 | 53 | 5.8 |
| - Leukaemia | 24 | 11 | 35 | 3.8 |
| - Lymphoma | 16 | 1 | 17 | 1.9 |
| - Gastric cancer | 9 | 2 | 11 | 1.3 |
| - Others | 28 | 14 | 42 | 4.6 |
| Total | 107 | 51 | 158 | 17.2 |
| Liver disease (excluding carcinoma) | 64 | 38 | 102 | 11.1 |
| Renal disease | 42 | 28 | 70 | 7.6 |
| Diabetes Mellitus | 44 | 20 | 64 | 7.0 |
| Other blood disorders | 28 | 18 | 46 | 5.0 |
| Gastroenteritis (no known cause) | 28 | 17 | 45 | 4.9 |
| Miscellaneous (CNS etc.) | 40 | 22 | 62 | 6.8 |
| Total | 546 | 371 | 917 | 100 |

Age distribution.

There is no doubt that adult leukaemia in the African probably occurs as often as in the caucasian (66, 104, 77, 82) but childhood leukaemia has been alleged to be rare (3, 55, 62, 63, 68, 77). However, the situation appears to be different in Kenya as all the series on leukaemia have documented significant numbers of childhood leukaemia (66, 78, 81), accounting for a variable 25-30% of all leukaemia cases. This is similarly borne out by the present series in which leukaemia in childhood forms 28% of the total and childhood acute leukaemia accounts for 48% (page 39, & Table 16) of all the acute leukaemias. Nevertheless, there is a deficit of total childhood leukaemia since Kenya's population of children under 15 years is 48% (106) of the whole country's population. The deficit is particularly evident in the 0-4 age group and for childhood acute lymphoblastic leukaemia in general. Notwithstanding this, the contention that childhood leukaemia was rare in the trans-Saharan Africa was overplayed.

The overall age distribution of acute leukaemia shows some obvious similarities to, as well as differences from, the established patterns in caucasians (107). Whereas ALL has a peak occurrence in the 0-4 age group and rapidly falls off (Tables 9 & 16) as expected from the literature, AML maximally occurs in the 2nd decade of life (Table 8) with a steep decline from the fourth decade onwards. This has also been observed in other African series (64, 77). There is thus no characteristically rising incidence noticed in caucasians during the sixth decade (107). The difference in the age pattern is even more marked in chronic granulocytic leukaemia which has a peak occurrence at 25-35 years (Table 15) and then steeply declines in the seventh decade. This contrasts with the steep rise in the CGL incidence after the age of 65 years in the caucasians. This pattern is however similar to what has been previously observed in Ugandan, Kenyan and Nigerian Africans (64, 66, 82). Childhood CGL accounted for 6.9% and 7.1% of all CGL and childhood leukaemia in this series, respectively. This confirmed what has been reported from Kenya (81) and elsewhere (108) but much higher than what other African series have indicated (63, 64, 82) although lower than the Sudanese experience (79) in which CGL accounted for 23.3% of childhood leukaemia. The peak incidence of CLL is in the sixth

decade (Table 17) although most of the cases occur between 40 and 70 years. This peak occurrence is earlier than is experienced in the western countries (107) but similar to the findings in other African series (63, 64, 66, 82, 84). There was no childhood CLL in the present series, unlike the earlier report (66) in which there was one case.

Sex distribution.

There is an overall male preponderance, which is most prominent in the first decade of life, in which it approaches 2:1 (Fig. 3). The overall childhood male to female ratio of 1.7:1.0, well in line with previous experiences (66, 81), is more significant when it is compared with the male to female ratio of 1.2:1.0 in paediatric ward admissions at KNH (Table 38). This sex differential disappears during the second decade (Fig. 3) and this is due to an increase in females with AML outnumbering males by 2:1 (Table 8). The less marked predominance of males in AML is well recognized (107). Chronic leukaemias, similarly, predominate in males (Table 14 & 17) in ratios comparable to those reported from Nigeria and Uganda (82, 64), unlike the British white population in whom both sexes are equally affected (109)

Type distribution.

There is an unequivocal excess of the myelogenous types of leukaemia (page 34), occurring twice as often as the lymphoid forms. This excess in the myelogenous types has been repeatedly documented for acute leukaemia in trans-Saharan Africa (Table 2) (64, 66, 68, 77, & 78), but not to the extent of the present experience (Table 7). However, childhood AML and ALL occur in almost equal proportions, although with a slight excess of AML (Table 16). This is unlike the distribution in the American or European whites who have a marked preponderance (upto 80%) of acute lymphocytic leukaemia (70, 110). About 20% of the myelogenous acute leukaemia are of the myelomonocytic type, rather more than is documented in most series in the literature.

Table 38: Two year analysis of KNH medical-paediatric ward admissions according to sex distribution.

| Age | Male | Female | M/F Ratio |
|---|---|---|---|
| Children | 1642 | 1364 | 1.20 |
| Adults | 2659 | 2632 | 1.01 |
| Total | 4301 | 3996 | 1.08 |

Note:-Male: Female ratio for paediatric/medical filter out-patient attendances is 0.94:1

Acute leukaemia of lymphoid origin shows three major variants: acute lymphoblastic, ALSCL and acute prolymphocytic (page 35). ALSCL, a leukaemic transformation of non-Hodgkin's lymphomas, is an entity that has received little attention in reports on leukaemia in trans-Saharan Africa. Even the large series reported by Essien (77) had no mention of it. However, Sonnet et al (63) refer to it as a "paraleukaemic syndrome" in two of their Congolese cases of leukaemia, and Ahmed et al (79) documented 9 cases out of 43 Sudanese cases of childhood leukaemia. This entity is more common than is realised as all patients presenting with non-Hodgkin's lymphoma may show up to 70% leukaemic transformation if they are adequately followed up. For example, almost all cases of lymphocytic lymphoma in Kenya present as disseminated disease with a large proportion of them having bone marrow involvement (111). ALSCL shows comparative and contrasting features that help to identify it from acute lymphoblastic leukaemia (Table 39), and a typical case is described in the appendix (case 3, appendix III). Its frequency in the 5-9 year age group in Kenya is in keeping with the high prevalence of childhood lymphoma which also has a peak occurrence in the same age group. Chronic granulocytic leukaemia occurs twice as often as CLL. This striking predominance of CGL over CLL in Kenya has been noted before (66). It, however, has not been reported in other African series (63, 64, 82) in which both types occurred in almost equal proportions but with a slight excess of CGL as in whites (70, 112). All the cases of CGL showed typical features apart from one atypical case (case 5, appendix III) which presented as a panmyelopathy with massive lymphadenopathy. No definite cases of chronic prolymphocytic leukaemia, alleged to be commoner in the tropics than temperate countries (83), or chronic lymphosarcoma cell leukaemia were encountered in the present study. One case of CLL converted to CGL (case 1, appendix III) after long term follow up.

Table 39: Comparison of ALSCL and ALL.

| Feature | ALSCL | ALL |
|---|---|---|
| Peak age occurrence | 5-9 | 0-4 |
| Patient Disability | + | ++ |
| M/F ratio | 3:1 | 1.3:1 |
| Lymphadenopathy | ++++ | ++ |
| Splenomegaly | ++++ | ++ |
| Anaemia | ++ | ++++ |
| WBC counts | +++ | +++ |
| Platelet count | Reduced | Markedly reduced |
| Size of cells | Variable | Monotonous appearance. |
| Maturity of cells | Variable | Primitive - uniform |
| Chromatin | Spongy | fine |
| Nucleoli | ++ large | + small |
| Cytoplasm | ++ | + |
| PAS | + | +++ |
| Median survival | $8\frac{1}{2}$ mo. | 10 mo. |

Aspects of clinical presentation, diagnosis, remission, survival and prognosis.

The nature and behaviour of leukaemia in the Kenyan African does not differ significantly from what is generally known about the disease. However, there are important peculiarities that need emphasizing. These include late presentation, the preponderance of myelogenous leukaemia already discussed, high frequency of chloromata, poor response to treatment, poor survival and the different pattern in the causes of death.

Late presentation and complications.

The pattern of orthodox clinicopathological features of anaemia, haemorrhagic tendency, infections and organomegaly is the same as is classically known, although they are usually of a more profound degree than is seen in industrialised countries. The prevalence of haemorrhagic tendencies of 40% was in keeping with the frequency of severe thrombocytopenia which occurred in about 45% of the patients (Table 25). More cases of CLL showed thrombocytopenia than could be correlated with the haemorrhagic complications. Severe haemorrhage into soft tissues in terminal cases of CGL was dramatic. On the whole, the high rate of infections and hyperleucocytosis complicated by consumption coagulopathy tended to increase haemorrhagic complications. It is however intriguing that none of Essien's (77) acute leukaemic patients had petechiae.

The overall frequency of pyrexia of 50% at presentation (Table 18) was higher than the infection rate of 37%. This indicates that about 75% of febrile episodes were due to infection, very much in keeping with figures from elsewhere (70, 99) and correlated well with the degree of neutropenia. Preinduction infective conditions were mostly bacterial, but anaerobic with viral during the remission induction. Disseminated fungal infections are not as common as is

documented from Europe and America (70). The rather high frequency of salmonellosis, probably a reflection of a common infection in the environment, is noteworthy, although its predilection for AM-ML patients cannot be explained. It has been alleged that African patients with CLL present typically with massive splenomegaly and less lymphadenopathy (4, 62, 82); the two features occurred with equal frequency in this series. Gross splenomegaly almost always accompanied marked lymph node enlargement (Table 18 & 20), indicating that they were an expression of advanced disease. This is further corroborated by the reasonably high frequency of organomegaly even in acute leukaemia.

Advanced nature of the disease was evidenced by high frequency of organomegaly and hyperleucocytoses (42% of acute leukaemics had leucocyte counts in excess of $30x10^9/l$ and 37% of chronic leukaemics had counts over $200x10^9/l$; Tables 23 & 24). This means that either the patients stay with the disease in progressive ill-health for a long time and only seek medical advice when they are completely defeated and hence carry a large leukaemic cell mass or leukaemia in the African is a more aggressive and thus a rapidly progressive disease than it is in the caucasian. The exception to this assumption is AM-ML, which appears to steer a subacute course in some patients.

Chloromas.

Chloromatous presentation in 10% cases of acute non-lymphocytic leukaemia is not as frequent as was reported by Davies and Owor (71). But it is nevertheless very common when compared with its occurrence in whites and especially so when the childhood frequency in ANLL is 23% (page 53) in this series. This high frequency is only comparable to that reported in Turkish children (113). Its high frequency is, however, just an expression of the preponderance of acute myelogenous leukaemia over ALL in the African. This behaviour of leukaemia is important as these patients have been mistaken for having retinoblastoma, Burkitt's lymphoma, disseminated neuroblastoma or even

intracranial hydatidosis clinically, as well as being misdiagnosed as Burkitt's on histology.

CNS involvement.

Cerebromeningeal involvement was an important terminal event in AM-ML, ALSCL and untreated cases of ALL. It was manifest at presentation in about 30% of all cases of acute leukaemia, 75% of ALL, and usually contributed to the rapid deterioration of patients in spite of systemic chemotherapy. CNS radiation was not usually feasible at this stage as the patients were clinically unfit. Intrathecal cytotoxic therapy did not influence the course remarkably. A fair number of patients suffered blindness, progressive coma and paraparesis due to brain infiltration.

Differential diagnosis.

Due to its systemic clinicopathological nature, leukaemia presents with protean manifestations. When a leukaemic process presents with anaemia per se, common parasitic infections such as malaria and hookworm are often considered to be causes. Aplastic anaemia and bleeding disorders, but not leukaemia, are usually thought of first in refractory anaemias of childhood (case 6, appendix III). In children who have bleeding as a dominant feature, hereditary bleeding disorders, such as haemophilia, are often considered as the initial diagnosis. Splenomegaly is a feature of many diseases in the tropics, e.g. malaria, leishmaniasis, schistosomiasis, brucellosis and the idiopathic splenomegaly syndrome. Since these diseases frequently manifest with fever and anaemia, they are pertinently considered top in the differential diagnosis and investigated for first. Consequently, CGL or CLL is often discovered incidentally if they are causing the splenomegaly. Where lymphadenopathy with splenomegaly co-exist, malignant lymphoma is the usual diagnosis. Leukaemic patients whose overt illness is preceded by protracted or recurrent respiratory infections, tuberculosis is often diagnosed (case 4, appendix III). Such patients are only found to have leukaemia on routine investigation for the

anaemia which requires frequent transfusions.

Sickle cell anaemia and rheumatic fever are often diagnosed in patients who present with bone pain and arthritis. It is not unusual for the anaemia in these patients to be overlooked, if mild, and all the investigations directed at confirming the presumptive diagnosis. Infact, two patients in this series were treated for juvenile rheumatoid arthritis for six months and one year respectively before ALL was diagnosed and the high antistreptolysin-O titres only added to the confusion. The misdiagnosis of chloroma for histiocytic lymphoma, retinoblastoma and Burkitt's lymphoma, even on histological examination has already been alluded to (see also case 2, appendix III).

It is therefore not surprising that in an environment which has so many alternative causes for symptoms which occur in leukaemia, the latter is very often not suspected and included in the clinical differential diagnosis. These problems being rampant in childhood, they dominate the picture and mask leukaemia which then kills undiagnosed. It may not therefore be difficult to understand why childhood leukaemia in Africans was considered rare in sub-Saharan Africa.

Infective disorders such as tuberculosis, severe pyogenic infections, post-abortal sepsis, bacterial endocarditis, which may be accompanied by anaemia as well as bleeding tendency may also cause bizarre granulocytic leukaemoid reactions. The diagnosis of CGL could therefore be difficult and made with great caution. Lymphocytic leukaemoid reactions, mimicking CLL and ALSCL are not uncommon in whooping cough, tuberculosis and viral infections. The differential diagnosis of chronic leukaemia from leukaemoid reactions can thus be an "itch in the back". Chronic granulocytic leukaemia is nevertheless usually the most easily diagnosed of the leukaemias on clinical and blood film features; but leukaemoid reactions in disseminated tuberculosis which is still a common problem (114) may perfectly mimick leukaemia.

Bone marrow diagnosis in acute leukaemia presents no difficulties in the majority of cases. But caution must be exercised in lymphocytic or monocytic infiltration of the bone marrow in pancytopenic cases of visceral leishmaniasis and malarial splenomegaly which must be differentiated from aleukaemic leukaemia. Similarly, dry taps in some cases of aleukaemic ALL has been misinterpreted as aplastic anaemia as it was in case 6, appendix III. Disseminated small cell-type neuroblastoma with bone marrow infiltration, which incidentally occurs with peak incidence in the same age group as ALL (115), should not be mistaken for the latter.

Cytochemistry and limited cytogenetic studies have been of great value in delineating the diagnosis of leukaemia in view of the high incidence of causes of leukaemoid reactions. A common mistake of taking blast cells for lymphocytes is also lessened by application of cytochemistry. Hence, every worker in this field in the tropics must be acutely aware of these limitations. For the haematologist, cytochemistry is invaluable in classifying the various species of acute leukaemia (116), for this is not a mere academic exercise but an important parameter in prognostication and decision on the modality of therapy.

Response to treatment.

This can only be accurately assessed in children for the years 1975-1977 as there was not well planned treatment in adults, and there are also no comprehensive reports on leukaemia treatment in the African that can serve for comparison. However, Essien (77) reports a remission rate of 26% in acute leukaemia in Nigerians, while Barr et al (78) and Cameron et al (91) reported remission rates of 32% in acute leukaemia and 50% in AML respectively in Kenyan Africans. Considering the overall complete remission rate of 69% (Table 29) in acute leukaemia in this series, there is tremendous improvement over the results reported by Barr et al (78) in 1972. But the 32.4% in AML for all ages is far below that reported by Cameron et al (91), although remissions currently achieved are about 60%. A failure rate of 6% in ALL is comparable to results currently obtained in large centres in America (94). Acute monocytic leukaemia and ALSCL

show the poorest response rates, being 0% and 30% respectively.

The situation in childhood acute leukaemia has improved remarkably, giving a remission rate of over 80% in ALL, 65% in ALSCL and 56% in ANLL (Table 40) when using the locally designed protocols (page 29-31). This is so when the largest tolerable doses of cytotoxic drugs are used. The dosage based on body surface area gives a better indication of a suitable quantity of a drug and that African children tolerate larger doses of cytotoxic drugs than white children as previously observed by Boesen and Davies, (100). Nevertheless, it is apparent that the response of even acute lymphocytic leukaemia to chemotherapy is less favourable in the Kenyan patients than their counterparts in the U.K. or U.S.A. This is true for patients without organomegaly as well. Whereas during induction, about three courses of vincristine would be enough to induce remission in the majority of white children, it takes more than five courses in our patients. This raises many problems:- many are likely to die during the induction period; the stay in the hospital is bound to be longer and therefore more expensive; risk of contracting opportunistic infections in the hospital is high.

The response of non-lymphocytic acute leukaemia to orthodox schedules developed for white patients has been observed to be poor in the majority of cases as only 27% remission rate was achieved (81). It has been extremely disappointing in spite of using up to six courses of a therapeutic protocol such as Bart's III (93) for remission induction. Further, children with acute myelogenous leukaemia appear to fare as badly as the adults despite the claim by Bodey et al (117) that it is not the morphological diagnosis but the age that is a major determinant of the response of acute leukaemia to treatment.

The chronic leukaemias, when managed along conventional lines, have shown no variation from what is known in Europe and America. However, most of the patients with CGL who presented with total counts of more than 800 x $10^9$/l tended to be refractory to busulphan. Hence, either cytosine

Table 40: Childhood acute leukaemia - response to chemotherapy.

| Response | ALL | ALSCL | ANLL* |
|---|---|---|---|
| Complete remission (CR) | 16 | 9 | 10 |
| Partial remission | 3 | 3 | 5 |
| No response | 1 | 2 | 3 |
| Total evaluable | 20 | 14 | 18 |
| Not evaluable | 5 | 1 | 13 |
| All patients | 25 | 15 | 31 |
| % CR | 80% | 65% | 56%. |

* ANLL includes AML, AMoL, AM-ML and AP-ML.

arabinoside or 6-mercaptopurine were used for effective cytoreduction. Those who were diagnosed during the accelerated phase (case 5 appendix III) did not respond to therapy at all. Occasionally, the total leucocyte count precipitously tumbled down but the spleen regressed very slowly. About 50% of the patients with CLL had stage IV disease (page 71). These responded poorly to single agent therapy such that a combination of vincristine, prednisone and cyclophosphamide had to be used on occasions. CLL appeared to be a more aggressive disease than CGL probably because most of the CLL could have been chronic prolymphocytic leukaemia. Alternatively, whereas CGL is a predominantly proliferative disorder, CLL is accumulative (33).

Survival and quality of life:

Ojiambo (74) commented a decade ago that, in Kenya, acute leukaemia patients were kept alive "at most for weeks" and that they were sustained on blood transfusions only. This could also have been the situation in other developing countries although at the same time, important break-throughs aiming at long survival were being reported from Europe and America (118). Infact, "cure" could be envisaged as the ultimate goal in leukaemia treatment. However, five to six years ago, Barr et al (78) reported a median survival of 3-4 months in acute lymphocytic leukaemia in Kenyan Africans. This progressive improvement in the survival of leukaemic patients in Kenya is corroborated by the report on childhood leukaemia in Kenya (81) in which the median survival was as follows: AML - $5\frac{1}{2}$ months ALL - 10 months and ALSCL - $8\frac{1}{2}$ months. Survival analysis (Fig. 21) in the present series indicates that survival has further improved in children with median survivals of 15 months in ALL, 8 in AML and 9 in ALSCL. It should however be emphasized that 65% of ALL and 32% of AML cases at all ages died within one month of diagnosis. Most of the AML relapsed within 3-6 months, but the majority of ALL relapsed within 12-15 months. ALSCL fell in between AML and ALL. The longest survivor in ALL was 40 months at the time

of writing, but almost all the patients with AML died within 12 months of diagnosis.

The quality of life in these patients is remarkably good, although it was not morbidity free as it was often interrupted by episodes of viral, bacterial and superficial fungal infections. Meningeal leukaemia manifested in several patients who were in haematological remission in spite of previous CNS prophylaxis. Post-radiation somnolence was frequent, but drug intolerance and direct toxicity was notable by its paucity.

Although CGL patients presented late in the course of their illness, long survivals of more than 8 years were recorded. It is however not possible to give the median survival time for chronic leukaemia from the results of the present study. Those who responded satisfactorily (partial or complete remission) had a reasonably better quality of life than patients with acute leukaemia. Most of them suffer trivial infections, i.e. dermatophytosis, scabies and pyoderma and the majority pursue their professions adequately. Although Zippin et al (119) reported prolonged survival in CLL patients, it is not easy to ascertain this from this study as pointed out above, as it is also time and sample-size limited.

Prognostic factors.

The discussion in the preceding pages suggests that ALL has the best prognosis among the acute leukaemias, followed by ALSCL and AML, with AMoL and APML being the worst. AM-ML is better than acute myeloblastic leukaemia. This is a strong point in favour of identifying the various subspecies of acute leukaemia. Treatment prolongs survival and improves the quality of life. It would however not be accurate to compare prognosis in adults and children, as the former did not have the benefit of organized management between 1975 and 1977. Nevertheless, children appeared to fare on better than adults, although AML has a uniformly poor prognosis. For the chronic leukaemias, CGL showed a better out look than CLL.

Clinico-haematologically, the majority of our patients presented late with severe anaemia, thrombocytopenia organomegaly and hyperleucocytoses. They thus already fall in poor prognostic groups (120, 121). Bone marrow was always completely replaced, with severely depressed or absent normal haemopoiesis. These features which indicate a big leukaemic cell mass, coupled with a high rate of preinduction infection and compromised immunocompetence augured bad prognosis. Bone infiltration be it in ALL, AML or CGL also indicated a bad out look. The fact that ALL has worse prognosis in the black American children than whites (122) is only a primer to the aggressiveness of leukaemia in the African.

In summary, when consideration is made of the genetic predisposition, high infection rate, late presentation, a high frequency of AML and ALSCL and general resistance to induction therapy, probably, acute leukaemia has a worse prognosis in the African than his white counterpart.

Causes of death.

The general pattern of the leading causes of death, i.e. haemorrhage, infection and organ failure or their combinations thereof, is similar to that reported from America (123) and Uganda (64, 101), but unlike the observations in Nigeria where haemorrhage as a cause of death in acute leukaemics accounted for 64% (77). Organ failure features prominently as a cause of death in this series probably because of the advanced stage of the disease at presentation as well as the extensive organ involvement in the leukaemic process (Table 35).

Notable peculiarities are the high frequency of chloroma, as previously reported from Uganda (71, 101) and the striking rarity of disseminated opportunistic deep mycoses. The high frequency of chloroma has been referred to above, as an expression of a common disease i.e. AML. It is however not easy to explain the rarity of deep mycoses, even as incidental autopsy findings. It is unlikely that these have been missed as the same observation has been made in Uganda (101). The explanation given by Owor and Madda (101)

that this could be due to the short time the patients are exposed to antileukaemic therapy is not adequate.

The coexistence of well differentiated lymphoma and CGL at post mortem in a previously untreated patient is worth of note.

## Problems pertaining to diagnosis and management.

### Diagnostic problems.

Apart from delays, difficulties in differential diagnosis and shortage of haematological expertise, bone marrow specimens from peripheral hospitals are often of very poor quality. The smears are usually badly made: they are thick, grossly haemodiluted, often unfixed or poorly fixed. This makes bone marrow interpretation an impossible task. To make the situation worse is the failure of the clinician to supply the patient's clinical data, peripheral blood indices and a peripheral blood film. As an accurate diagnosis is unlikely to be made without these requisites, misdiagnosis with underdiagnosis of leukaemia are the usual consequences. Diagnosis is occasionally further complicated by corticosteroid therapy and transfusions which are administered prior to doing a bone marrow. These procedures not uncommonly mask the leukaemic process at the beginning. The role of viral infections, particularly measles, in masking ALL (124) leading to its underdiagnosis has yet to be defined. As stated by Trowell in 1938 (125), "anaemia is the commonest pathological condition in hospital patients", whether primary or secondary. As it is never adequately investigated, its causes are not accurately delineated and leukaemia is likely to be missed as one of these causes. Patients are instead fed on iron.

### Management problems.

The first priority of a clinician is to destroy the tumour as quickly and completely as possible and this is not a responsibility to shy off. The majority of leukaemia patients in Kenya do not have this privilege. Diagnosis is usually made late in the course of the disease either because of late

presentation due to non-specificity of symptoms pertaining to the leukaemic process or low index of suspicion for the disease on the part of the doctor. Even with an early presentation and early clinical diagnosis, haematological confirmation which is unfortunately centralised, due to lack of haematologists, takes too long because of slow communication.

For the acute leukaemia cases, the haematological diagnosis is usually received when the patient is either moribund or already dead. Patients often die before they get to hospital making the confirmation of the diagnosis good, only, for statistical purposes. Furthermore, only a few of those with established diagnosis benefit from useful specific therapy for reasons such as shortage of drugs, the cost of which may be prohibitive, and non-experience or lack of expertise of the attending physician, be it at regional or central hospitals.

For the lucky few who receive modern chemotherapy while in hospital, the initial response is encouraging, although not comparable to today's good results from centres in developed countries. Evaluation of the effectiveness of chemotherapy is difficult, and follow up is beset with a lot of problems. Most patients or parents of paediatric patients do not often understand the concept and implications of a neoplastic disease, such that once they have symptomatic improvement, they do not see the value of continued painful and stereotyped drug treatment or even clinic attendance from which they automatically default. Communication to and from the hospital is frequently difficult, either because of long distances, lack of finance or poor accessibility.

Chronic shortage of the key drugs is a further drawback to the effective follow up of these patients. The effective therapeutic regimens are thus interrupted or even terminated. This leads to great difficulties in attempting to hold the leukaemic process in abeyance. Relapse rates are consequently high and median survivals short. For those patients who attain good remissions, home environment does not usually support long survivals because of the high prevalence of

infectious diseases which frequently hasten the natural course of leukaemia. A substantial number of patients is lost to follow up and maintenance treatment is not effected if remission induction had been previously successful. The inevitable outcome of all these problems is poor prognosis, an issue that is confirmed by the present study.

The ethics of whether to actively treat or not treat the non-lymphocytic acute leukaemias are questionable when the cost and priorities are considered in the perspective of the prodigious task of attempting to eradicate leukaemic cells. The problem is further magnified by the low therapeutic index of the drugs in use in acute myelogenous leukaemia, which is well known to be fairly resistant to chemotherapy. A more serious practical problem is the inexperience and lack of understanding of the pathophysiology of the disease and its complications by both the resident doctors and the nursing staff. For example this lack of understanding leads to use of repeated intramuscular injections in severely neutropenic and thrombocytopenic patients.

Delay in the commencement of therapy is common and the meticulous care required in the management of a leukaemic patient is often lacking. Isolation of patients during remission induction is a facility that would probably be of great advantage when consideration is taken of the high frequency of infectious diseases that occur in a general ward in the tropics. This facility is not available and when added to lack of uniform specialist supervision, the chances of good remissions are further compromised. Haphazard treatment regimens and lack of team work spirit among the physicians prevails. Psychological counselling, an important aspect of the "total care" of leukaemic patients, is never thought of by the medical or nursing staff.

These problems make the management of leukaemia very difficult, frustrating and often unrewarding in our setting. It is not surprising that Essien (77) has blamed similar adverse factors for shorter period of survival in Nigerian patients with acute leukaemia.

## The present and future perspectives.

### Aetiological implications.

The geographical distribution of leukaemia as observed from the present study does not show a definite pattern that would incriminate any specific environmental factor as a leukaemogen. Instead, the spatial distribution correlates with the availability of medical services. However, the age, sex and type stratification appears to implicate multiple aetiological factors that could be working on vulnerable population groups at various stages of life. For instance, a peak occurrence of ALL in the 0-4 age-group suggests that a prenatal leukaemogenic stimulus is at work as has been shown by Tomatis et al (126) in experimental animals. This is unlikely to be artificial radiation as the mothers of the entire group did not have prenatal x-rays of any form. The likely possibilities are:- intrauterine viral infections; prenatal natural background radiation in small doses on vulnerable tissue, and effect of the diverse traditional herbs used by mothers in pregnancy. The fact that embryonal tumours which are well known to be causally associated with prenatal carcinogenic agents, have a peak occurrence in Kenyan children of the same age group (Table 41), lends further support to the contention of a prenatal stimulus. Postnatal factors such as leukaemogens transmitted from the mother to the infant through milk, as well as transient infantile immunodeficiencies cannot be underestimated although I have no supporting evidence. However, this may not be the whole story as there must be a modulating inherent factor to explain the sex differential. The female hormones may be playing an important role in this respect. Genetic factors do not appear to have played a discernible role in patients in this series, as there were no familial cases and no cases were documented in twins.

The peak occurrence of ALSCL in the 5-9 age group conforms to the age distribution pattern of lymphomas (Table 41).

Table 41: Age distribution of childhood malignancies at KNH.

| Type of cancer | Age in years | | | |
|---|---|---|---|---|
| | 0-4 | 5-9 | 10-14 | Total |
| All types of leukaemia. | 24. | 28 | 29 | 81 |
| Lymphomas (excluding Burkitt's) | 12 | 30 | 14 | 56 |
| *Solid tumours | 44 | 10 | 4 | 58 |

* Including nephroblastoma, neuroblastoma and embryonal sarcoma.

This implies that the causative agent for lymphoma is the same as for ALSCL. Could this be a virus acting on the vulnerable subjects in early childhood? Although the cases of ALSCL leukaemia are too few for any credible statistical evaluation, there appears to be no correlation with malaria endemicity.

The progressive rise in the prevalence of acute non-lymphocytic leukaemia (ANLL), attaining a peak in the 2nd decade of life, but continuing in to the 3rd decade, coupled with the disappearance of the sex differential is manifestly in favour of an environmental leukaemogen to which both sexes are exposed. This is also the period during which there is maximum spurt in tissue growth and activity, the haemopoietic system not excepted. Thus, the leukaemogen which could be a chemical or radiation in the environment, acts on a haemopoietic tissue that is highly labile such that minimal stimulus is required to trigger off the leukaemic process. The role of agricultural chemicals, insecticides, carcinogens in food and sex hormones needs to be carefully investigated as far as the cause of ANLL in this age group is concerned. Viral leukaemogens are unlikely to have any significant role during this age group because, as adolescents, they would already have been exposed to diverse viral infections of early childhood, and allowing for the latent peak period of 3-4 years, most of the ANLL would occur by the tenth year of life. The role of genetic factors cannot be accurately evaluated, as none of the patients had constitutional defects and no cytogenetic studies were carried out to rule out chromosomal abnormalities.

Chronic granulocytic leukaemia attains a peak prevalence in the 25-35 year period; this is two to three decades before the peak reported in whites. This suggests that the leukaemogen operational in ANLL might be the same one responsible for causing CGL in the Kenyan population. It may be probable that large doses of the leukaemogen induce ANLL and small repeated doses of the same agent induce CGL at a later period in life as the latter has a longer doubling time. It is however difficult to explain the difference in sex distribution. It is probable that the decreased female predilection in CGL is either due to a protective female hormone or that males are more exposed to the leukaemogen in the environment than females as they are the principal wage earners.

Chronic lymphocytic leukaemia is typically a disease of old age and it is probably a product of the waning immuno-competence as well as viral leukaemogens. The persistent stimulation of the lymphoreticular tissues by malaria and other parasitic agents prepares fertile ground for the viral leukaemogen. But unlike the case in ALSCL, the waning immunity may be a permissive factor for early bone marrow involvement with the consequent early leukaemic component in CLL.

The foregoing discussion on the aetiological factors in leukaemia in the Kenyan environment is purely speculative. However, this speculation is important ground-work in planning research, which will first identify the leukaemia problem adequately and secondly open further avenues for studies to identify causal factors. With the positive identification of causal factors, then appropriate preventive measures can be instituted. This concept has been aptly expressed by WHO as follows: "the first priority in developing countries is the measurement of the extent and nature of the cancer problem and the development of the appropriate social and scientific technology necessary for control" (127). This is of prime importance with regard to leukaemia in Kenya as there is clear evidence that it is prevalent and that it accounts for 4% of deaths at KNH. Since the causes of a great majority of cancers may be environmentally determined, and thus preventable (128, 129), leukaemia is not an exception. Hence, community based studies to correlate the type of leukaemia with specific environmental factors and the understanding of its biological behaviour may throw light on its causes in this country. This step is prerequisite for preventive measures. Animal experiments for scientific proof of aetiology can follow later.

Diagnosis and treatment.

Prevention of leukaemia is not feasible at the moment and in the foreseeable future. An effort must therefore be made to effectively tackle it therapeutically. The clinicians should however be aware of it and their index of suspicion for the disease must increase for the diagnosis to be made early

Leukaemia should be considered in a patient who has hepato-splenomegaly, anaemia, lymph node enlargement with or without a bleeding tendency and fever. It is time clinicians changed their out-dated attitude that leukaemia is uncommon and hence unimportant in Kenya. Its prevalence must be emphasized to the undergraduates; technicians should be taught how to diagnose it in the laboratory, and health authorities as well as medical planners should have knowledge of its size.

There is no doubt that successful treatment of leukaemia not only increases the life expectancy of the patient but also improves the quality of survival. Past data did not indicate that treatment improved survival in chronic leukaemias but recent data show that it has significantly improved (119). Newer and improved therapeutic regimens, particularly those using a multimodal approach, with the understanding of cell kinetic patterns, are increasingly producing higher rates of remission than have been previously achieved in acute lymphocytic leukaemia (130). Complete remissions, currently achieved, tend to be longer lasting than in the past and the outlook in acute myelogenous leukaemia has also changed remarkably for the better (131).

What policy should then be adopted? As previously suggested (132), the confirmation of the diagnosis and first-phase treatment should be conducted at a centre where the expertise, drugs, and supportive services such as radiotherapy, radio-diagnosis, and laboratory facilities are available. This calls for skilled interdisciplinary team work, which renders decentralization of leukaemia management extremely difficult in a developing country such as Kenya. Physicians in peripheral hospitals have a vital role to play in the follow-up of these patients, and the execution of the second phase of management, i.e. supervision of maintenance therapy and surveillance. For the patients, this is of great advantage because they stay with their families and they do not have to travel long distances. Only by more awareness, early diagnosis and aggressive total therapy can we hope to improve survival of leukaemic patients in this country.

## CONCLUSIONS.

Leukaemia is not uncommon in Kenya as it has, a calculated incidence of of 1.2 per 100,000 of the population at present. It is probably much higher because, due to underdiagnosis and hospital non-attendance by the majority of patients, the cases seen represent only a small portion of the undiagnosed pool. Childhood leukaemia, particularly ALL, is under-represented in the 0-4 age group because of misdiagnosis as well as missed diagnosis.

Myelogenous leukaemias, both acute and chronic, are almost twice as common as the lymphocytic forms. This is probably a function of leukaemogenic agents at work and not a mere under-representation of the lymphocytic leukaemias that may appear to explain the relative excess of ANLL.

The geographical distribution of leukaemia reveals no obvious aetiological affiliations, including malaria endemicity; but instead closely correlates with the availability of medical services. However, the age pattern vis-a-vis the type distribution seem to be causally determined. The aetiological agents which should be investigated should include herbs which are in common use as traditional medicine; agricultural insecticides; viruses; excessive background radiation, and the commercial pharmaceutical agents which are flooding the markets of developing countries. The high carrier rate of hepatitis B antigen is a point that needs careful evaluation in relation to the preponderance of ANLL.

The real overall and age/type-specific incidence of leukaemia in Kenya needs to be determined from community based studies of anaemia for the following reasons. First, it is with the knowledge of the size of the leukaemia problem that medical planners and health authorities will be accordingly advised. Secondly, it is with such knowledge that aetiological implications based on epidemiological data will be carefully evaluated. Lastly, preventive measures can only be instituted successfully if such information is available.

At present, leukaemic patients almost invariably present with advanced disease for reasons which have already been discussed. If early diagnosis - which is also one of the vital factors that contribute to successful treatment - is a dream that will once come true, all cadres of health personnel must be made conscious of the remarkably high prevalence of leukaemia in Kenya; it is infact the highest that has been reported from sub-Saharan Africa up to date. The clinician should also be acutely aware of the protean manifestations of the disease and its mimickry of a whole diversity of tropical diseases.

The outlook in Kenyan leukaemic patients is evidently poorer than it is in American whites or Europeans. The disease appears to be more aggressive as remission induction results are poor and a large proportion of acute leukaemia patients die within the first month of diagnosis. Survivals are short in the patients who attain remission but the quality of life is reasonable.

In spite of the underlined medical priorities in national policies of a developing country such as Kenya and the heavy costs that are incurred in treating leukaemic patients, these patients should be admitted for evaluation, diagnosis and terminal care. For, unless the latter is the only form of treatment that can be offered, intensive initial evaluation should be carried out at a centre where there is expertise, well integrated team work and supporting services; this is then followed by the first phase of treatment at the same centre. The second phase of treatment is subsequently effected at a peripheral hospital or the haematology clinic of the referral centre. These patients need to be treated without reservation so that they may benefit from the modern advances in cancer chemotherapy. Thus, the changing aspects of leukaemia in Kenya should not only be realised in data collection, but also in the care of the patient. The debate of whether to treat or not to treat is an age-old scandal that should be relegated to the past to give way to how best leukaemic patients can be treated.

CHAPTER FIVE

APPENDIX I - III

FIGURES

BIBLIOGRAPHY.

## 1. Periodic acid-Schiff's (PAS) reaction:

Reagents:-

(i) Fixative:- Ethanol-9 parts and formalin (40% formaldehyde) 1 part.

(ii) 1% Periodic acid (wt/v) in distilled water. Store in a dark bottle and renew every three months.

(iii) Schiff's reagent (basic fuchsin). Add 1 g basic fuchsin to 400 ml of boiling distilled water. Allow to cool and filter. Add 1 g sodium metabisuphite and leave for 24 hours. Add 2 g activated charcoal to decolorize and filter. Store in a dark bottle and renew every 2-3 months.

(iv) $SO_2$-water 10% (wt/v) sodium metabisuphite in distilled water - 10 ml.

(v) M-HCl - 10 ml.

(vi) Distilled water to -200 ml.

(vii) Counterstain: Harris's haematoxylin - (any aqueous haematoxylin is satisfactory).

Method:-

(i) Fix air-dried smear for 10 minutes in 10 percent formol-ethanol. Wash in tap water. Note that old methanol-fixed or Romanowsky-stained smears, even if years old, can be satisfactorily stained. Decolorization is unnecessary.

(ii) Treat with 1% periodic acid for 10 minutes. Wash briefly in tap water.

(iii) Immerse in Schiff's reagent for 30 minutes.

(iv) Immerse in three changes of $SO_2$-water for 2-3 minutes each.

(v) Wash in tap water and counterstain with Harris's haematoxylin for 10 minutes.

## 2. Sudan Black.

Reagents:-

(i) Fixative:- Formalin (40% formaldehyde).

(ii) Sudan Black B.

(iii) Stock solution:- 0.3% (wt/v) in absolute ethanol.

Phenol - 16 g.

Absolute ethanol - 30 ml.

hydrogen phosphate ($12.H_2O$).

(iv) Working solution:
Stock Sudan Black B - 40 ml.
Phenol buffer - 60 ml.
Filter. Renew after 2-3 months.
70% Ethanol (v/v) in distilled water.

Method:-

(i) Fix smears in formalin vapour for 5-10 minutes.
(ii) Wash in tap water for 10 minutes.
(iii) Stain in working solution Sudan Black B for 1 hour.
(iv) Wash in 70% ethanol for 2-3 minutes to remove excess stain.
(v) Wash briefly in tap water and counterstain by a Romanowsky method.

3. Leucocyte alkaline phosphatase.

Reagents:-

(i) Fixative:- Methanol - 9 parts and formalin (40% formaldehyde) - 1 part.
Store at $4^{o}C$.
(ii) Propanediol buffer, pH 9.75 (0.05 M)
(iii) Stock solution:- 0.2 M propanediol - 10.5 g.
Distilled water - 500 ml.
(iv) Working solution:- Stock propanediol buffer - 25 ml.
0.1 M-HCl - 5 ml.
Distilled water to 100 ml.
Store at $4^{o}C$.
(v) Sodium-naphthyl phosphate and Brentamine Fast Garnet -35 mg amounts stored in sealed polythene bags.
(vi) Counterstain:- 2% methyl green (wt/v) in distilled water. Extract with one-half volume of chloroform for 48 hours to remove contaminating methyl violet.

Method:-

(i) Fix air-dried smears of fresh unanticoagulated blood for 30 seconds in 10% formol-methanol at $0-4^{o}C$. Wash for 10 seconds in tap water. Note that anticoagulants, particularly EDTA inhibit staining to a variable degree.

(ii) Prepare the following substrate solution immediately before use and filter through rapid filter paper on to the slides.
Sodium naphthyl phosphate - 35 mg.
Brentamine Fast Garnet - 35 mg.
Working buffer - 35 ml.
Note that fresh substrate must be used as Bretamine Fast Garnet is unstable in solution. Substrate should be applied within 3 minutes of prepration as coupling activity falls rapidly. Allow to react 8-10 minutes. Wash in tap water for 10 seconds.

(iii) Counterstain with methyl green-15 minutes. Wash in tap water. Positive control is smears from a pregnant woman or a patient with a polymorphonuclear leucocytosis due to an infection. A normal smear should also be included with each batch of slides.

4. Feulgen reaction.

Reagents:-

(i) N. Hydrochloric acid.
(ii) May-Grunwald stain.
(iii) Giemsa stain.
(iv) Buffer pH 6.8
(v) Fixative - 1 part of 40% formaldehyde added to 9 parts of 95% alcohol.

Method:-

(i) Fix the slides in the fixative for 5 minutes.
(ii) Wash in tap water.
(iii) Hydrolyse in N.HCl at 56°C for 15 minutes.
(iv) Wash in tap water.
(v) Stain with May-Grunwald - Giemsa, as routinely.
(vi) Wash in buffer, dry and mount.
When using leucobasic fuchsin, after stage (3) flood the slide with the fuchsin for 5 minutes, and wash in water, dry and examine.

Appendix Ia - Sample of information cards used for data collection.

| | | |
|---|---|---|
| | JOHN KENNEDY NJENGA | KNH 2/71 |
| | Age - 4 Male | Kikuyu |
| | Bilateral Proptosis.<br>(R) otitis media.<br>? Leukaemia. | |
| | Hb - 7.8; WBC - 29,600 (Blasts - 30%)<br>Platelets - 50,000. | |
| 00/460<br>1971. | Dx. ACUTE MYELOBLASTIC LEUKAEMIA WITH RETROBULBAR CHLOROMATA. | |

Appendix II - Total supportive care of leukaemic patients

(1) The technique for i.v. administration of cytotoxic drugs.

(i) Select a site and use veins in arms and hands whenever possible. Use ankle or foot veins only when a suitable upper extremity vein cannot be found. Even then, do this only in an emergency and preferably only in children.

(ii) Try not to use the same vein repeatedly. For frequent infusions, rotate the sites of venipuncture.

(iii) The use of scalp vein needles is strongly recommended. Use a size 21 or 23 (size 23 is better for children). If you use a straight needle, use a size 21. Larger needles cause more vein scarring than smaller ones.

(iv) Prepare the skin by rubbing alcohol on the surface. Mechanical, hard rubbing is required to prepare the skin properly.

(v) Place a tourniquet around the arm above the site selected.

(vi) If, after applying the tourniquet, a vein will not become prominent enough for needle insertion, try the following manoeuvres:-

(a) Hang the arm down, open and close fist slowly and deliberately. While the arm is still down, apply a tourniquet. Then bring the arm up to normal position.

(b) Alternatively, soak the arm for five minutes in a basin of warm water.

(vii) Have all of your material ready- adhesive tape torn in proper length, infusion set or syringe set up ready for use, and the drugs already dissolved and drawn up in syringes.

(viii) Insert needle into the skin, remembering to keep the level of the needle up. Once under the skin, go into the vein, then secure the needle with a piece of tape.

(ix) Connect the syringe to the needle and push some saline in to be certain that the needle is in the vein properly. After the vein is clearly found to be open, begin the infusion of the drugs, <u>starting with the most irritant.</u>

(x) If the needle becomes dislodged, the saline or drugs will go into surrounding tissues, and the infusion site will swell and be quite painful. Discontinue the infusion and start over with a fresh needle. At the end of drug injection, flush the vein with 10 ml normal saline.

(xi) After pulling the needle out of the vein, apply gentle pressure to the puncture site with a piece of dry cotton. You may then cover the site with a bandaid, although this is not necessary if bleeding has stopped.

Points to remember:

(i) Always use a clean technique - do not touch the needle or tip of the infusion set. If any of these parts become contaminated, discard and use fresh equipment; the risk of infection is much greater if these precautions are not observed.

(ii) The veins are the patient's most precious possession. Take care of them! The patient's life depends on them!

(iii) A thrombocytopenic patient should not be given intramuscular injections.

2. Dealing with anaemia and bleeding. (96, 134)

(a) General considerations.

Anaemia, particularly mild (8-10 g/dl), is invariable in patients suffering from haemopoietic malignancy. A good proportion of the patients suffer severe anaemia (less than 6 g/dl). The anaemia is of multiple aetiology: bone marrow infiltration and replacement, bleeding, nutritional deficiency, myelosuppression due to the primary disease as well as cytotoxic therapy and accelerated destruction at both intra- and extramedullary sites (96 )

Bleeding complications, on the other hand are mainly a function of the platelet count (134). Spontaneous haemorrhages are most likely to occur at platelet counts of less than $20 \times 10^9/l$. Bleeding invariably complicates over 95% of the cases with platelet counts of less than $10 \times 10^9/l$. Aggravating factors include consumption coagulopathies, infections, high leucocyte counts and qualitative platelet abnormalities. The haemoglobin and platelet count values should be carefully monitored.

(b) Anaemia:

For all the patients on treatment, haemoglobin level must be maintained above 8 g/dl. All the patients dropping the haemoglobin level below 6 g/dl should be transfused with red cell concentrates according to the following formula for children: $\frac{V}{2} = \frac{D \times W \times 6}{}$, where V is the volume of the red cell concentrate in ml that would raise the haemoglobin in g/dl by a deficit D in a subject of weight W Kg; 6 is a constant factor. One unit of packed cells infused should raise the haemoglobin level by about 1 g/dl in a subject whose surface area is $1M^2$

Precautions must be taken to ensure that acute pulmonary edema is not precipitated in the chronically anaemic patient.

c) Bleeding complications.

Patients maintaining platelet counts of above $50x10^9/1$ are unlikely to suffer a life threatening spontaneous haemorrhage, but platelet concentrates or platelet rich plasma should be administered to all patients having a platelet count below $20x10^9/1$ and having evidence of active bleeding. All patients with platelet count below $10x10^9/1$ need a platelet infusion, but every patient should be considered on merit. Repeated platelet infusions readily lead to the development of platelet alloantibodies. HL-A typed platelets if available would delay this phenomenon. Nevertheless, one unit of platelet concentrate contains $10^{11}$ platelets and may raise the platelet count by $10-12x10^9/1$ in a subject with surface area of $1M^2$. In cases of DIC, heparin therapy is recommended, but very careful monitoring of the coagulation status is mandatory.

3. Dealing with infections. (99, 135)

(a) General considerations.

The incidence of infection is high and accounts for about 2/3 of deaths and certainly the commonest cause of death in leukaemic patients in Kenya whereas intracranial haemorrhage accounts for 20%. Seventy percent of the patients who have pyrexia, have infection. Fifty percent with pseudomonas septicaemia die within 24 hours of presentation unless energetically treated. The predisposing factors include:-the neutropenic state arising from chemotherapy and the leukaemic process and defective function of the phagocytes; effect of cytotoxic drugs on the mucosae of the respiratory and gastro-intestinal tract inflicts damage, which thus facilitates the entry of bacteria, which are otherwise commensals, in to the blood stream; immunological aberrations such as monocyte dysfunction; high blast cell counts plus thrombocytopenia which predispose to easy bacterial invasion. The causative organisms may be categorized as follows:- bacterial - Staph. aureus and the pneumococcus; the majority of gram negative organisms (50%) are Pseudomonas, then Bacteroides, Klebsiella, Proteus and Salmonellae. Others are fungal - moniliasis, mainly oral and tinea corporis; protozoa - include malaria.

The possibility of viral infection should not be ruled out:- measles, chicken pox, herpes zoster and herpes simplex.

(b) The policy of dealing with bacterial infections.

Investigations should include:- swabs of laryngeal secretions for culture or sputum if available; stool cultures; urine culture and any obviously septic areas; within 24 hours, preferably before commencing on therapy.

Management takes the following pattern:- prophylactic neutropenic regimen of mouth wash with hibitane, hibitane cream for nasal and axillary regions, and daily alteration of linen; antibiotic therapy in which it is advisable to give massive doses in the first 24 hours (LOADING). All this is done with immediate effect when a patient develops pyrexia (over 38°C) and it does not subside within 12 hours.

Antibiotics should be witheld until pathogens are isolated, but if the clinical state does not permit delay, monitor as above and commence on antibiotics; then treat as sensitivity indicates when bacteriological results are available.

If the organism is unknown, commence on broad spectrum bactericidal therapy, with gentamicin, lincomycin in combination with crystalline penicillin as the first choice. For gentamicin, the first 24 hours, 6 mg/kg/24 hours, given in 4 (6-hourly) divided bolus injections; subsequently, 4 mg/kg/24 hours, given in 3 (8-hourly) divided bolus injections. Additional antibiotics would be indicated in the following situations:- fulminating septicaemia - if Pseudomonas is suspected - add carbenicillin (5 G i.v. 4-hourly) and probenecid (1 G oral b.d.); possible pneumococcal (usually respiratory infection), add cephalothin ( 1-2 G i.v. 4-hourly); possible Bacteroides (usually intra-abdominal infection), add clindamycin (300 mg infusion 12-hourly); organisms other than bacterial or viral, such as candidiasis should be treated conventionally.

4. Administration of protective gamma-globulin (136).

(a) General considerations.

Gamma-globulin is fully effective only if administered during the first 7 days of incubation:- injections should therefore be given, if possible, within 7 days of the first exposure to measles or chicken pox. A primary case may be considered infective at least 4 days before and 5 days after

the first appearance of the rash.

The injection of gamma-globulin is of little value after the 7th or 8th day of incubation. However, double the 'protective' dose given on the 9th to 12th day may lead to some modification of the symptoms, and this course is indicated in gravely ill patients who have been exposed to measles, when it has not been possible to give an earlier injection.

(b) Dosages.

These will depend on the commercial product being used and as recommended by the manufacturer but in deciding whether a protective or modifying dose is to be given, the following points should be taken into account:- after a 'modified' attack of measles, lasting immunity results but not after complete protection, hence a modifying dose is preferable to the protective, but a smaller dose may occasionally fail to give substantial modification, and if the contact was seriously ill, the full protective dose should be given; even after a protective dose measles may still occur, though in a greatly modified form; the immunity conferred by a protective dose lasts for only about 4 weeks, therefore in event of repeated exposure, a further prophylactic injection will be required after this time, if continued protection is desired.

(c) Group prophylaxis.

When a group of children in the ward have been exposed to measles and chicken pox, each contact should be considered individually and a protective or modifying dose given in accordance with the above recommendations. Whenever it is practicable, the spread of infection is also prevented by isolation of contacts.

## Appendix III - Illustrative case reports.

### Case 1 - Unit No. 18372/70 (Coexistence of CLL & CGL).

G.N., a 40-year male-Kikuyu, was admitted to KNH towards the end of December 1970. He complained of left sided chest pain, dizziness, bilateral ankle oedema and palpitations, for three weeks. On clinical examination, he had severe pallor; generalised, rubbery, discrete and non-tender lymphadenopathy in the cervical, axillary and inguinal regions; the liver was enlarged to 4 cm below the costal margin but the spleen was not palpable. He had signs of pneumonia on the left side.

Initial laboratory investigations included the following:- haemogram - Hb - 4.8 g/dl, WBC - $60.6 \times 10^9$/l (with a differential count of neutrophils - 26% and lymphocytes - 74%); platelet count - $236 \times 10^9$/l; chest x-ray showed consolidation of the left lower lobe - consistent with a pneumonic process; serum electrolytes and urea were normal; serum proteins revealed a reduced globulin content (1.4 g/dl); bone marrow examination showed features "consistent with chronic lymphocytic leukaemia or lymphosarcoma cell leukaemia"; lymph node biopsy showed "lymphocytic infiltration; not diagnostic".

A diagnosis of chronic lymphocytic leukaemia was made and he was treated with chlorambucil and prednisone for two months (January and February 1971). Chlorambucil alone was continued until June 1971 and then stopped. At this time, the peripheral blood picture had reverted to normal, although a bone marrow examination was not done.

He was followed up without any treatment until January 1973, when he presented with back pain. X-ray of the spine revealed erosion of $L_2$ anteriorly. He was not anaemic; neither the spleen nor the liver was palpable; lymphadenopathy was not elicited. Haematological evaluation consisted of Hb - 15.0 g/dl, WBC - $5.8 \times 10^9$/l (with a normal differential) and platelet count - $87 \times 10^9$/l. For some unknown reason, (probably because of thrombocytopenia) chlorambucil therapy was reinstituted. It was continued until April 1973, then, stopped and resumed again from September 1973 and continued until June 1974.

For the whole of 1973, the haemoglobin level varied between 13 and 15 g/dl; the total WBC count oscillated between 5 and $13 \times 10^9$/l but the differential count remained within the normal

limits; platelet counts remained below the lower normal limit, varying between $42x10^9/l$ and $125x10^9/l$. This situation persisted until August 1974 when it was noticed that the total white cell count was rising, but strangely, due to a neutrophil leucocytosis and not lymphocytosis (Table 43).

He was readmitted in September 1974 for further evaluation. At this time, he had bilateral cervical and submandibular lymphadenopathy but the spleen and liver were not palpable. A bone marrow showed "increased myeloid activity", which was considered to be a leukaemoid reaction although CGL was queried. He was discharged for follow up in the clinic without antileukaemic therapy.

He was readmitted, in December 1974, with severe backache, upper respiratory tract infection and a painful right hip-joint. X-ray of the spine was interpreted as showing "features of degenerative spondylitis". After being investigated, he was discharged, to be closely followed up until June 1975 when he had a recurrence of backache and generalised bone pain. Chlorambucil therapy was reinstituted at the same time and continued until November. In October 1975, he developed a tender right hip with an ischio-rectal abscess due to tuberculosis. Treatment for this was instituted.

A leucocyte alkaline phosphatase estimation done at this time, demonstrated a diminished activity, (down to a score of 2, when the normal range is 70-130). From this result and the bone marrow appearance, a diagnosis of CGL was established. This was further confirmed by cytogenetic studies which demonstrated a positive Philadelphia chromosome. He developed cervical and inguinal lymphadenopathy in June 1976. A lymph node biopsy was reported as "lymphocytic lymphoma compatible with chronic lymphocytic leukaemia". Neither the liver nor spleen were palpable. Busulphan was commenced in October when the total WBC count had risen to $154x10^9/l$. Busulphan therapy was continued until June 1977, when the WBC count had come down to $20.3x10^9/l$ with a normal differential count. He had a bout of Herpes Zoster in April. Chlorambucil was resumed in October 1977 and continued until the patient was lost to follow up in December 1977.

Table 43: Serial haematological parameters in case 1.

| YEAR | 1971 | 1972 | 1973 | | 1974 | | 1975 | | 1976 | 1977 |
|---|---|---|---|---|---|---|---|---|---|---|
| MONTH | JAN. | JUNE | JAN. | DEC. | MARCH | AUG. | SEPT. | MAY | JUNE | NOV. |
| Hb g/dl | 4.8 | 14.0 | 15.0 | 14.3 | 13.4 | 15.0 | 14.4 | 14.6 | 10.0 | 12.2 |
| Total WBC x $10^9$/l | 60 | 8.8 | 5.8 | 12.2 | 12.2 | 24.8 | 23.3 | 59 | 96.9 | 92.0 |
| Neutros. % | 26 | 68 | 66 | 53 | NORMAL | - | 56 | 37 | 59 | 50 |
| Lymphos % | 74 | 30 | 34 | 17 | | - | 19 | 30 | 30 | 45 |
| Monos % | - | - | - | 3 | | - | 5 | 1 | - | - |
| Eosinos % | - | - | - | 27 | | - | 2 | 1 | - | - |
| Myelos % | - | 2 | - | - | | - | 12 | 23 | 11 | 5 |
| Blasts % | - | - | - | - | | - | 6 | 8 | - | - |
| Platelets x$10^9$/l | 236 | Normal | 87 | 90 | 125 | - | - | 170 | - | 394 |
| P.B. Film | - | - | - | - | - | ?CGL | - | - | - | - |
| Bone marrow | CLL | - | - | - | - | - | CGL | - | - | - |

In summary, this patient suffered from lymphoproliferative and myeloproliferative disorders, concurrently, which were complicated by tuberculosis.

Comment: This is an extremely intriguing case, which started off as an uncomplicated stage III CLL, whose degree of anaemia was very severe. There is no doubt that the patient later developed CGL as was evident from the haematological picture, low leucocyte alkaline phosphatase activity and the positive Philadelphia chromosome. Two processes coexisted; CGL involved the bone marrow while the lymphoproliferative process predominantly affected the lymph nodes, (node biopsy results consistently showed a lymphoproliferative disorder and at no time was the spleen palpable in the course of the patient's illness). This indicates that whereas CGL is a primary bone marrow proliferative process, CLL infiltrates the bone marrow secondarily. If they coexist in the marrow, CGL would necessarily crowd out the lymphoproliferative process.

The crucial question is did the two processes arise independently or did they have the same underlying aetiological factor but developed from two different stem cells? Alternatively, did they arise from the same stem cell and developed along two separate cell clonal lines? The first proposition is probably the most favourable for the proponents of the dualistic origin of the haemopoietic stem cell. If the alternative proposal is true, then this case supports the unifying concept of the myeloid and lymphoid stem cells. This is a concept that appears to be gaining ground, as Gibbs et al (138) have recently detected the Philadelphia chromosome in lymphoblasts of two patients with ALL. Further, the lymphoblastoid transformation of some cases of CGL, associated with P.A.S. positivity of transformed blast cells, as well as more favourable response to chemotherapy (139), tends to support the unitary origin of the haemopoietic stem cell. Nevertheless, where the present case falls is anybody's guess because the Philadelphia chromosome studies were not done in the leukaemic lymphocytes.

Tuberculosis, as a complication of CGL or other haemopoietic malignancies, is not uncommon in the tropical

environment. But the problem it raises at times is whether the haematological abnormality is a leukaemoid reaction. There is no doubt in this case that CLL antedated tuberculosis and the myeloproliferative process was proved to be CGL.

Loss to follow is one of our leading problems in leukaemia management. It would have been very informative to have finally done an autopsy on this patient to determine the extent of the two processes. Two other patients in the series had coexisting CGL with lymphoma. One had CGL with poorly differentiated lymphoma and the other had CGL with a well differentiated lymphoma. These have been referred to in the main text.

Case 2 - Unit No. 127296. (Illustrating typical chloromatous presentation).

S.G., a $4\frac{1}{2}$ old-year male Kikuyu presented to KNH, ENT unit, on 10-1-75 with a 3-weeks' history of asymmetrical bilateral proptosis which was more marked on the right than the left side. He also complained of eye-ache and right sided blindness of the same duration.

On clinical examination, he was febrile, pale and had bilateral proptosis. The right eye had normal extra-ocular movements, but it was completely blind and the pupil reacted to light only sluggishly. The left eye had good residual vision and the pupil reacted to light normally. He had axillary and inguinal lymphadenopathy, but the spleen and liver were not palpable. A differential diagnosis of neuroblastoma or Burkitt's lymphoma was considered.

Laboratory evaluation included the following tests:- haemogram - Hb - 8.0 g/dl, platelet count - $27 \times 10^9/l$, WBC - $12.3 \times 10^9/l$ (neutrophils - 21%, lymphocytes - 65%, myelocytes - 14%; orbital x-ray showed a soft tissue mass in both orbits, causing protrution of the eye balls; I.V.P. was normal; supraorbital biopsy was histologically interpreted as "tumour,= considered to be lymphoma" (S3310/75).

The histological report was taken to mean Burkitt's tumour and the patient was accordingly started on cytotoxic therapy (vincristine and orthomelphalan) on 1-2-75. In spite of a blood film report in February on which blast cells were seen

(Table 44) and a diagnosis of leukaemia suggested, cytotoxic therapy was continued for a further two months. The general condition of the patient improved and the bilateral proptosis is said to have "much regressed". A lumbar puncture done at this time was normal. He had an episode of orbital cellulitis but this was successfully treated.

At the beginning of May 1975, the presence of blast cells was again reported on peripheral blood film. This time, a blood transfusion was given to correct anaemia and a bone marrow was done. This bone marrow was reported as having been "totally replaced by primitive mononuclear cells ---- the overall picture being that of acute myelomonocytic leukaemia". A review of the biopsy showed a granulosarcoma.

The patient was at this time, transferred to be under my care. After baseline evaluation (liver function tests, haemogram, serum electrolytes, urea and uric acid were done), he was started on "Bart's III" protocol (daunorubicin and cytosine arabinoside) and was given 6 courses of the regimen. As it is, however, apparent from Table 44, remission was never achieved.

His general condition continued, in status quo until June 1975 when he developed hepatomegaly ( 5 cm below the costal margin), joint pains and painful right calf muscles. He started deteriorating and he developed bed sores. Several episodes of bronchopneumonia in August 1975 were successfully treated. His general condition did not improve and the bed sores became worse in spite of dressing them, blood transfusions for anaemia and antibiotic treatment for infection.

The patient started bleeding from the gums, nose, per rectum and per urethram in mid-October 1975. This continued relentlessly in spite of platelet infusion as well as blood transfusion. He terminally developed fever with generalised purpura and died of what was clinically believed to be an intracranial haemorrhage. Consent for autopsy was not given.

Comment:-

This case was interesting in a number of ways:-

(i) It was a bilateral retrobulbar chloroma which was clinically thought to be either Burkitt's lymphoma or neuroblastoma.

Table 44: Monthly haematological parameters for case 2.

| Month | Jan. | Feb. | March | April | May | June | July | Aug. | Sept | Oct. |
|---|---|---|---|---|---|---|---|---|---|---|
| Hb g/dl | 6.8 | 7.4 | 13.0 | 9.7 | 7.0 | 8.8 | 6.8 | 7.1 | 8.5 | 7.6 |
| Total WBCx$10^9$/1 | 6.7 | 4.1 | 9.4 | 9.5 | 7.8 | 7.3 | 6.8 | 11.8 | 14.9 | 29.5 |
| Polys % | 31 | 30 | - | - | 78 | 18 | 9 | 22 | 46 | 8 |
| Lymphos % | 63 | 30 | - | - | 10 | 33 | 56 | 39 | 16 | - |
| Monos % | 5 | - | - | - | - | 8 | 3 | 6 | 3 | 7 |
| Eosinos % | 1 | - | - | - | 4 | 1 | - | - | - | - |
| Myelos % | - | 6 | - | - | - | - | 5 | 3 | 28 | - |
| Blasts % | - | 34 | - | - | 8 | 40 | 27 | 30 | 7 | 85 |
| Platelet count x $10^9$/1 | 92.5 | - | 128 | 162 | 289. | 48 | 55 | 89 | 152 | 19 |

(ii) The histological diagnosis was non-specific, although a lymphoma was suggested.

(iii) Blast cells must have been counted as lymphocytes in the first blood film report. This is a common mistake made by the technical staff. In spite of a report of blast cells in one of the peripheral blood films, the patient was treated as Burkitt's lymphoma without any confirmatory evidence for the latter diagnosis.

(iv) Although the patient clinically improved and the proptosis regressed, his haematological picture did not change much. Thus, the cytotoxic therapy which was used was only partially effective.

(v) He never responded to the appropriate therapy when it was started. This is probably because the disease was either resistant to chemotherapy ab initio or resistance had developed as a result previous therapy.

This particular case was undiagnosed clinically and histologically, and missed haematologically on initial appraisal. However, the most important lesson to learn from this case is the clinical confusion between chloroma and Burkitt's lymphoma or neuroblastoma and the grave oversight and misinterpretation of laboratory reports by the clinicians.

The haematological report of blast cells was overlooked while the histological diagnosis of "lymphoma" was taken to mean Burkitt's tumour. The easily mistakable histological appearance of chloroma for lymphoma is well known (140, 141). Histopathologists working in sub-Saharan Africa (in the lymphoma belt) should be aware of this to be able to avoid being misled by clinical impressions. This, I am sure, is a common mistake and many cases which have been labelled as Burkitt's lymphoma are likely to be chloromatous deposits around the face.

Case 3 - Unit No. 219211. (Illustration of the course of ALSCL).

E.M., a 6-year male-Kikuyu, was admitted to KNH on 7-3-77 with complaints of bilateral, painless submandibular and parotid swellings of two-weeks' duration. He had had chicken pox previously, which had left scars on the whole body. He also had developed a left axillary lymph node enlargement, a biopsy of which had been done at a peripheral hospital.

The salient findings on clinical examination were marked submandibular and parotid lymphadenopathy (Fig. 27); slight bilateral axillary lymph node enlargement; a mass in the left iliac fossa; multiple small scars all over the body; non-tender testicular enlargement. The liver and spleen were not palpable at this time.

Initial laboratory investigations included the following:- a lymph node biopsy (S/8292/76) done at the referring hospital was reported as "lymphoblastic lymphoma, the morphology of which was in keeping with Burkitt's lymphoma"; the first three successive blood counts and the subsequent ones are shown in Table 45; the bone marrow was reported as showing "normal erythroid and granulocytic activity with mild lymphocytosis"; serum electrolytes, urea and uric acid, and liver function tests were normal; chest and skull x-rays were normal.

A diagnosis of lymphocytic lymphoma, poorly differentiated, was made and the patient was due to start on chemotherapy when subsequent laboratory reports showed a sudden surge in leucocyte count (Table 45). A repeat bone marrow at this time showed "95% replacement by primitive lymphoid cells, that exhibited a maturation spectrum and had P.A.S. positive granules in the cytoplasm. ----------compatible with acute

Table 45: Haematological parameters during the course of case 3.

| Month | March | | | April | | May | June | July | Aug. | Sept. | Oct. | Nov. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | 2 | 3 | 4 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 3 |
| Hb g/dl | 12.5 | 12.5 | 10.4 | 9.6 | 7.1 | 9.9. | 12.0 | 11.6 | 6.0 | 11.2 | 12.0 | 8.6 |
| WBC (total) $x10^9/l$ | 9.5 | 22 | 350 | 225 | 3.0 | 3.1 | 5.9 | 3.0 | 5.6 | 11.4 | 8.6 | 86 |
| Neutros % | - | 65 | 5 | 5 | 28 | 66 | 59 | 84 | 84 | 55 | 80 | 20 |
| Lymphos % | - | 18 | 30 | 41 | 48 | 26 | 35 | 8 | 8 | 25 | 17 | 52 |
| Monos % | - | 7 | 1 | - | 4 | 2 | 6 | 8 | 6 | 11 | 3 | 8 |
| Eosinos % | - | 10 | - | 2 | - | 6 | - | - | 2 | 9 | - | - |
| Blasts % | - | - | 64 | 52 | 20 | - | - | - | - | - | - | 20 |
| Platelets $x10^9/l$ | 180 | 187 | 126 | 50 | 30 | 190 | 235 | 175 | 91 | 130 | 180 | 20 |
| Other | BM* | | BM | O | N | T | R | E | A | M | E | N T | | BM |
| Blood film | Numerous Basket cells | | | | | | | | | | Basket cells | |

*BM - Bone marrow done.

lymphosarcoma cell leukaemia" (Fig. 17E). A lymph node biopsy done at the same time (S/2389/77) was reported as showing "a diffuse, poorly differentiated lymphocytic lymphoma".

Thus, within two weeks of admission, the patient had developed a leukaemic component which was shown to be of the B-cell type, on B and T lymphocyte studies. He developed anaemia (Table 45), and the spleen and liver became enlarged (3 and 6 cm respectively).

He was started on the remission induction regimen for ALL, and he had a dramatic response, such that by 13-5-77, the bone marrow was in complete remission. He was given consolidation therapy in June 1977, followed by maintenance treatment. CSF from a lumbar puncture done at the end of June, showed "large, primitive lymphoid cells". Cranio-spinal radiation, as well as therapeutic intrathecal methotrexate were administered with good results such that by the end, the CSF was clear of abnormal cells.

During the short period of remission, he suffered several episodes of pneumonia, then hepatitis B infection and Herpes zoster of $T_6 - L_1$ on the right side. In October 1977 he suddenly became blind and ophthalmoscopy revealed papilloedema. EEG done at the time showed changes of increased intracranial pressure. In November, he developed severe bone pain which was radiologically shown to be due to leukaemic bone infiltration. At this time, he had gone in to haematological relapse (Table 45). His condition never improved in spite of reinduction measures. He terminally developed convulsions and he died of what was clinically believed to be relapsed meningeal leukaemia. Consent for autopsy was refused.

Comment: There are several interesting facets of ALSCL illustrated by this case.

(i) The natural course of a poorly differentiated lymphocytic lymphoma complicated by a leukaemic transformation, a feature that may occur in up to 70% of the undifferentiated, non-Burkitt's lymphomas (142) is clearly noted. The complicating meningeal involvement is a feature of both lymphomatous and leukaemic processes. This occurs in up to 50% of poorly differentiated lymphocytic lymphomas.

(ii) The sudden onset of the leukaemic process was dramatic. The bone marrow done on admission showed no obvious leukaemic process, yet another one done two weeks after was completely replaced by primitive lymphoid cells. The rapidity with which the leucocytosis developed to over $300 \times 10^9/l$ is also noteworthy, although it is a well recognized phenomenon of such a process (143).

(iii) The cytological features of numerous basket cells on the blood film, a variable maturation spectrum of the primitive cells along with the pleomorphic appearance described in this case help to differentiate ALSCL from ALL. One granule P.A.S. positivity is a typical feature.

(iv) The hyperleucocytosis, early meningeal involvement, and the very short duration of remission, coupled with poor quality life during remission are features that underline poor prognosis in ALSCL as has been emphasized in this study.

(v) Finally, apart from showing that ALSCL is a leukaemic transformation of lymphoma and that it is an entity, this case confirms the unifying concept of lymphoproliferative disorders. The dividing line between lymphocytic leukaemias and lymphomas is occasionally nebulous.

Case 4 - Unit No. 160838. (A Diagnostic problem).

J.O., a 27-year-old male-Luo, was admitted to KNH on 24-12-75 with a two-week history of generalised body aches and pains, central abdominal pain, fever and non-productive cough. On clinical examination, he was found to be ill-looking, wasted, moderately pale, febrile and had generalised bone tenderness with palpable inguinal lymph nodes. The epigastric region was tender but neither the spleen nor the liver was enlarged. Chest examination revealed features of bilateral lower lobe infection.

Initial laboratory investigations included: Hb - 5.6 g/dl; total WBC - $10.8 \times 10^9/1$ (with a differential of neutrophils - 46%, lymphocytes - 30%, stabs - 20%, monocytes 4%; some of the lymphocytes exhibited cytoplasmic vacuolation); platelets were assessed as normal in numbers; a chest radiograph confirmed the presence of bilateral lower lobar pneumonia; serum electrolyte estimation showed sodium - 130 mEq/1, potassium - 3.2 mEq/1, chloride - 91 mEq/1, bicarbonate - 30 mEq/1 and blood urea - 24 mg%.

Due to the persistent fever, anaemia and chest signs, the patient was thought to have pneumonia and malaria. He was therefore transfused and then given a course, each of chloroquin and crystalline penicillin. The temperature and bone pains persisted although the chest became clear by 2-1-76.

Further laboratory evaluation consisted of the following:- two attempts at bone marrow aspiration were unsuccessful; a skeletal survey was normal; all bacteriological cultures were negative; serum proteins revealed a reversion of the albumin/globulin ratio; serological tests for syphilis using the USR technique showed a positivity of 3-pluses; a peripheral blood count done on 5-1-76 revealed Hb - 5.3 g/dl, WBC - $3.1 \times 10^9/1$, and the platelets were reported as normal.

At this stage, the following diagnoses were considered:- leukaemia, typhoid fever, occult Hodgkin's disease, multiple myeloma, brucellosis and disseminated tuberculosis. The following tests were however negative:- Widal and Brucella agglutination tests, antihuman-globulin test, Mantoux, the Paul-Bunnell and further blood cultures. As tuberculosis was still strongly suspected, the patient was started on thiazina.

After three weeks of hospital stay, he developed jaundice, gum bleeding, hepatomegaly and bouts of epistaxis. A haemogram done at this time showed:- Hb - 5.1 g/dl; WBC - $5x10^9/l$ (neutrophils - 5%, lymphocytes - 95% and bizarre looking vacuolated blasts were identified at this time); platelets were reduced. A bone marrow done at the time was reported as "hypercellular and 80% replaced by pleomorphic mononuclear cells which are primitive and heavily vacuolated. The vacuoles contained P.A.S. positive material (Fig. 17D)". The overall picture was thought to represent malignant histiocytosis. Dr. D. Catovsky of London in his opinion thought of "an acute leukaemia of undifferentiated blast cells". A lymph node biopsy was reported as " a myeloproliferative disorder".

The patient's condition progressively deteriorated, in spite of blood transfusions and commencement on cytotoxic therapy, until he died on 29-1-76.

At autopsy (A/17/76), there was an enlarged spleen (450 g), generalised petechial haemorrhages, pulmonary oedema and generalised lymph node enlargement. At histology, the bone marrow was 100% replaced and all organs were infiltrated by pleomorphic primitive cells similar to those seen in the bone marrow and lymph node in life. A final pathological diagnosis of a myeloproliferative syndrome was made.

Comment: This case illustrates the protean manifestations and the unusual puzzling picture that can be presented by some types of acute leukaemia. It further underlines the clinical, haematological and pathological problems in diagnosis that are often posed by a leukaemic process. Infact, the rapidly progressive clinical course of this case and the negative investigational findings could have easily contributed to a misdiagnosis or missed diagnosis. The diagnosis was not settled even at autopsy.

Case 5 - Unit No. 219310. (Accelerated phase of CGL-unusual picture).

S.N., a 43-year-old male-Kikuyu, was admitted to KNH on 9-3-77 with a 4-month history of abdominal pain, left upper quadrant abdominal swelling and generalised massive lymph node enlargement involving the cervical, axillary and inguinal regions. He had bone pains, night sweats and anorexia. He previously suffered progressive constipation and general body

weakness since 1972.

Clinical examination showed a well built young-adult, who was febirle (37.5°C), but without anaemia, jaundice and purpura. He had massive bilateral cervical lymphadenopathy as well as bilateral inguinal and axillary nodes (Fig. 7). These were rubbery, mobile and non-tender. The spleen and liver were enlarged, 15 cm and 5 cm respectively, below the costal margins; they were smooth and non-tender. Fundoscopy revealed a left sided retinal haemorrhage.

Initial laboratory investigations were as follows:- the haemogram showed Hb - 18.8 g/dl, PCV - 0.62, red cell count - $7.7 \times 10^{12}/l$, WBC - $65 \times 10^{9}/l$, (neutrophilia with a moderate shift to the left; eosinophilia) and a platelet count of $18 \times 10^{9}/l$; chest x-ray was normal; a bone marrow aspirate was reported as "a myeloproliferative disorder, the nature of which is uncertain"; a lymph node biopsy showed "myeloid cell infiltrate consistent with leukaemic infiltration". A bone marrow trephine biopsy showed features of myelofibrosis.

The clinico-haematological differential diagnosis lay between histiocytic lymphoma and a myeloproliferative disorder, considered to be chronic granulocytic leukaemia. The enigma to unravel was the presence of thrombocytopenia and the apparent polycythaemia. Cytogenetic studies revealed that the Philadelphia chromosome was absent.

Two weeks after admission, he developed features of the superior vena caval syndrome, which was accompanied by haemoptysis and a non-productive cough. In view of this, he was given 2,000 rads of radiotherapy to the neck to shrink cervical lymph nodes. Although he slightly improved, the cough persisted and he developed bilateral hydrothorax and mediastinal lymph node enlargement increased. Oedema of the lower extremities and scrotum (Fig. 7) with ascites, developed with great rapidity. All these features were attributed to massive lymphadenopathy.

He was started on cytotoxic therapy consisting of vincristine and prednisone in May and was given several platelet transfusions for thrombocytopenia. Abdominal radiation shrunk the spleen. His haemoglobin progressively dropped to 10.5 g/dl with a PCV of 0.33. His general condition also deteriorated. Table 46 shows the progressive fall in the red cell indices and the initial progressive rise in leucocyte counts with a terminal fall due to chemotherapy and radiotherapy.

Table 46: Weekly haematological indices in case 5.

| Month | March | | April | | May | | June |
|---|---|---|---|---|---|---|---|
| Week | 2 | 3 | 4 | 2 | 2 | 4 | 2 |
| Hb g/dl | 18.8 | 19.4 | 18.6 | 15.0 | 12.1 | 10.5 | 11.8 |
| PCV | 0.62 | - | - | - | - | 0.33 | - |
| WBC $x10^9/l$ | 68.6 | 83.0 | 119.0 | 52.0 | 6.1 | 4.3 | 6.2 |
| Platelet count $x10^9/l$ | 18.0 | 23.0 | - | - | 112.0 | - | - |

The diagnoses contemplated at this stage included acute myelo-fibrosis, acute transformation of $Ph_1$ negative CGL and chronic myelo-fibrosis in changing phases of CGL to polycythaemia rubra vera to acute phase of CGL. Respiratory distress became severer, as the patient's general condition deteriorated, until he died.

Autopsy examination (A/224/77) showed massive paratracheal, mesentric and retroperitoneal lymph node enlargement. Ascites and bilateral pleural effusion was present. The spleen and liver were normal in size.

Comment: This is an unusual presentation of a myeloproliferative disorder exhibiting features of three components:- CGL, myelofibrosis and polycythaemia rubra vera but having thrombocytopenia. This case also demonstrates that CGL in its accelerated phase can present with bone pain, thrombocytopenia and massive lymphadenopathy. The down hill course was rapid and refractory to all forms of therapy. This was probably not a case of acute myelofibrosis as the latter rarely shows fibrous tissue in the marrow and it is unlikely to present with a picture of polycythaemia. The picture also required defferentiation from lymphoma which is occasionally confused to be coexistent (144) in the terminal phase of CGL when the latter has lymphadenopathy as a predominating component.

Case 6 - Unit No. 127476. (Misdiagnosed Case).

J.W., was a $2\frac{1}{2}$-year female-Kikuyu at the time of the first hospital admission to KNH on 3-1-75. She presented with one-week's history of anorexia and vomiting. She had previously suffered recurrent upper respiratory infections.

Clinical examination at the time revealed that, although she was in a good general condition, she was febrile and markedly pale. The liver and spleen were enlarged to 2 and 3 cm, respectively, below the costal margin. No lymph node enlargement was noted at the time. Laboratory investigations included:- a haemogram, Hb - 3.0 g/dl, WBC - $3.9 \times 10^9/l$ with a lymphocytosis of 94%; platelets were reported as reduced on the peripheral blood film; liver function tests as well as blood urea and electrolytes were normal; chest x-ray showed features of bronchopneumonia; three attempts at bone marrow aspiration yielded dry taps.

A differential diagnosis of aplstic anaemia, malaria and iron deficiency with complicating bronchopneumonia was made. She was transfused with two units of red cell concentrate and then given antibiotic treatment for bronchopneumonia and chloroquin for malaria. She was discharged home for follow up in the general paediatric clinic. The spleen regressed spontaneously and apart from having poor appetite, she had no problem during the time of follow up until June 1975 when she stopped attending the clinic. No definite diagnosis had been established.

At her second hospital admission in March 1976, she complained of poor appetite, cough and dyspnoea. She had generalised lymphadenopathy, moderate pallor and hepatosplenomegaly. Chest examination revealed features of bronchopneumonia. The following investigations were performed:- haemogram, Hb - 7.5 g/dl, WBC - $11.7 \times 10^9/l$ (neutrophils - 4%, lymphocytes - 12%, monocytes - 2%, eosinophils - 1%, lymphoblasts - 81%); platelet count - $40 \times 10^9/l$; serum electrolytes and liver function tests were reported as normal; a bone marrow was reported as showing "complete replacement by primitive cells with features of lymphoblasts - the overall picture of acute lymphocytic leukaemia".

Remission induction using vincristine, prednisone and cyclophosphamide was successfully effected. The patient was then started on maintenance therapy after CNS prophylactic

radiation and intrathecal methotrexate. She was discharged on 22-6-76 for follow up in the haematology clinic. At this stage, her Hb was 13.2 g/dl, WBC - $2.4 \times 10^9/l$, platelet count $120 \times 10^9/l$; the bone marrow was in complete remission.

During the 3rd admission on 13-8-76 for vomiting and sweating, she was not anaemic and had no organomegaly. However, the bone marrow showed "features of early relapse". This was again successfully re-induced and in October 1976, the bone marrow was reported as being "hypoplastic but in remission from ALL". She was discharged home on maintenance treatment to be followed up in the clinic.

She remained in complete remission and well until June, 1978, when she presented with neurological symptoms. These comprised abnormal behaviour, irritability, neck-stiffness, sudden blindness, and right hemiparesis. Examination revealed papilloedema with complete blindness. She was not anaemic (Hb - 12.4 g/dl and WBC - $3.8 \times 10^9/l$ with normal differential) and she had no organomegaly. A lumbar puncture was done and the CSF cytocentrifugation revealed "numerous leukaemic cells". The bone marrow was still in complete remission from ALL. A diagnosis of meningeal leukaemia was made. She was treated with intrathecal cytosine arabinoside and methotrexate. She had remarkable recovery because she regained her eye-sight and most of the symptoms regressed, except a residual right hemiparesis. She was discharged on systemic maintenance therapy on 30-7-78. This patient is still alive and in haematological remission, but she still has gradually progressive neurological deficits. These are probably due to brain scarring as a complication of meningeal leukaemia or intrathecal drug therapy or both.

Comment: This case illustrates various aspects of the behaviour of leukaemia in childhood, as well as the unsatisfactory approach to the investigation of anaemia in this country.

Several attempts at bone marrow aspiration resulted into dry taps. This could have been due to a faulty technique, which is quite common (111) or a genuine dry tap as is often encountered in ALL (107). The genuine dry tap may be a manifestation of bone marrow hypoplasia that may precede acute leukaemia (107) or due to the bone marrow being tightly packed with blast cells with a consequent failure of aspirating out any particles (108).

This patient was inadequately investigated and although aplastic anaemia was considered, treatment was commenced before the underlying cause was ascertained. This unsatisfactory approach to the investigation of anaemia in this country has been amply discussed (145) and probably contributes to the underdiagnosis of leukaemia. Moreover, what was called lymphocytes on the first admission could have been blast cells.

The vicious and relentless course of ALL, complicated by recurrent anaemia and repeated chest infections is very clear as illustrated by this case. The probable transfusion induced partial remission which has been reported in ALL (146) is a phenomenon also illustrated by this case. The indistriminate transfusion of anaemic patients could be an important contributory factor in misdiagnosing cases of leukaemia of childhood in developing countries.

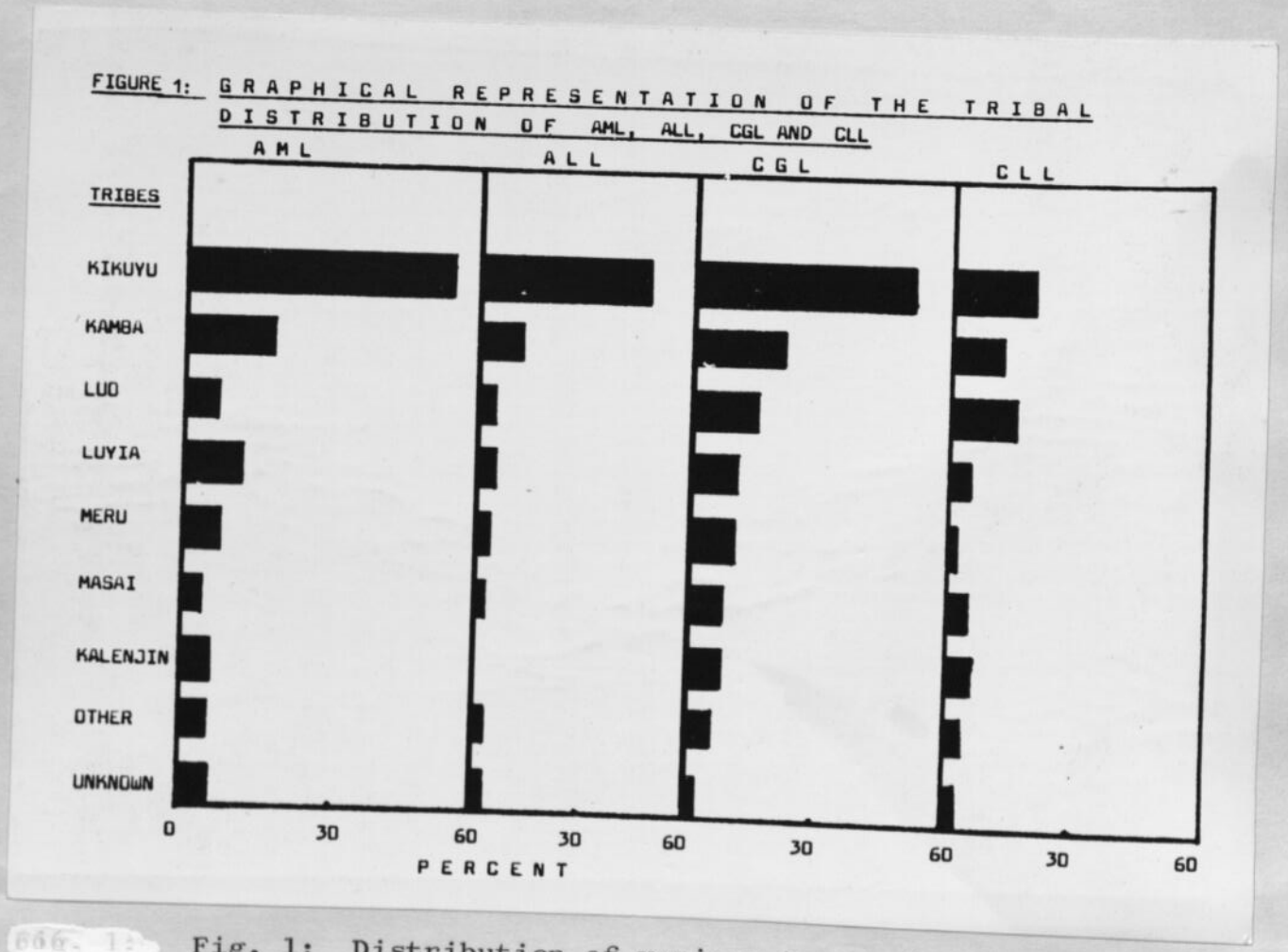


Fig. 1: Distribution of various types of leukaemia according to tribes. The Kikuyus dominate the picture in all types of leukaemia.

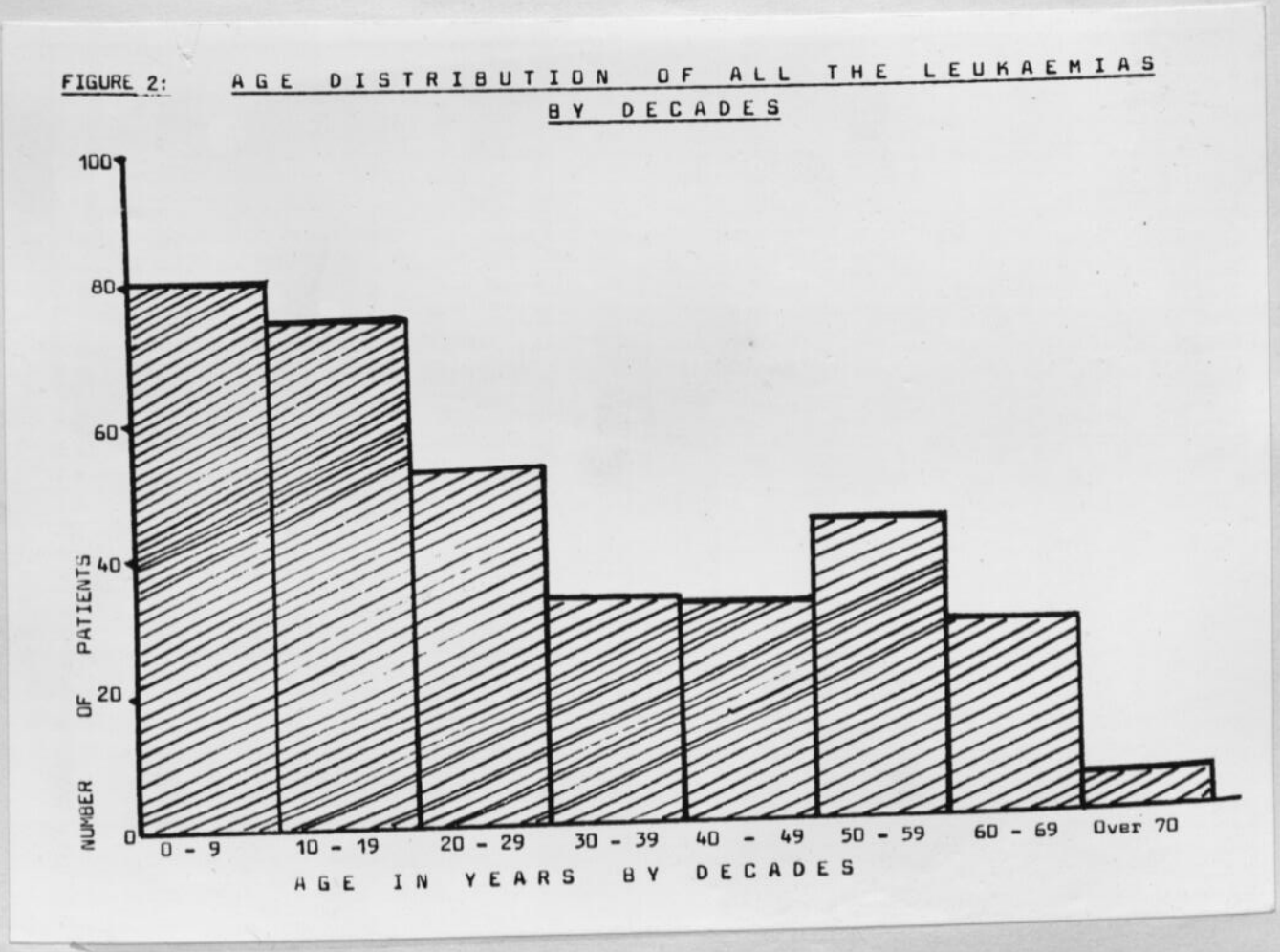


Fig. 2: Histogram of the age distribution in all types of leukaemia. Note the presence of a peak in the first decade of life and another in the sixth decade.

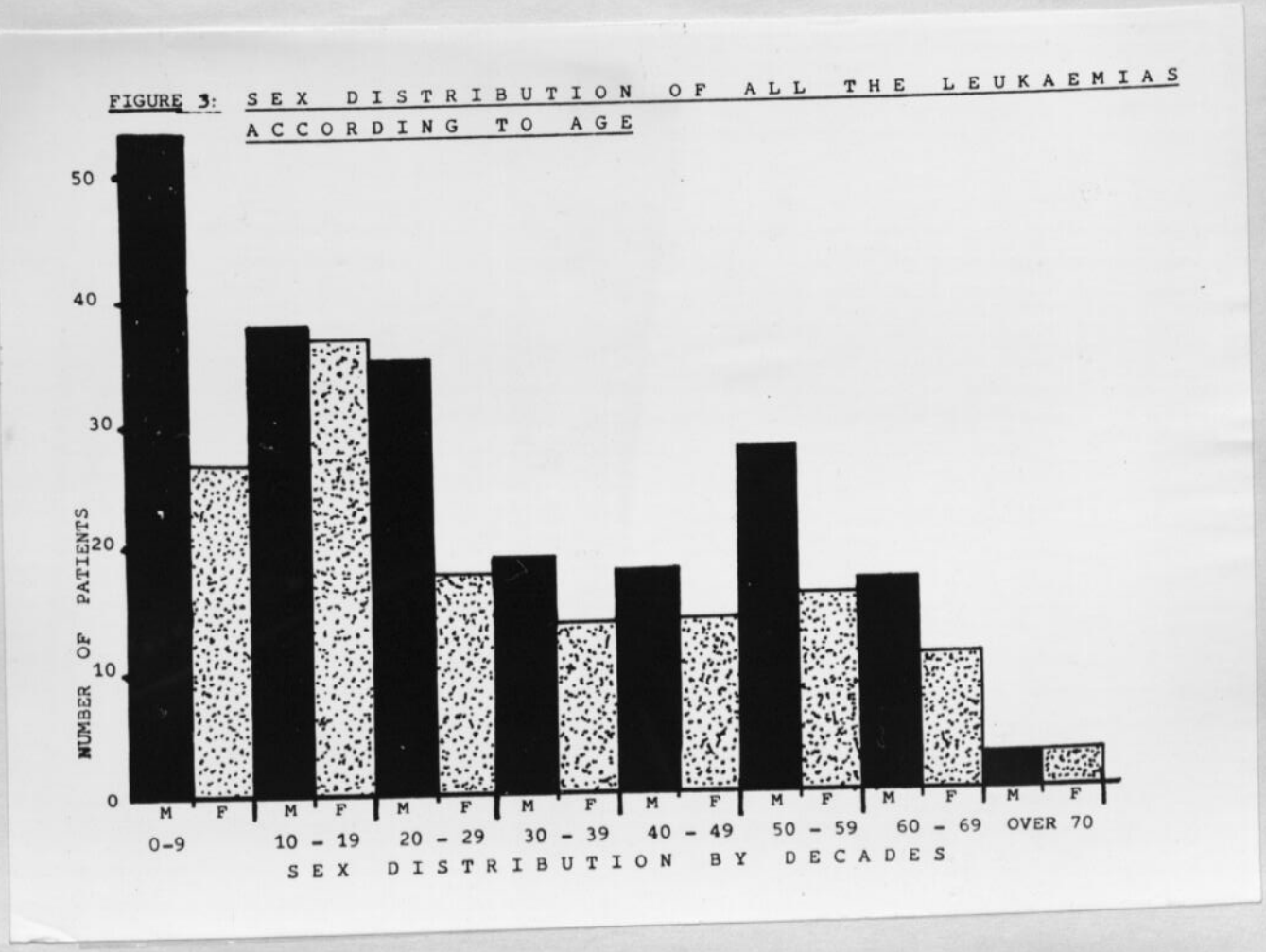


Fig. 3: Sex distribution in all the leukaemias. Note the decisive male predominance in the 1st, 3rd and 6th decades of life. The ratio is about equal in the 2nd decade.

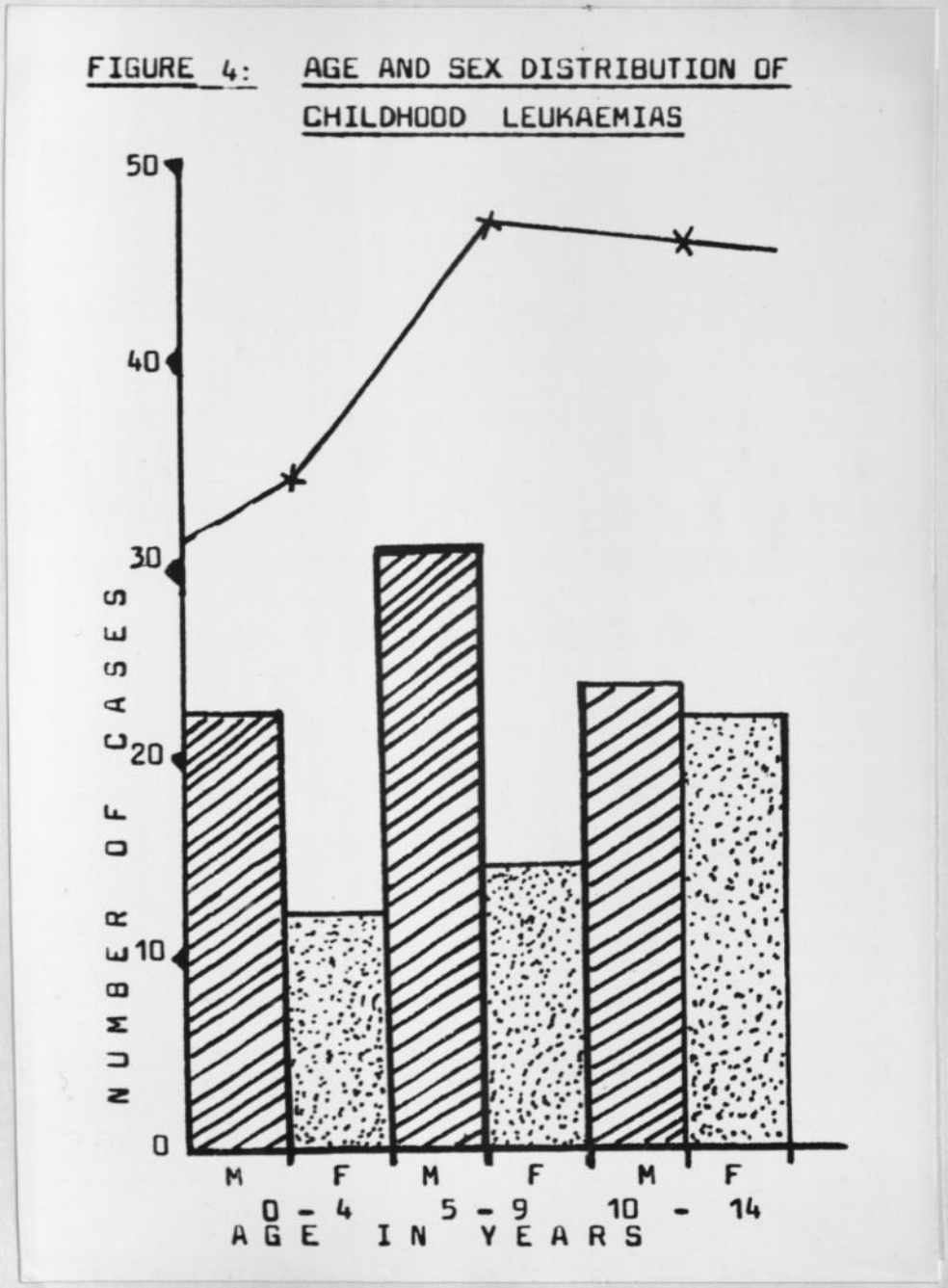


Fig. 4: Age and sex distribution in childhood leukaemia. The males predominate in the 0-9 years, but the ratio is approximately equal in the 10-14 age group. There is a peak, mainly due to males in the 5-9 age group.

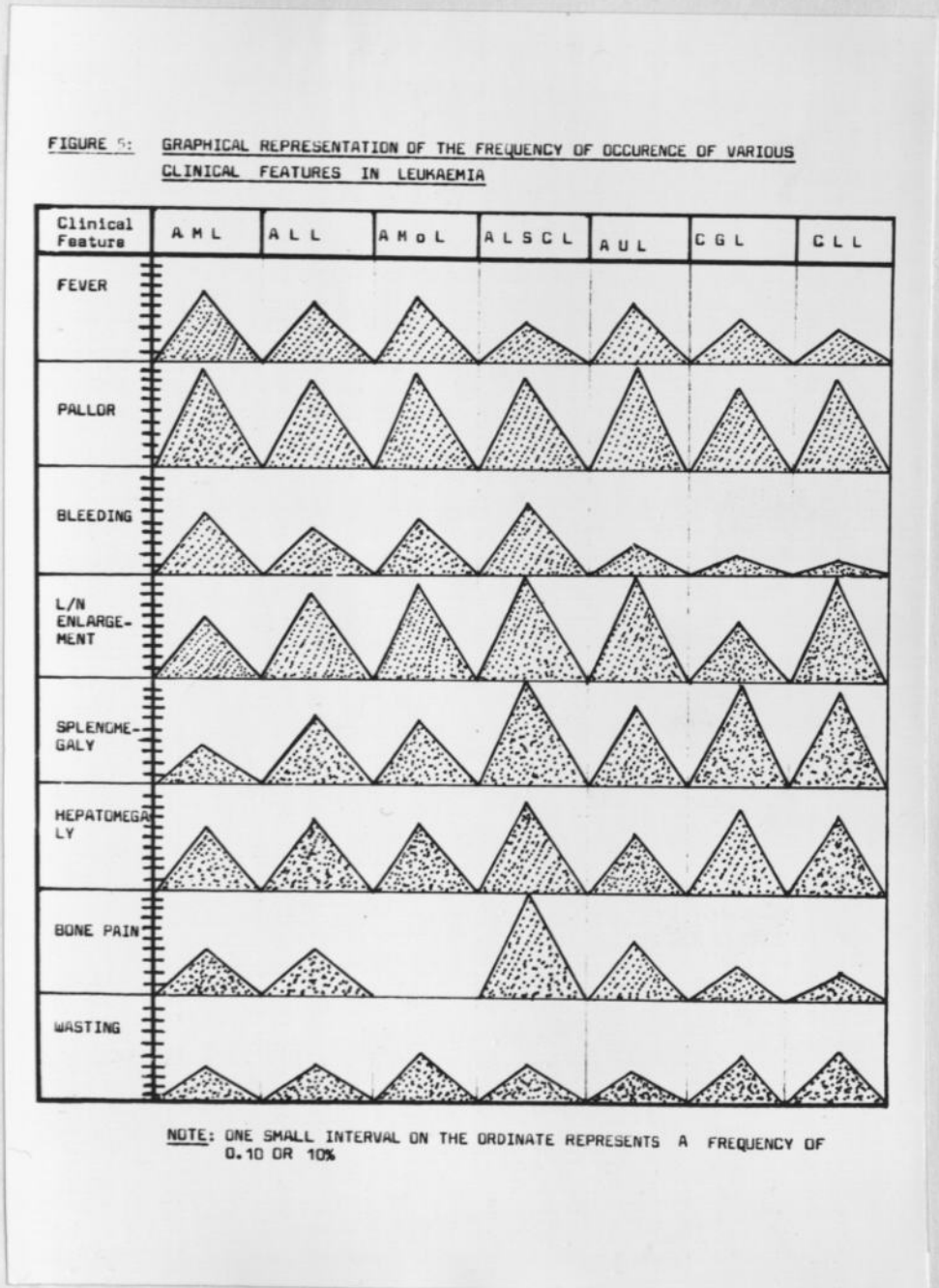


Fig. 5: Frequency of occurrence of the dominating clinical features in the various types of leukaemia.

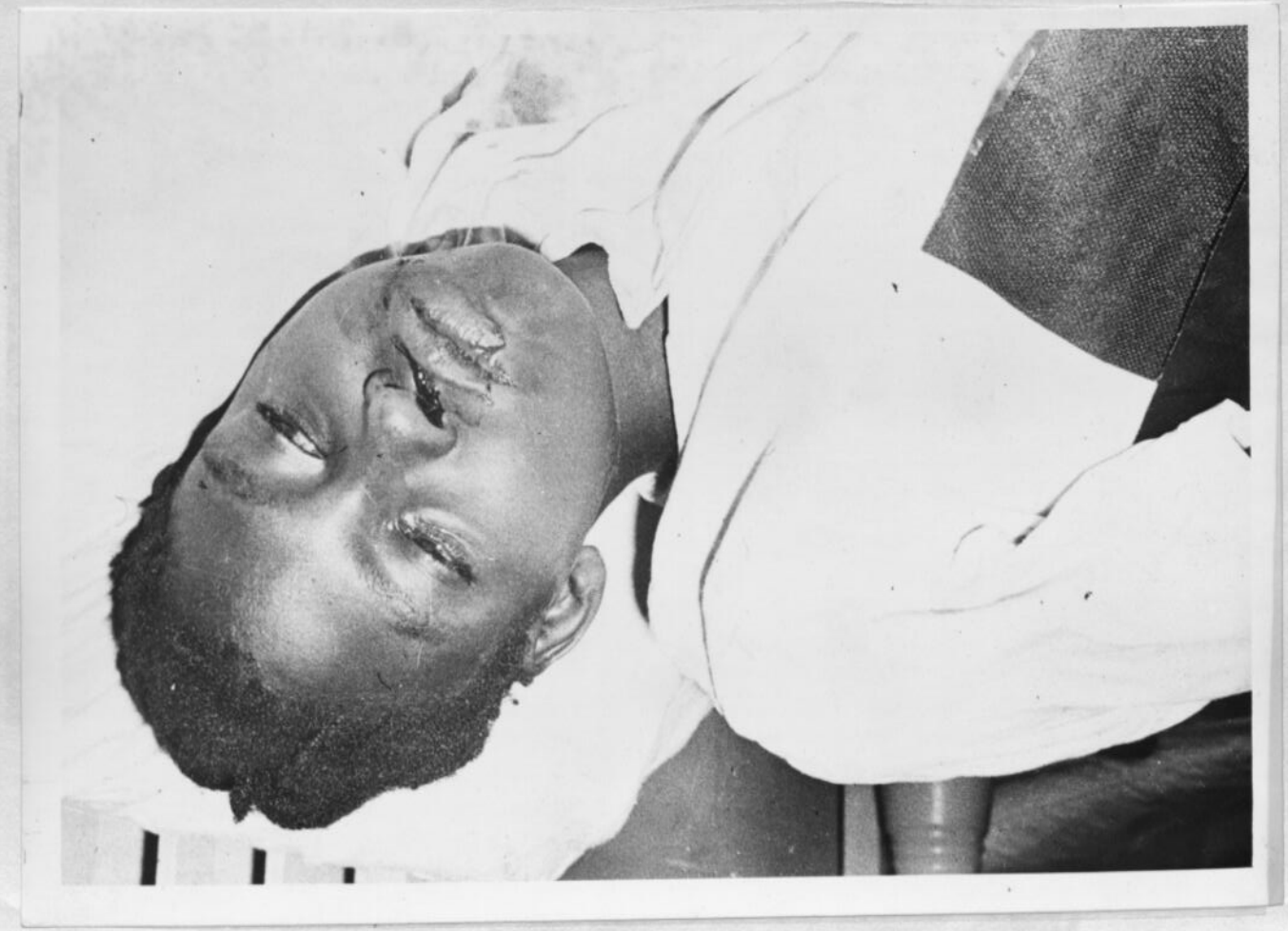

Fig. 6: Epistaxis in acute leukaemia. The most common form of bleeding from the orifices in severely thrombocytopenic patients.

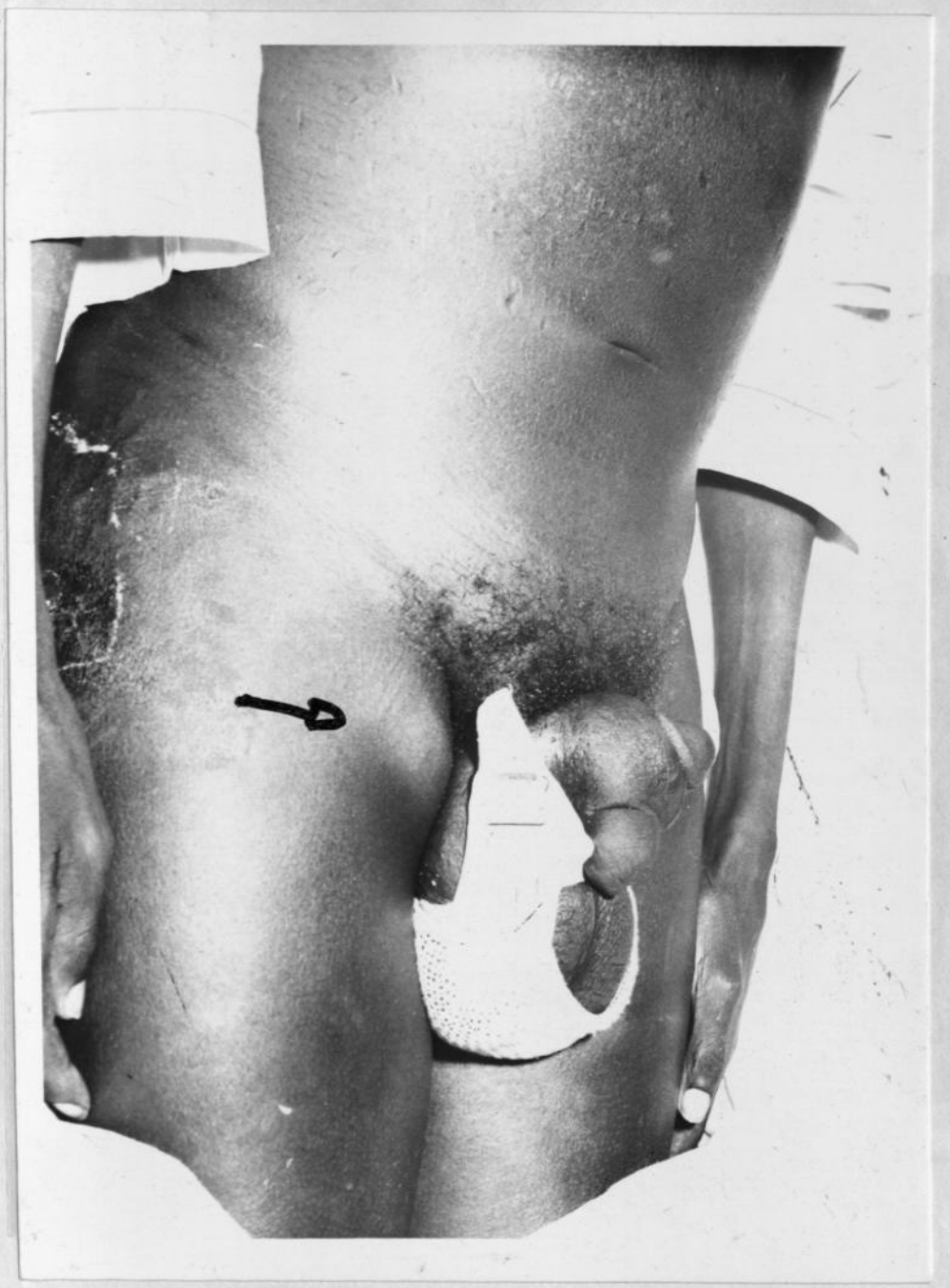

Fig. 7: Lymphadenopathy occurring in the accelerated phase of CGL. Note the inguinal lymph node enlargement that was part of the generalised lymphadenopathy. There was scrotal oedema and ascites as well (See case 5 Appendix III).

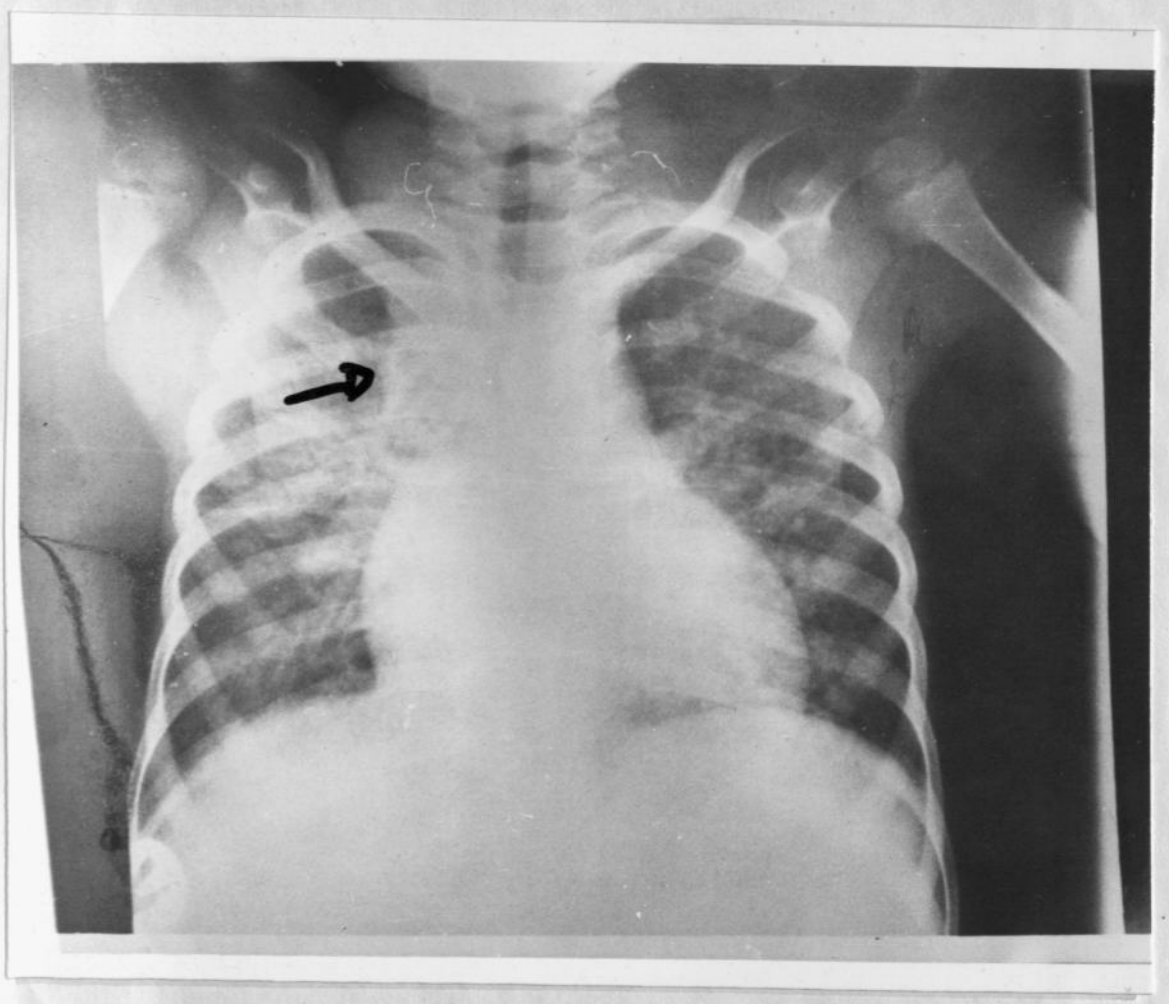

Fig. 8: Chest radiograph in one case of AMoL showing large mediastinal nodes (arrow pointing at them) which caused the superior vena caval syndrome in the patient. Note also the enlarged lymph nodes in the cervical region.

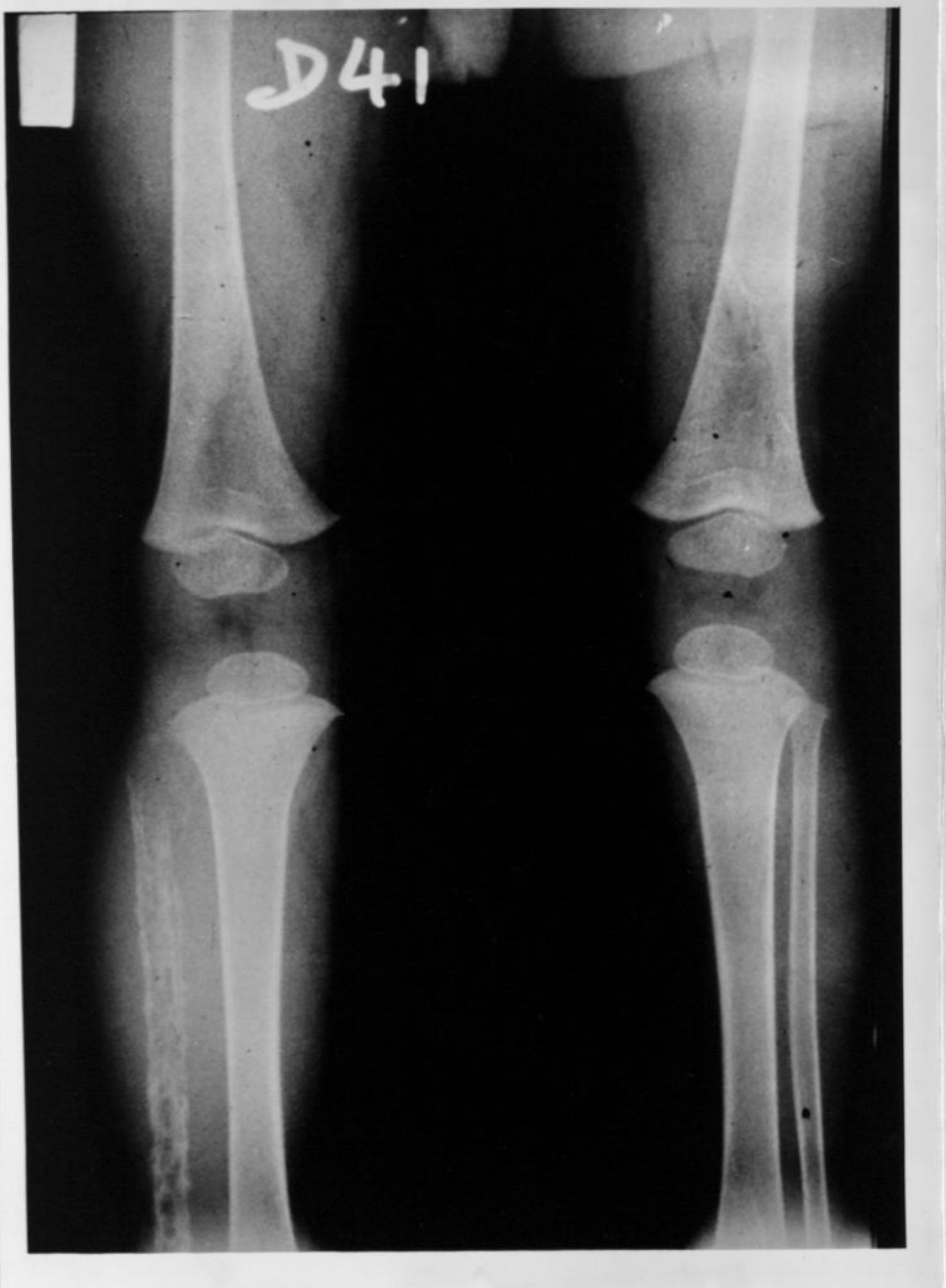


Fig. 9: Salmonella osteomyelitis of the fibula in a boy of $4\frac{1}{2}$ years with ALL. There is severe bone destruction. This child had many septicaemic episodes and never attained remission. It was initially doubtful whether this was not due to leukaemia, but biopsy of the bone and culture of some of the material ascertained the diagnosis.

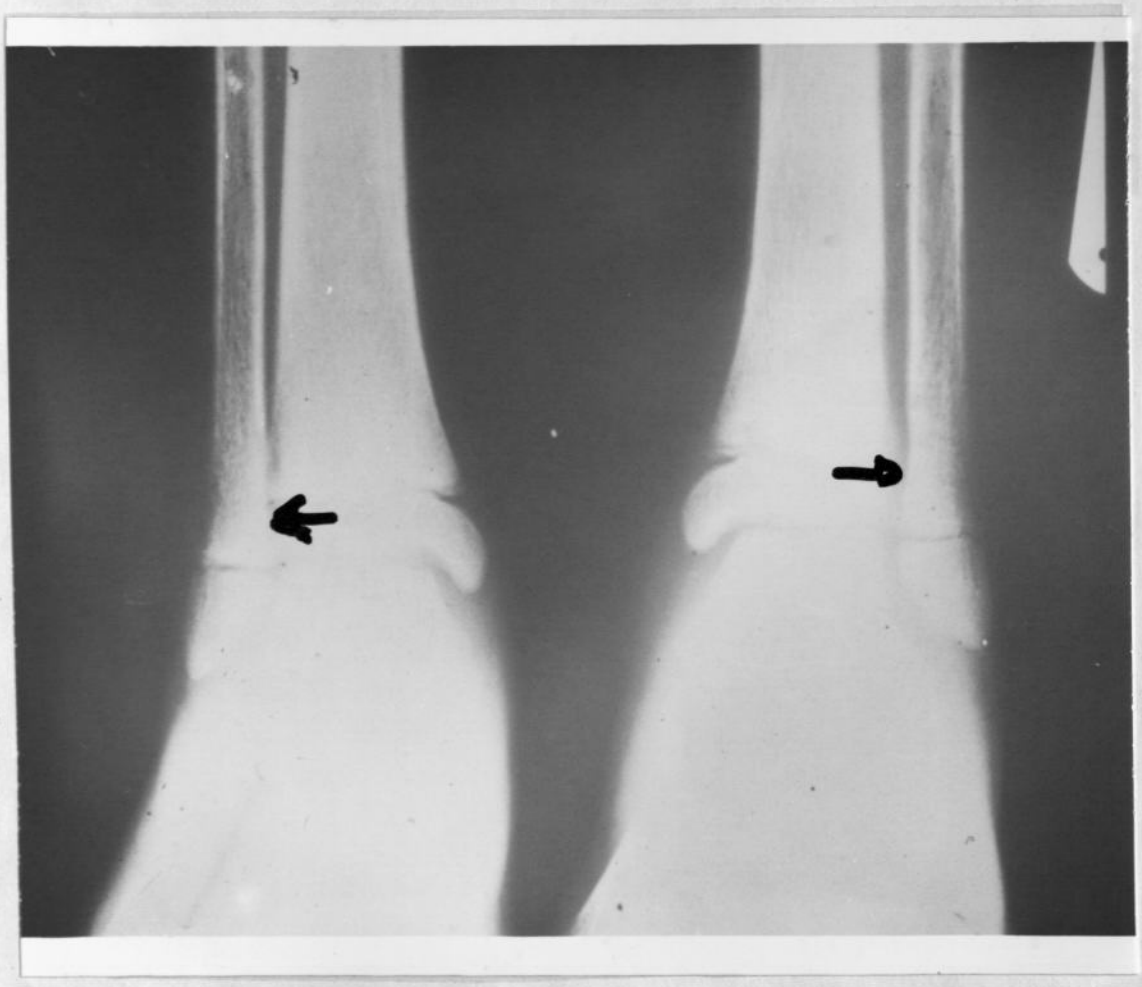

Fig. 10: Bones of the lower extremity showing radiological changes due to leukaemic infiltration in ALL. The arrow points at a severely affected ( osteolytic) lower end of the fibula.

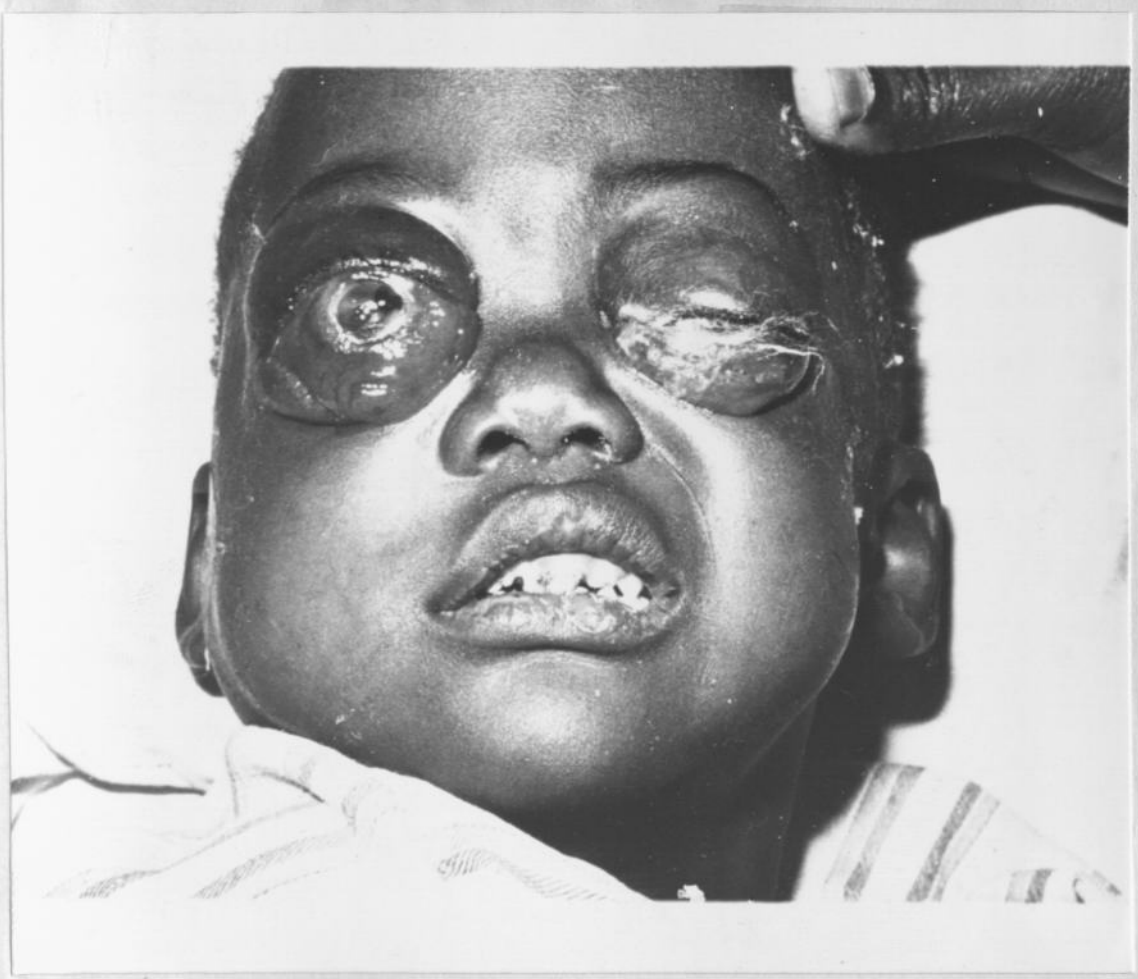

Fig. 11a: A case of retrobulbar chloroma. Note the marked proptosis, right exophthalmos and severe corneal destruction due to exposure xerosis. This patient was blind at presentation and had sickle cell anaemia as well.

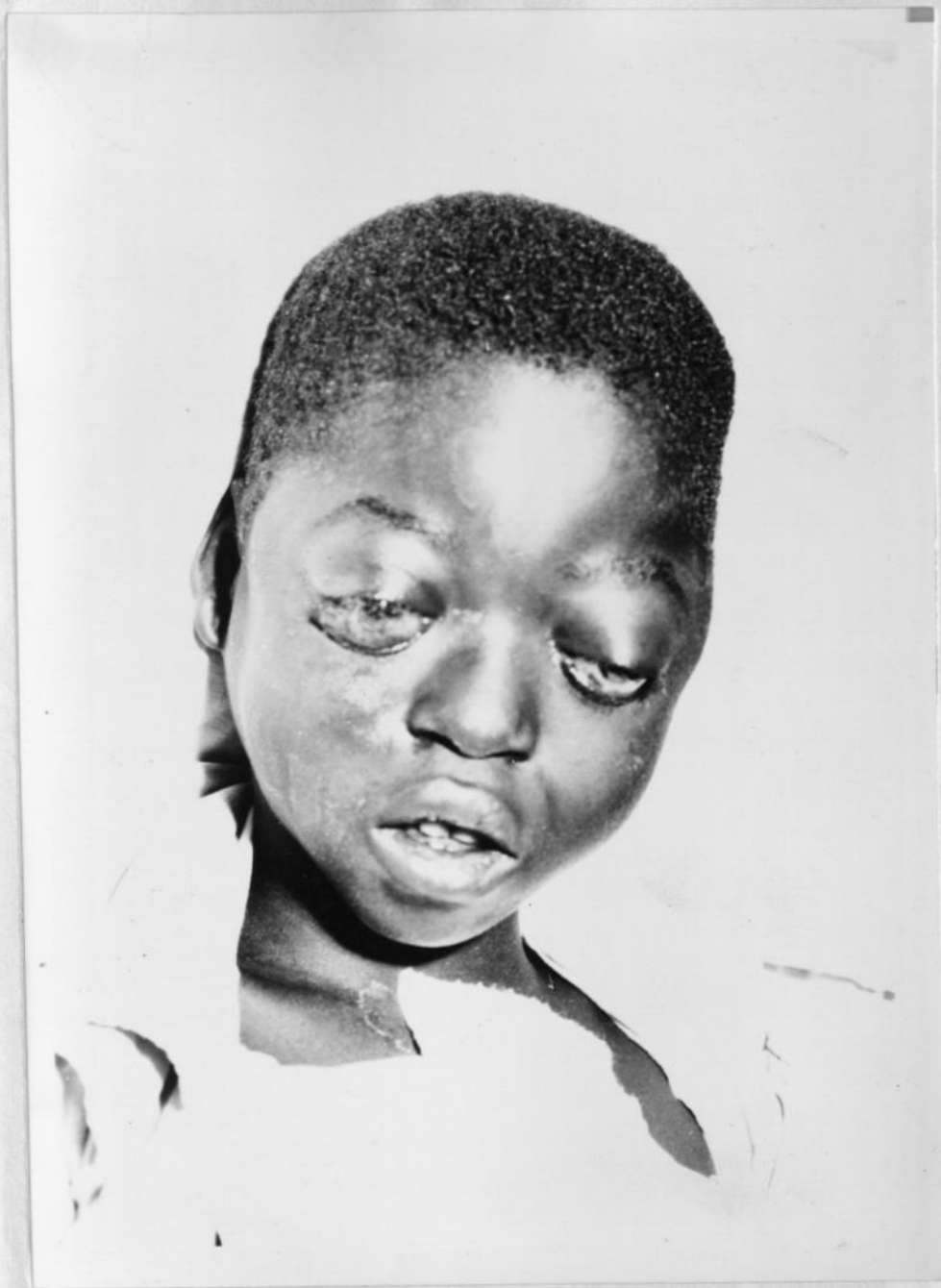

Fig. 11b: Chloromatous presentation, less severe than in Fig. 11a. This patient was semi-blind and had been diagnosed as bilateral neuroblastoma clinically.

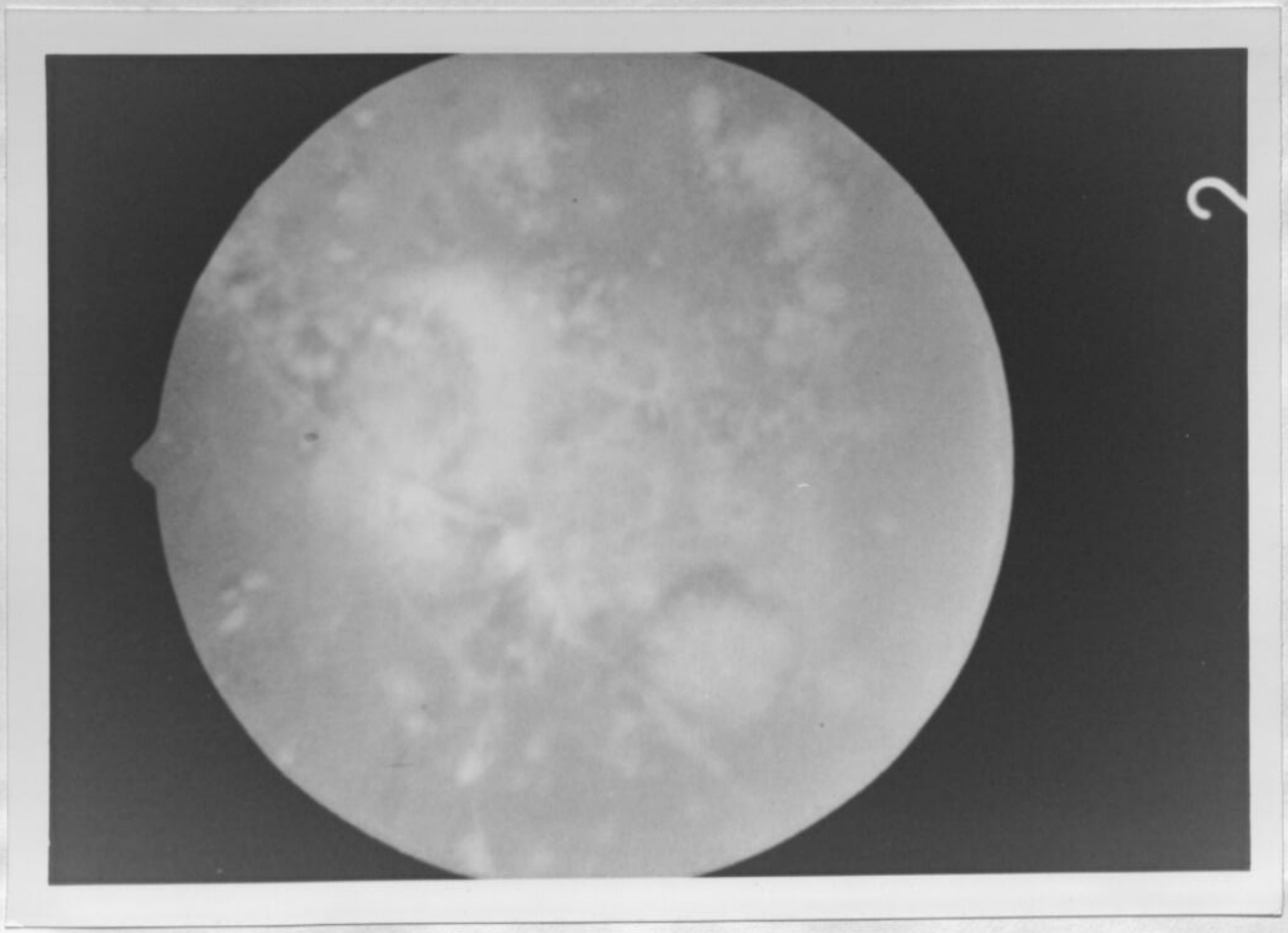

Fig. 12: Ocular changes in CGL. Note the haemorrhages and Roath's spots. The haemorrhage is due to hyperleucocytosis leading to stasis and vascular infiltration.

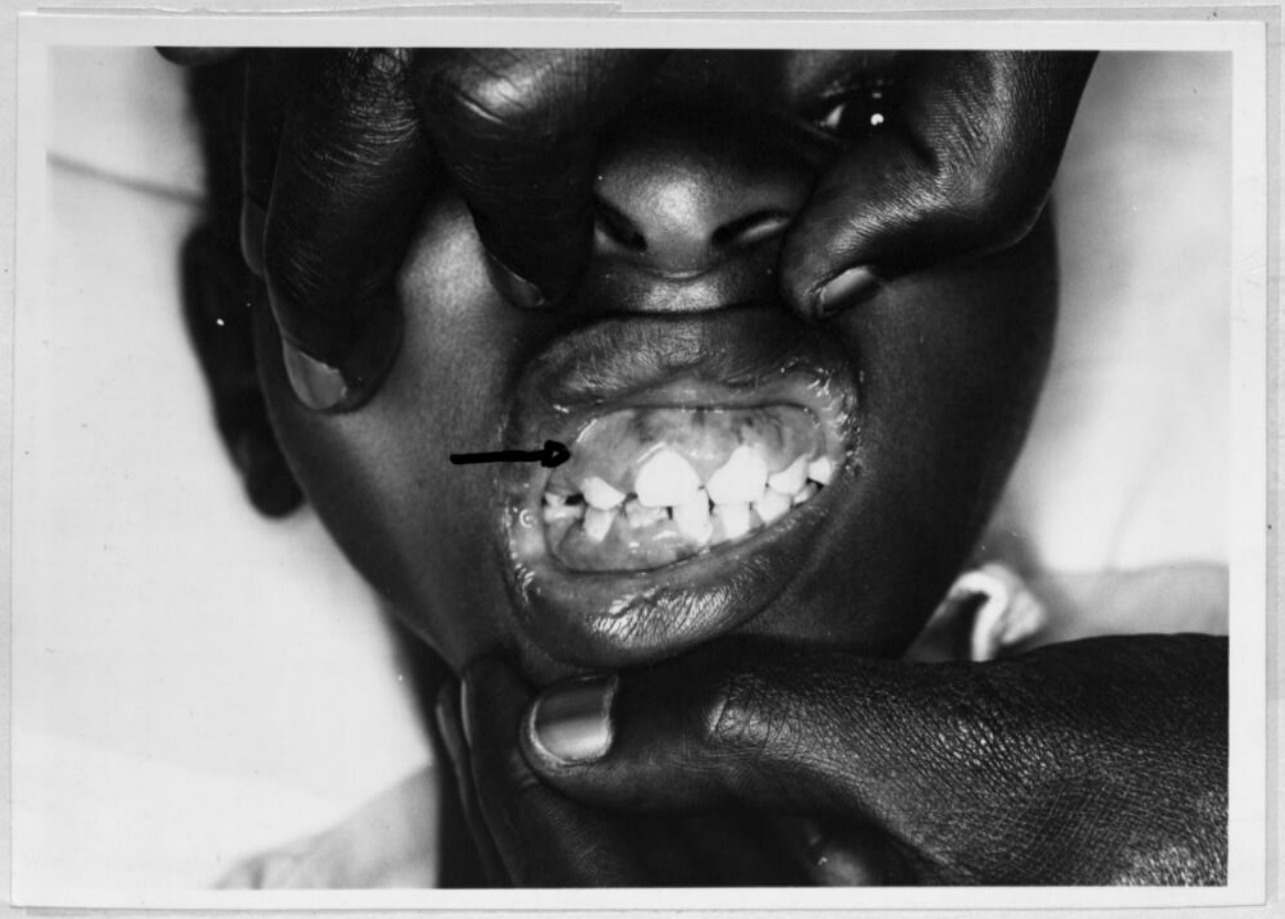

Fig. 13: An example of gum hypertrophy in AMoL and AM-ML. This was a patient with AM-ML.

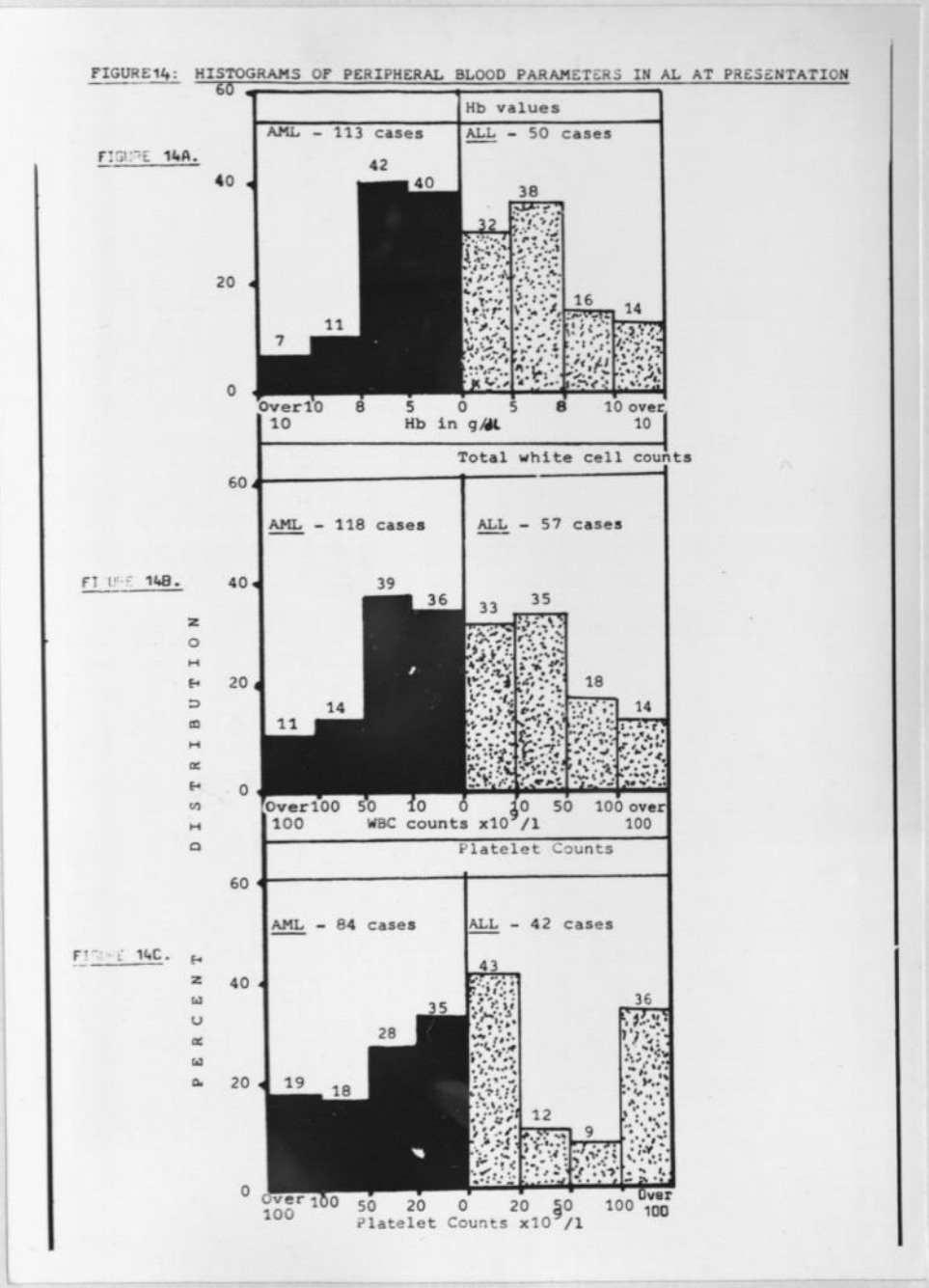


Fig. 14A-C: Peripheral blood parameters (Hb, total WBC and platelet counts) at presentation.

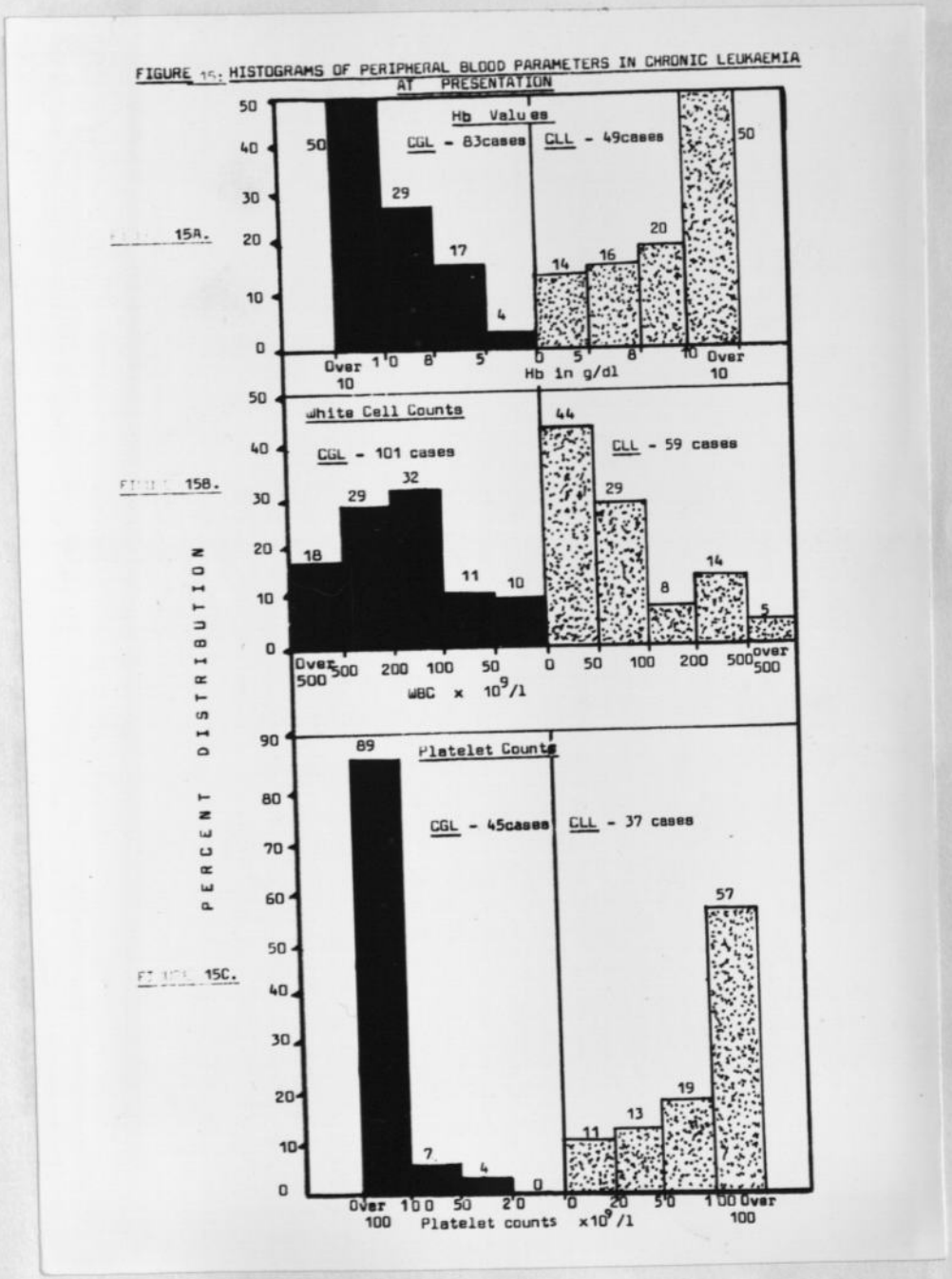


Fig. 15A-C: Peripheral blood parameters in chronic leukaemias (Hb, total WBC & total platelet counts) at presentation.

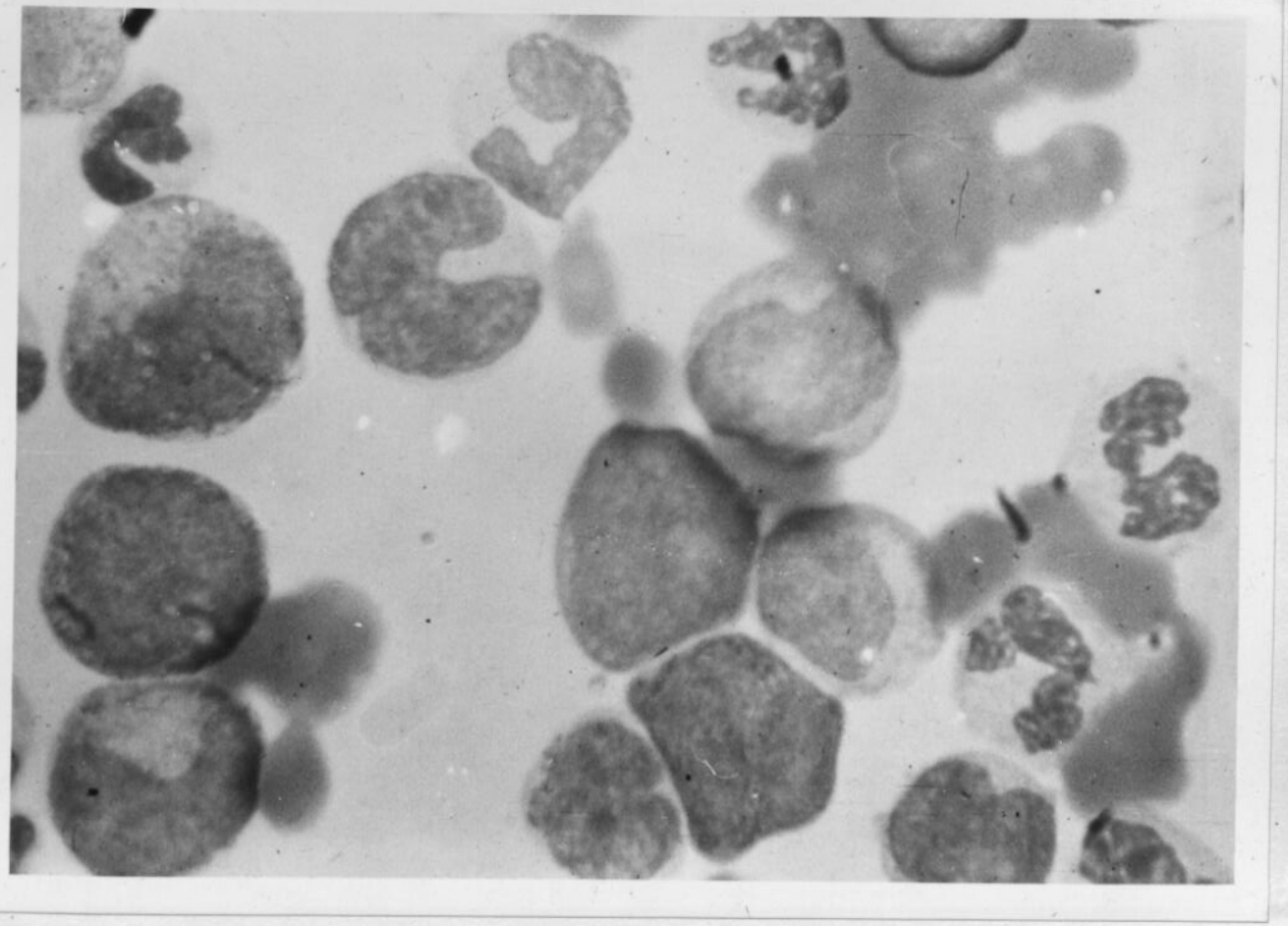

Fig. 16: Peripheral blood film (Oil-immersion) typical CGL picture; note the spectrum of maturation from blast cells to segmented forms.

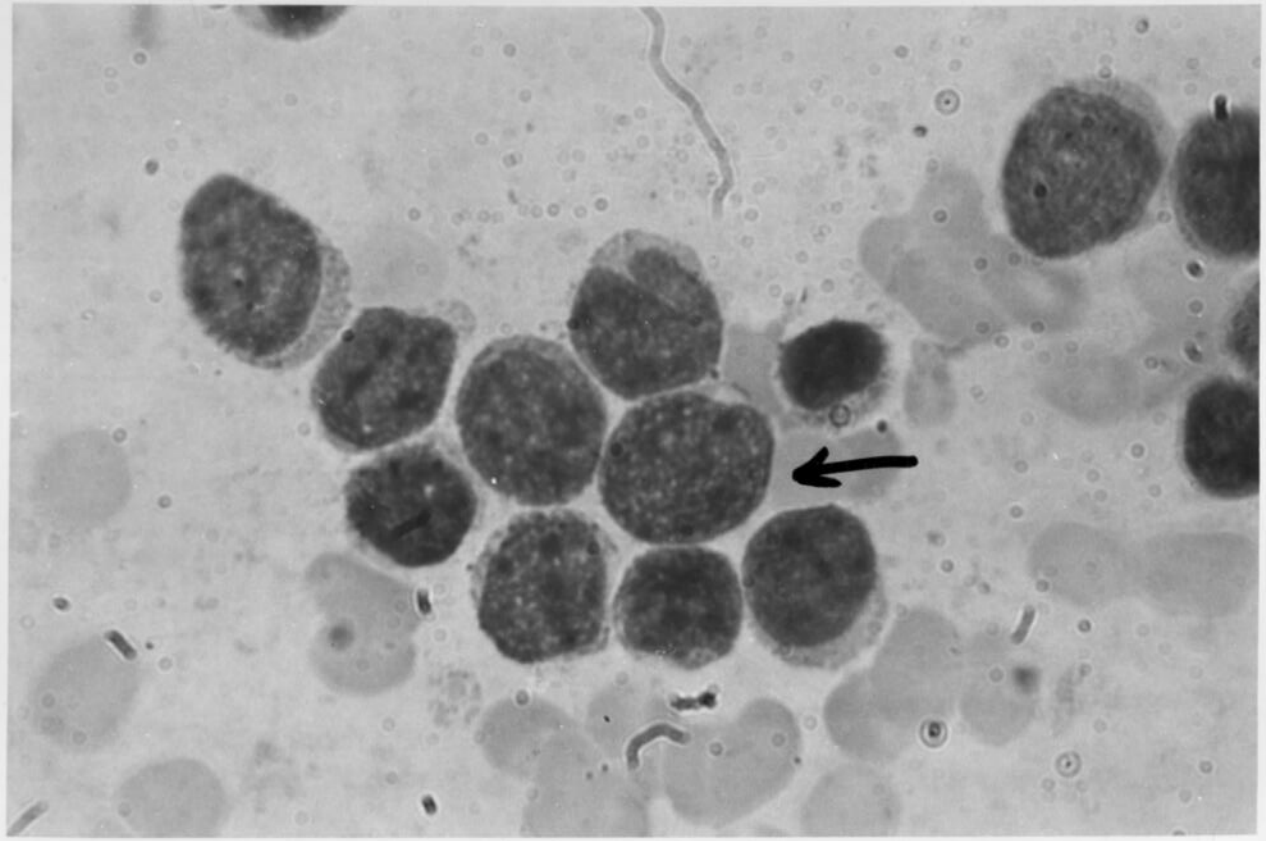

Fig. 17A: Peripheral blood film appearances (Oil-immersion) in AML. Note the rather moderately abundant cytoplasm not seen in ALL (Fig. 17B), granules in the cytoplasm and large parachromatin areas in the nucleus. Obvious nucleolus in one of the blast cells (see pointer).

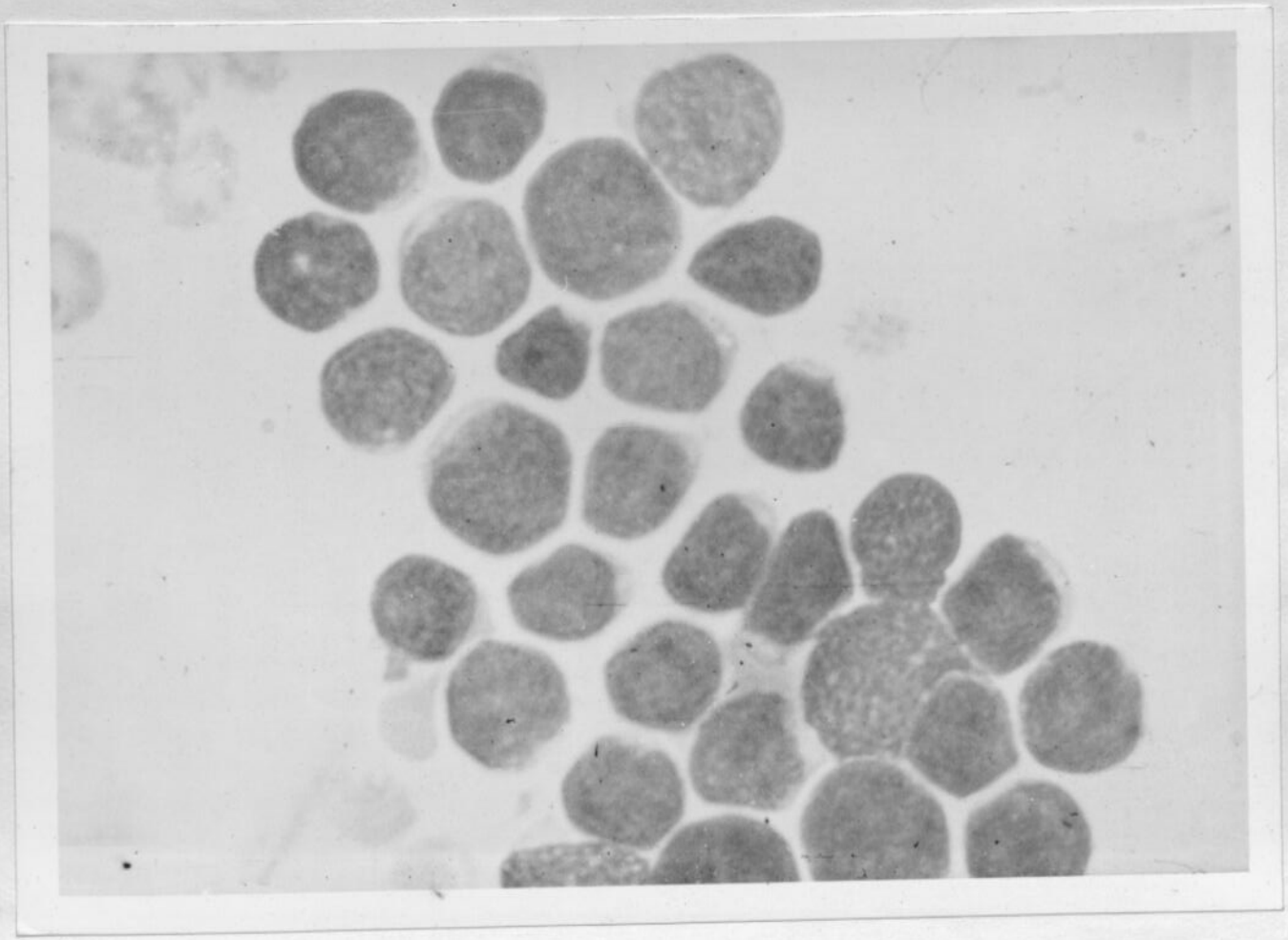

Fig. 17B: Peripheral blood film appearances (Oil-immersion) in ALL. Note the large blast cells with a high nucleo-cytoplasmic ratio and the rather monomorphic appearance (cf. ALSCL in Fig. 17E).

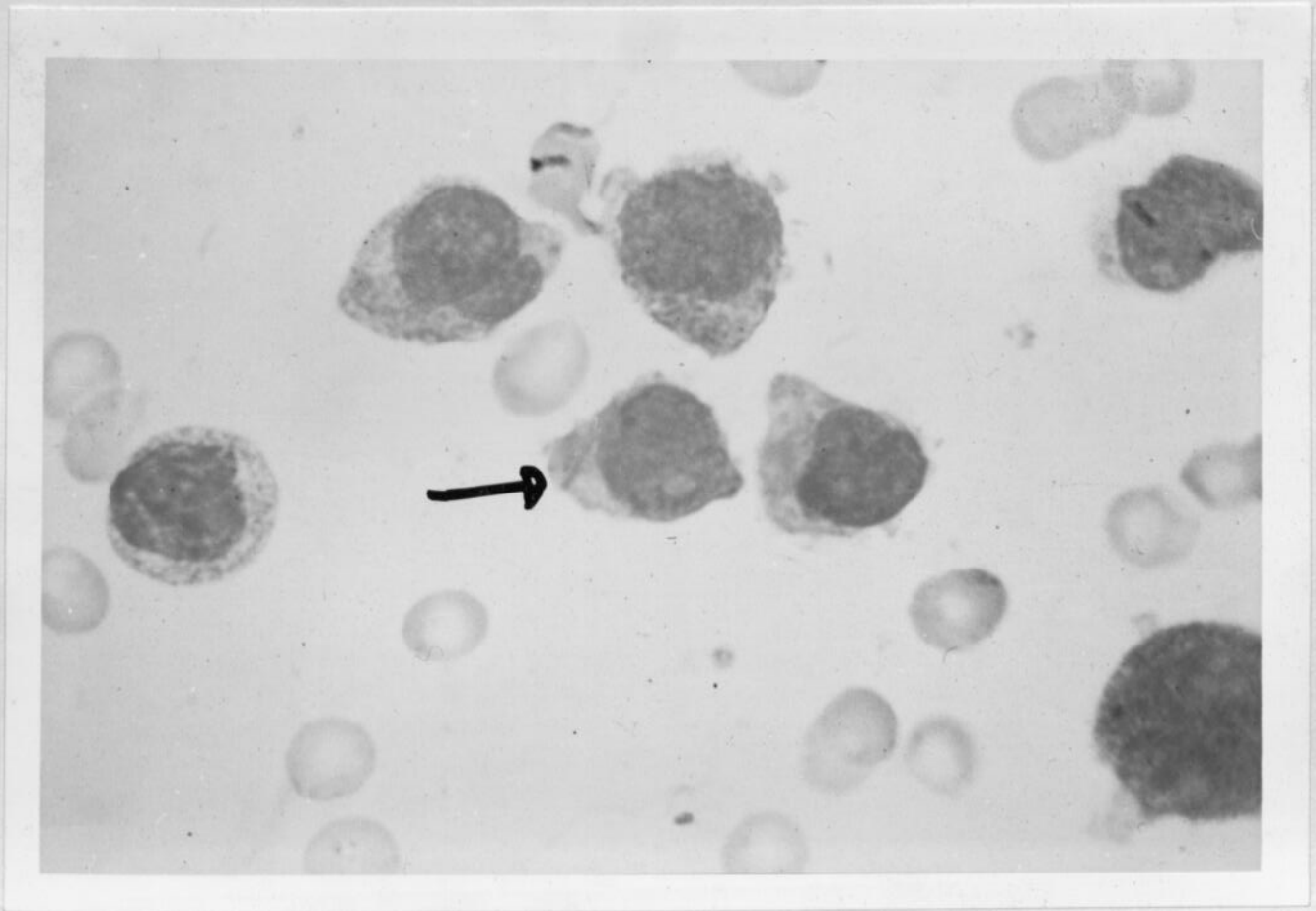

Fig. 17C: Peripheral blood film (Oil-immersion) appearances in APML. All the cells show granular, abundant cytoplasm; one cell has an Auer rod (Arrow). The nuclei show marked folding with prominent nucleoli.

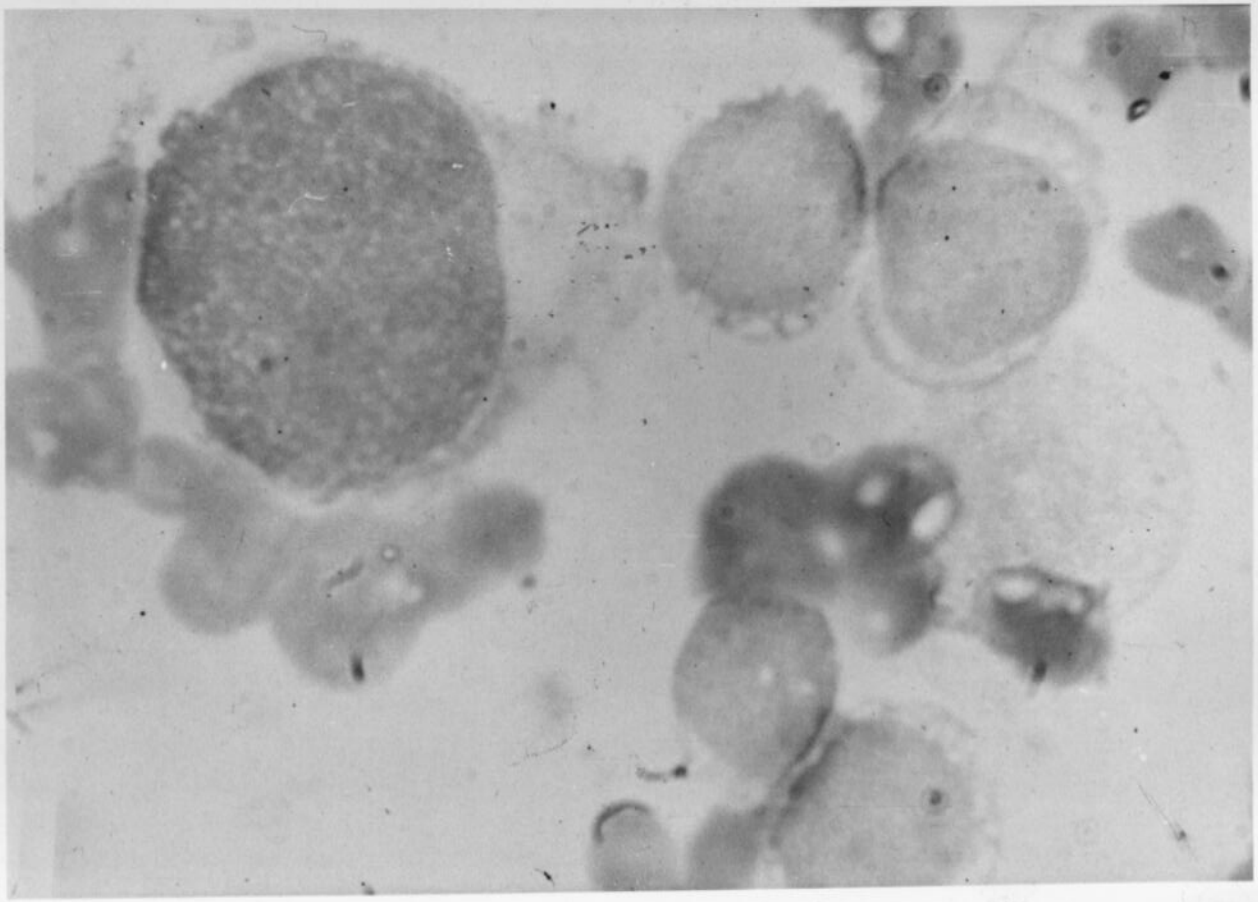

Fig. 17D: Peripheral blood picture (Oil-immersion), in acute leukaemia of undifferentiated blast cells from case 4 appendix III. Note the marked pleomorphism, abundant cytoplasm and cytoplasmic vacuolation. The vacuoles contained PAS positive material.

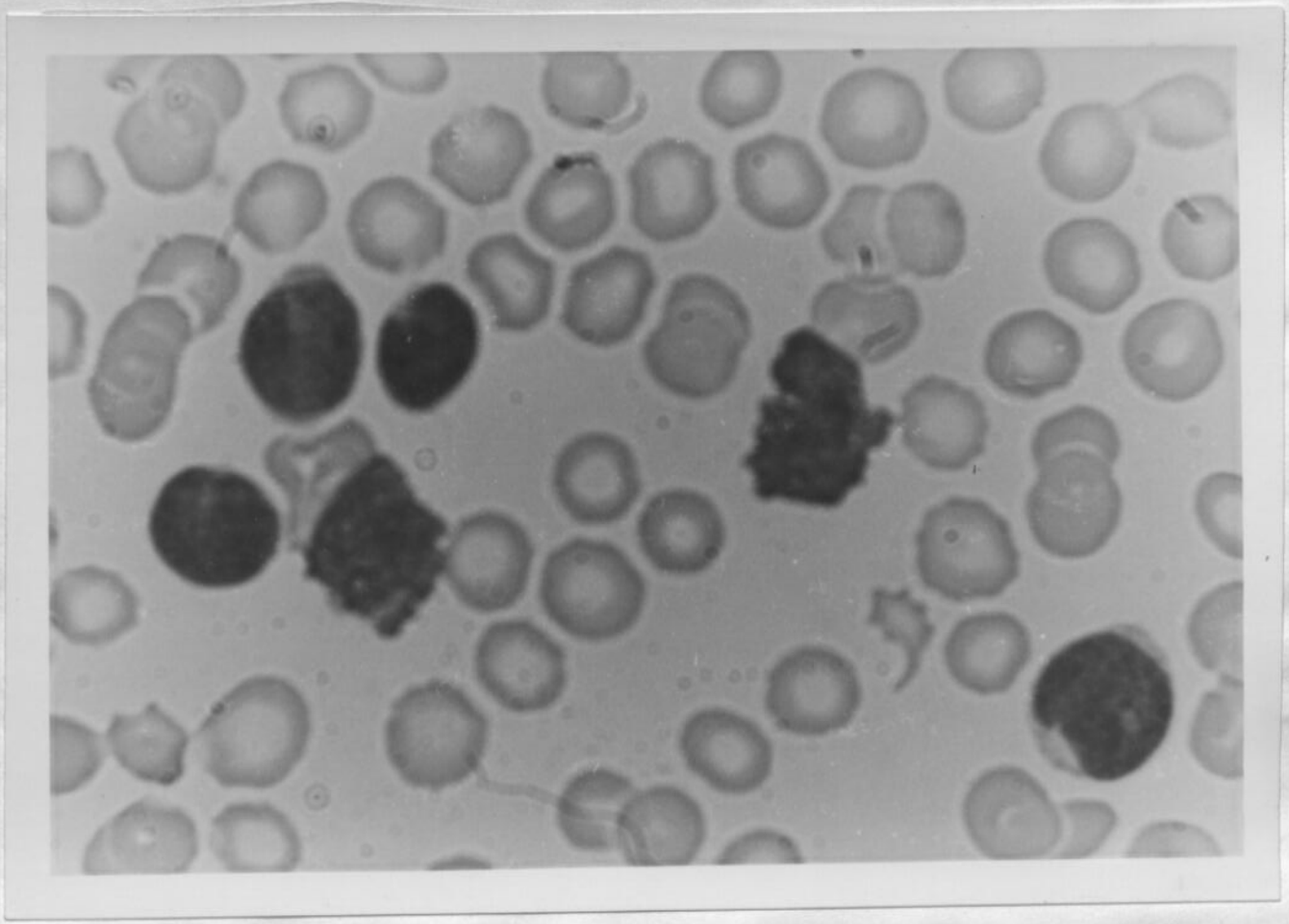

Fig. 17E: Peripheral blood picture (Oil-immersion, May-Grunwald-Giemsa) in ALSCL. Note the polymorphism of the lymphosarcoma cells, from the large to small ones. Nuclear clefting is evident in most of them. The chromatin pattern is coarse and lacy (cf. ALL in Fig. 17B). Basket cells are present, a feature which is unusual in ALL.

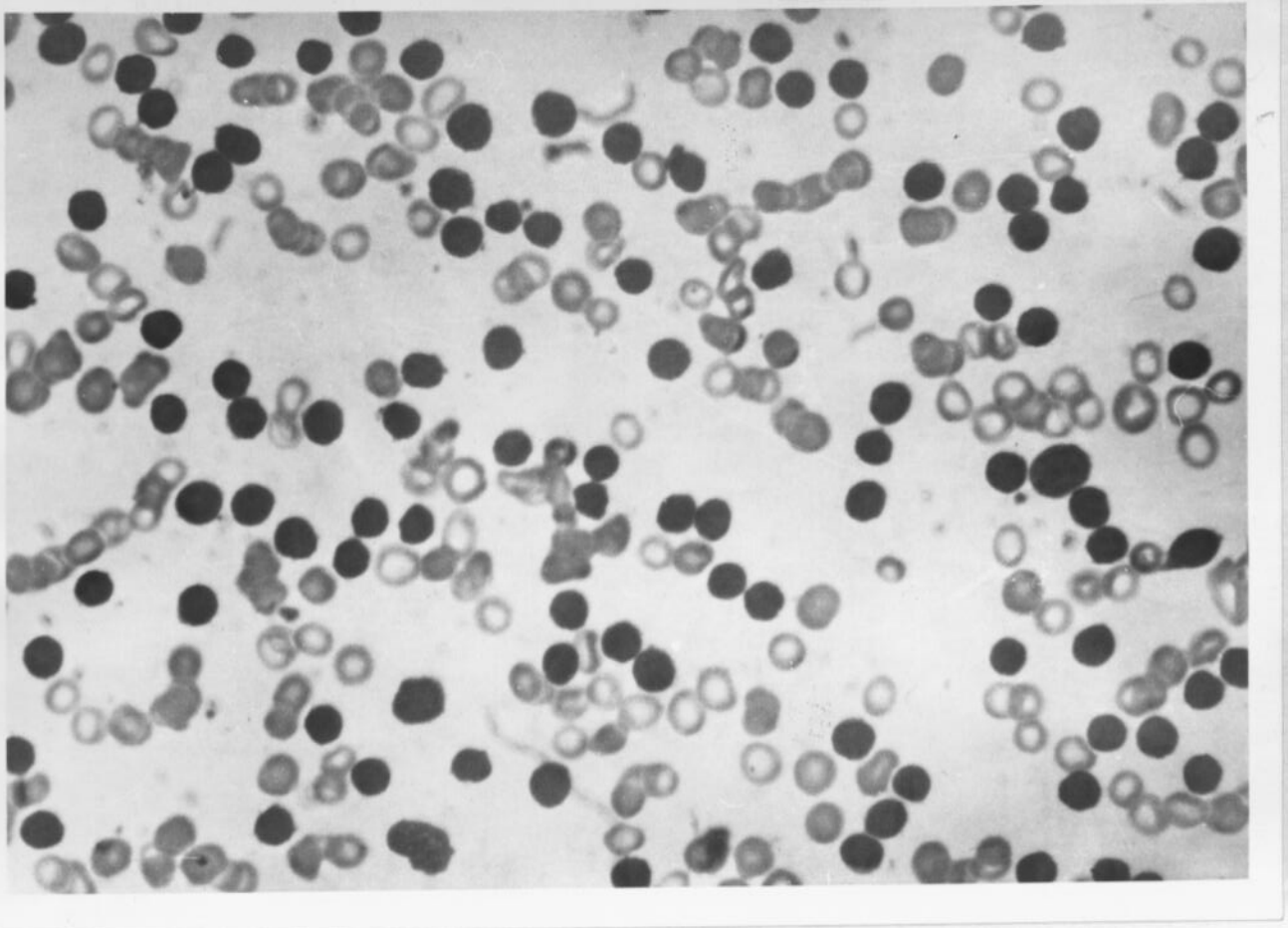

Fig. 17F: Peripheral blood film (x40 objective) appearances in CLL. Note the uniformly small and mature lymphocytes.

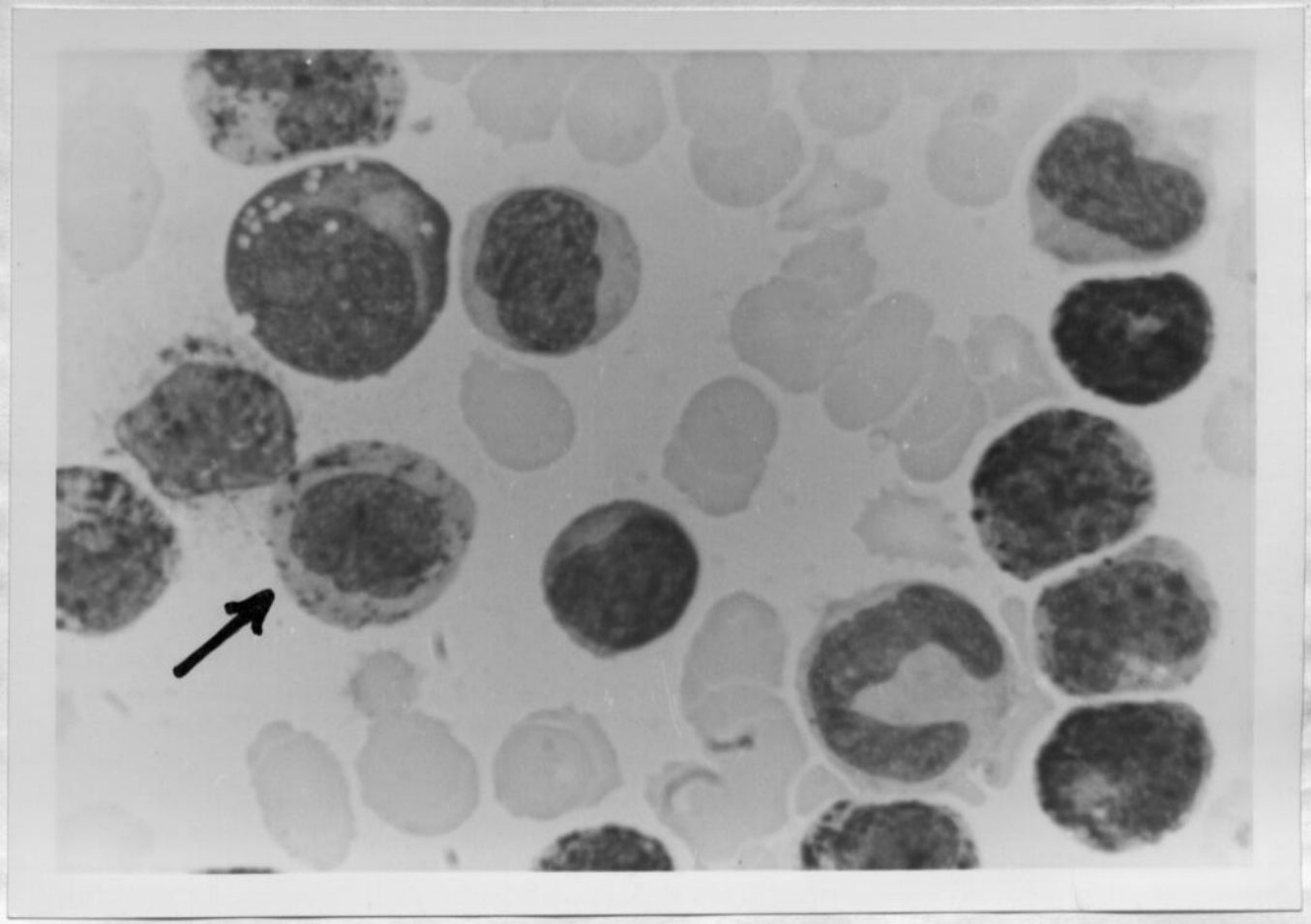

Fig. 18A: Peripheral blood appearances (Oil-immersion - Sudan Black staining) in AM-ML. Note the twin population consisting, on one part, of negative staining monoblasts and promonocytes, but positive staining myelocytes (see arrow) and promyelocytes on the other.

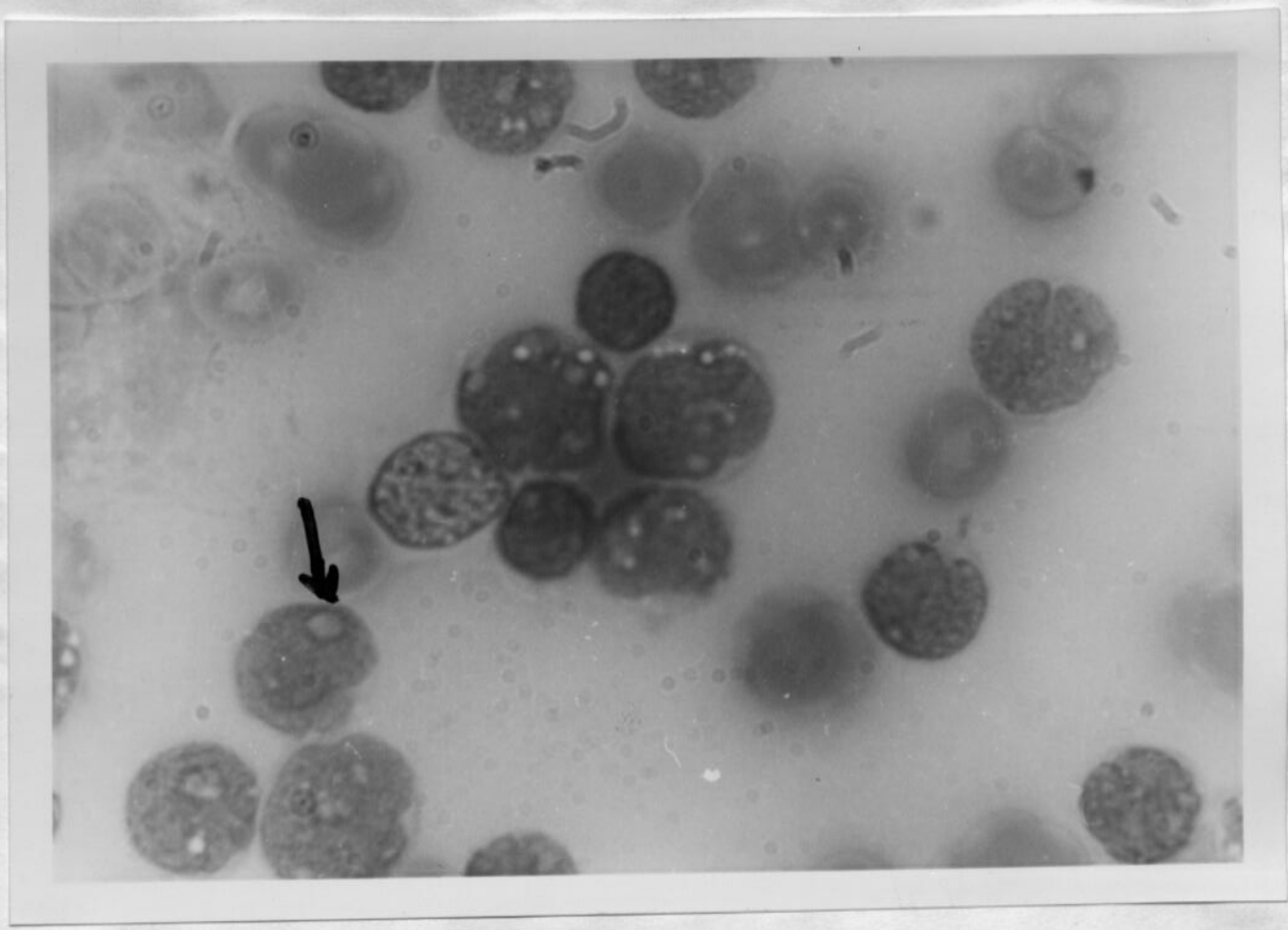

Fig. 18B: Peripheral blood film in ALSCL (Oil-immersion - Feulgen staining). Note the pleomorphism and the polymorphic nature of the cells. The nuclear chromatin pattern is coarse and reticular. The nucleoli are prominent (see arrow) and show perinucleolar chromatin condensation.

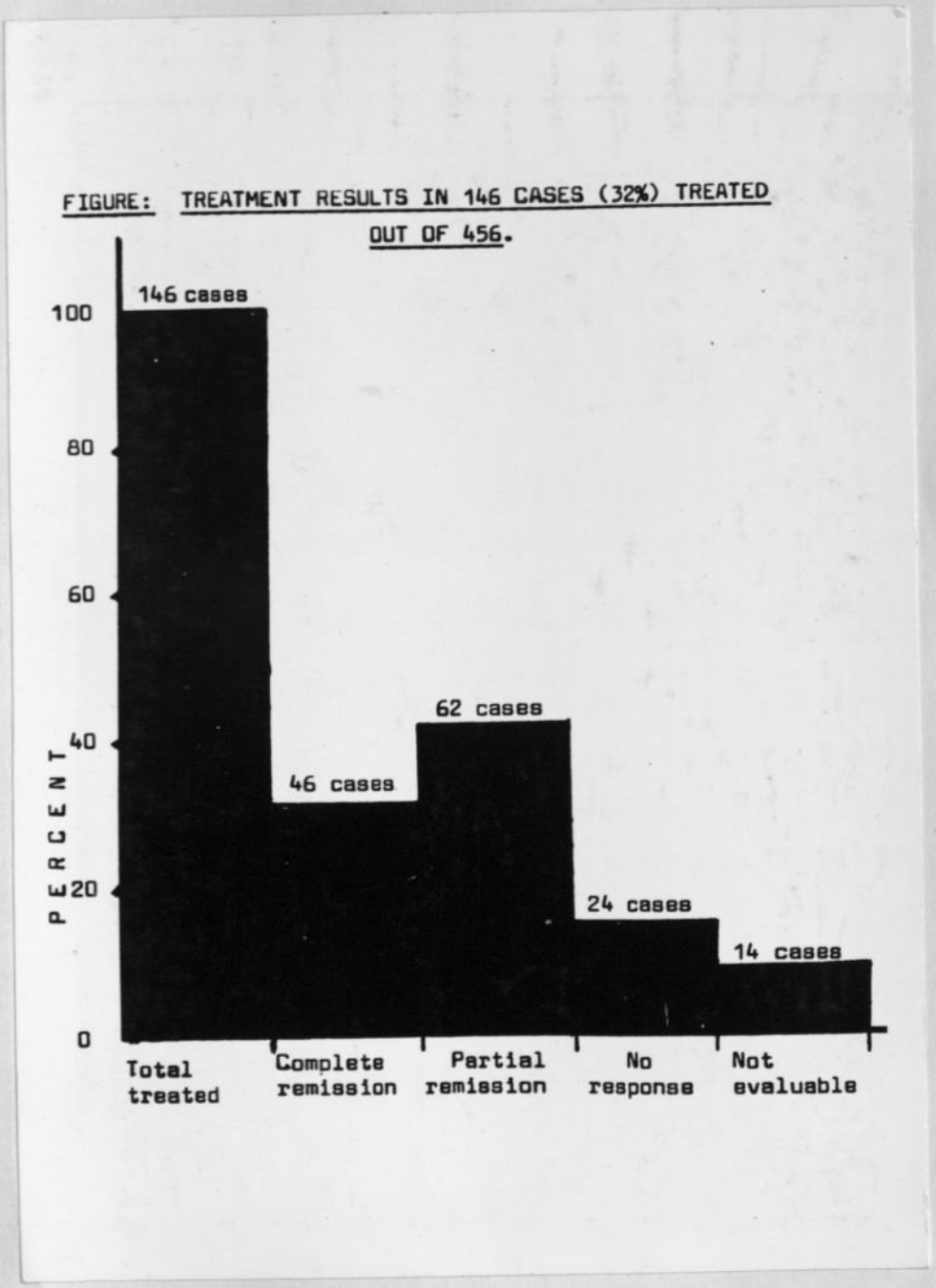


Fig. 19: Treatment results in 146 cases. The high figure of partial remissions is due to the chronic leukaemias.

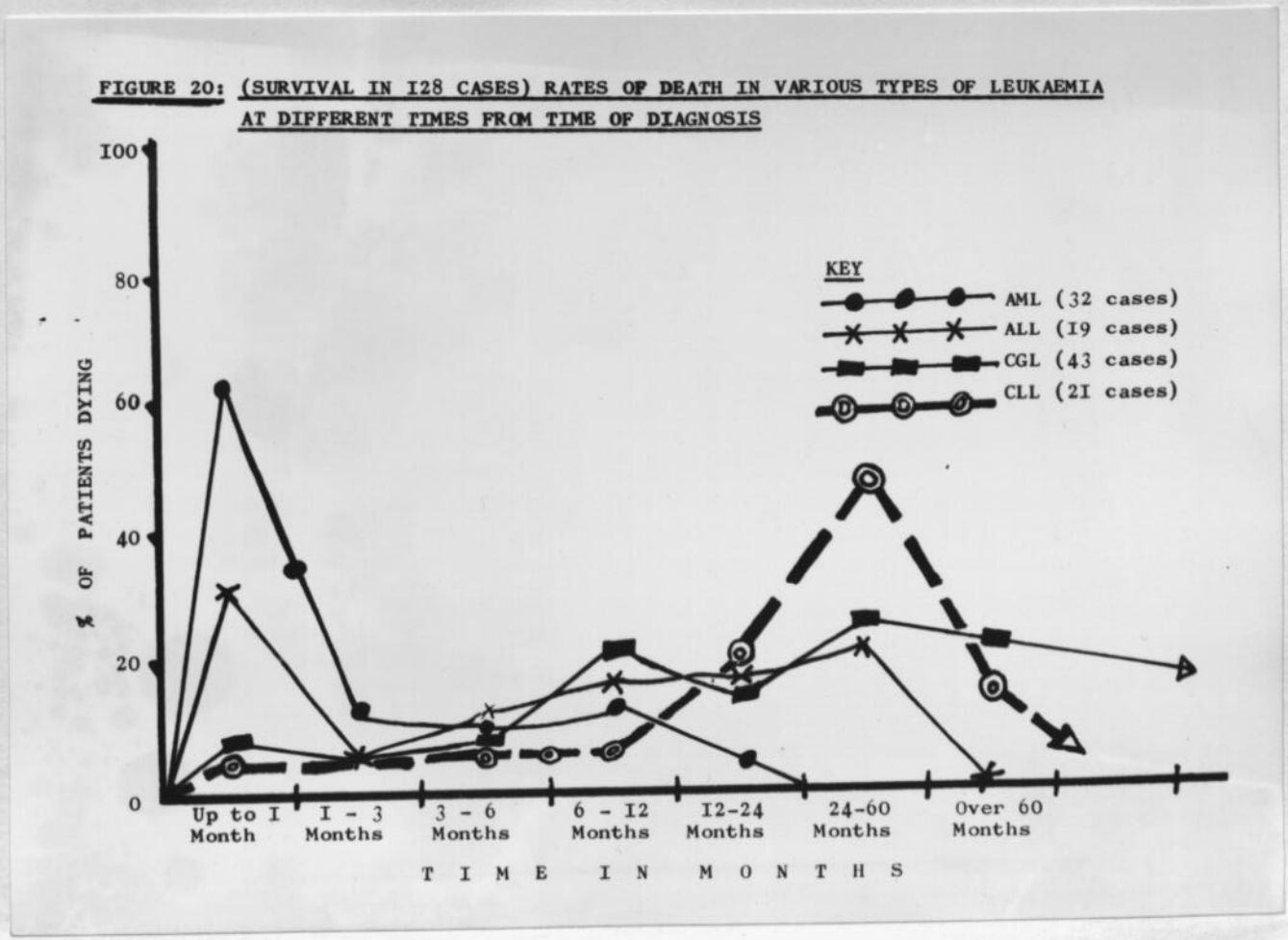


Fig. 20: Survival results in 128 cases of the various types of leukaemia.

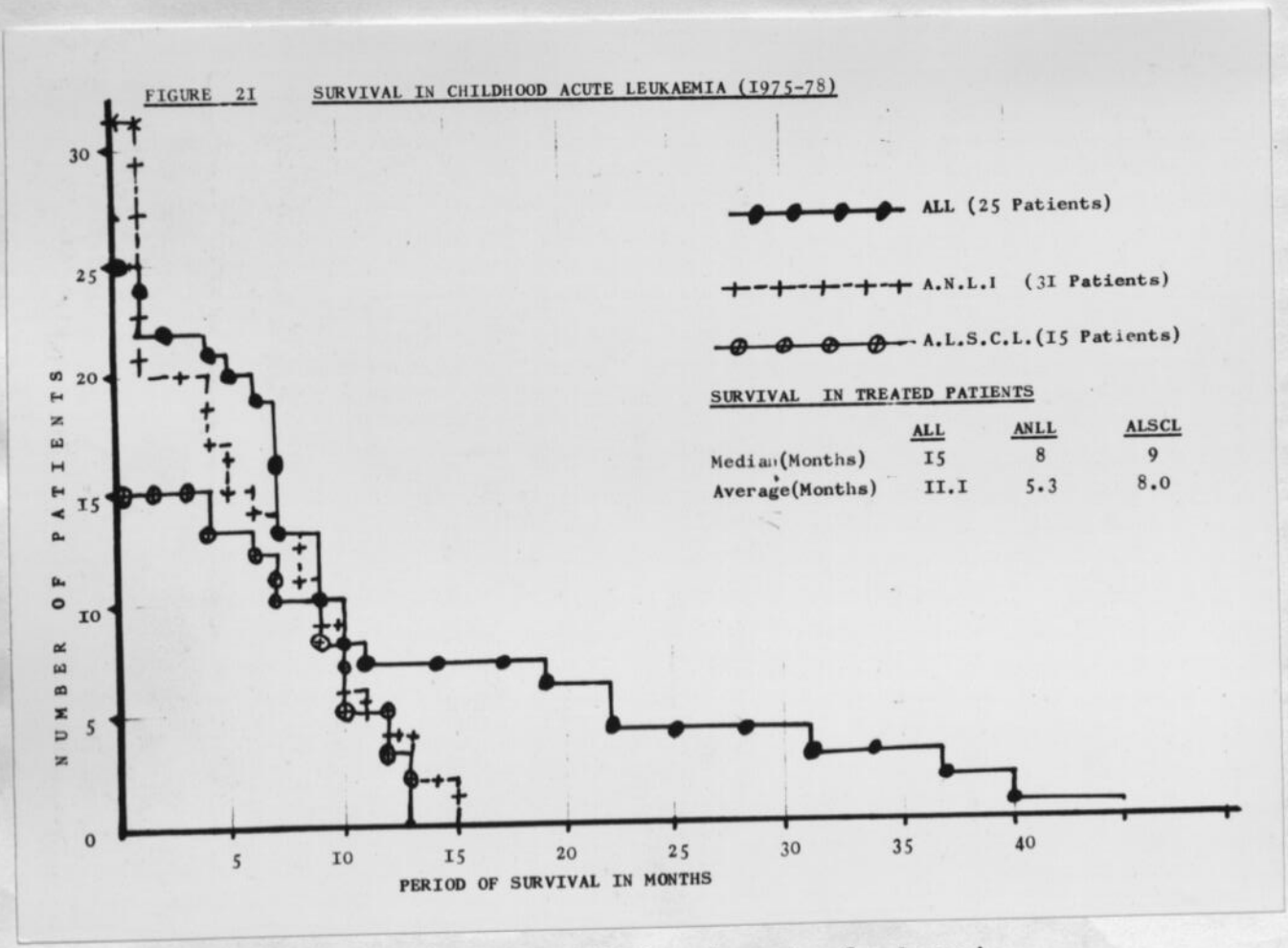


Fig.21: Survival curves in childhood acute leukaemia.

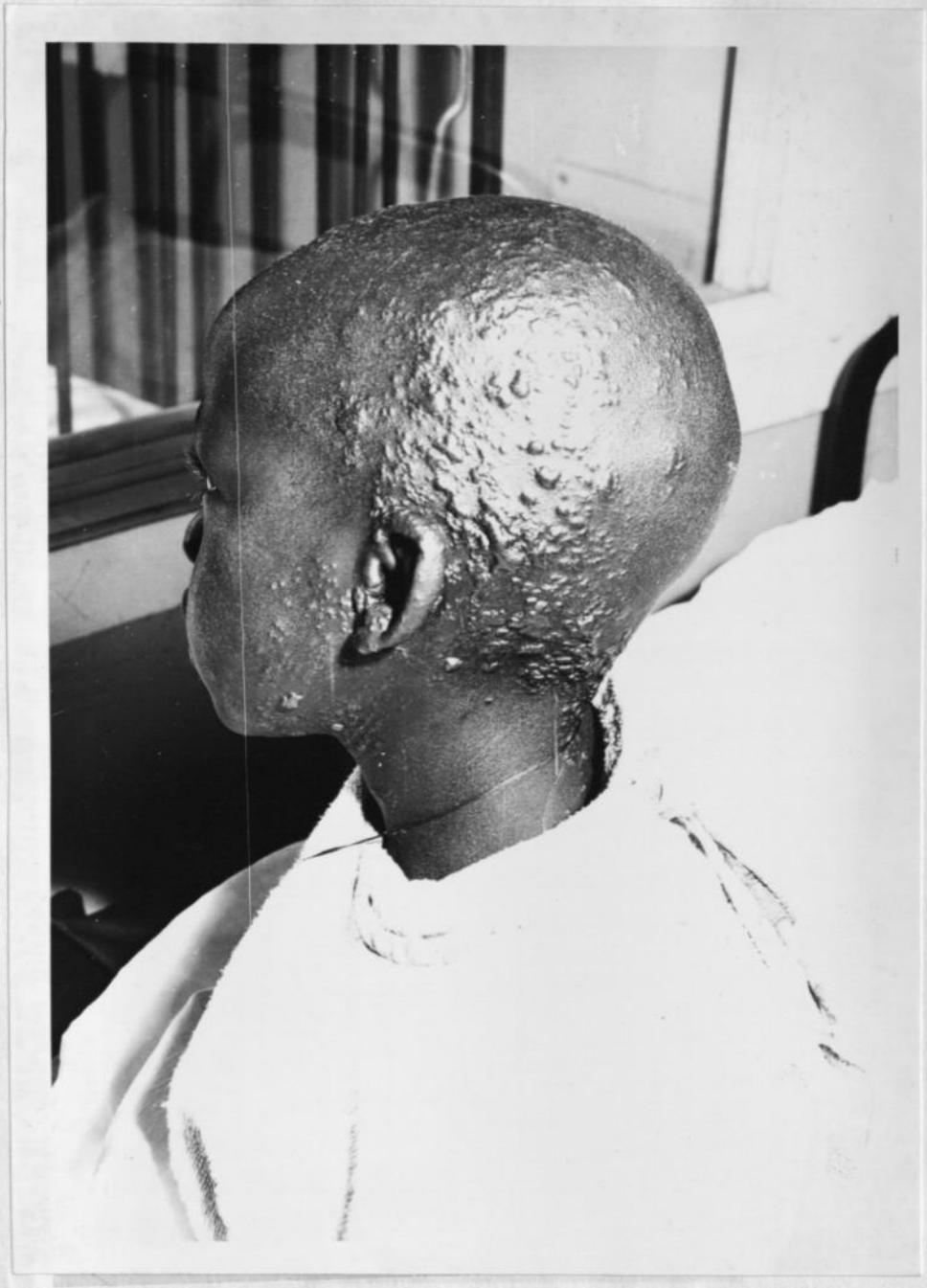

Fig. 22: Herpes zoster in a case of ALL during complete bone marrow remission. The eruption occurred in the distribution of the auriculo-temporal branch of the mandibular division of the trigeminal.

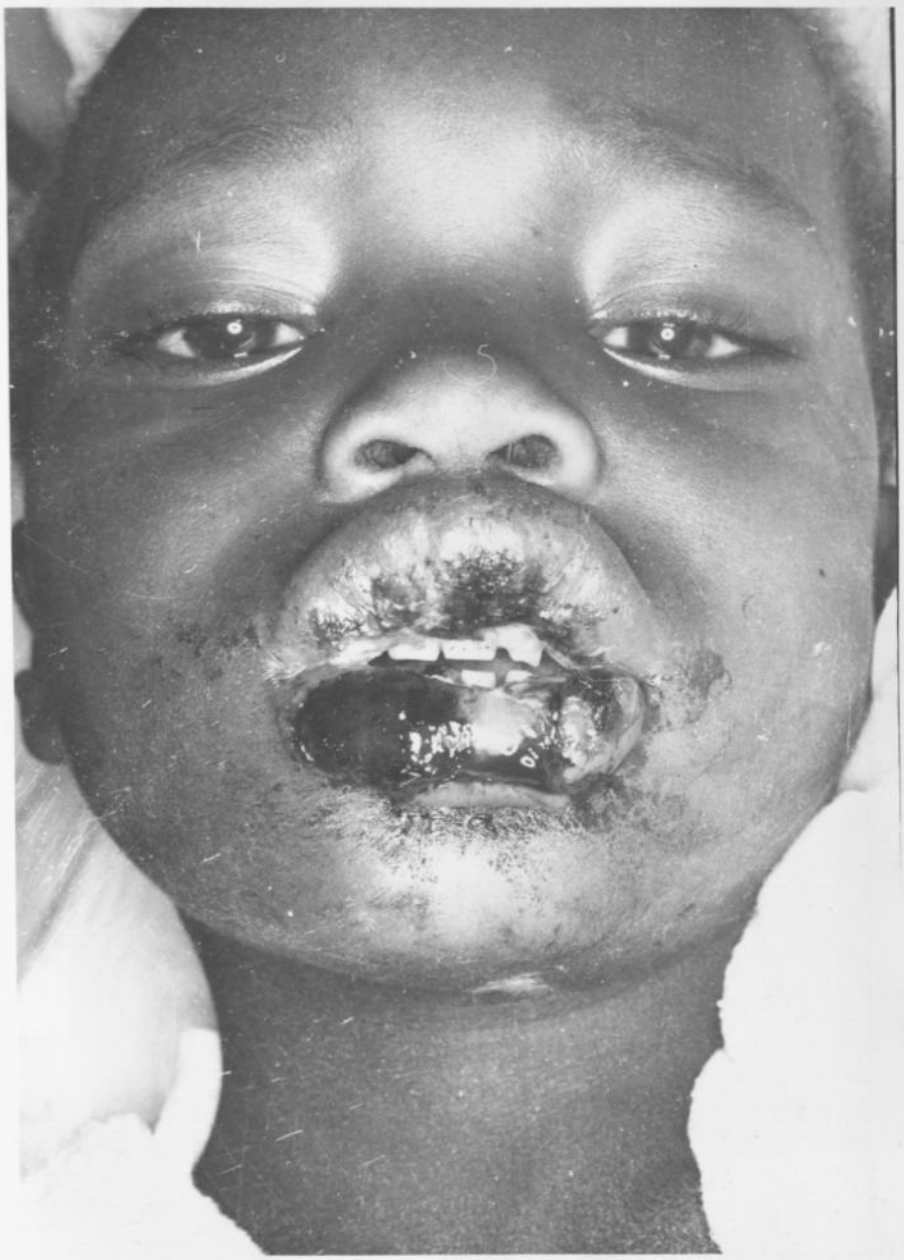

Fig. 23: Severe stomal ulceration due to ulcerative candidiasis in a patient with ALSCL in relapse. High dosage methotrexate may give rise to similar lesions.

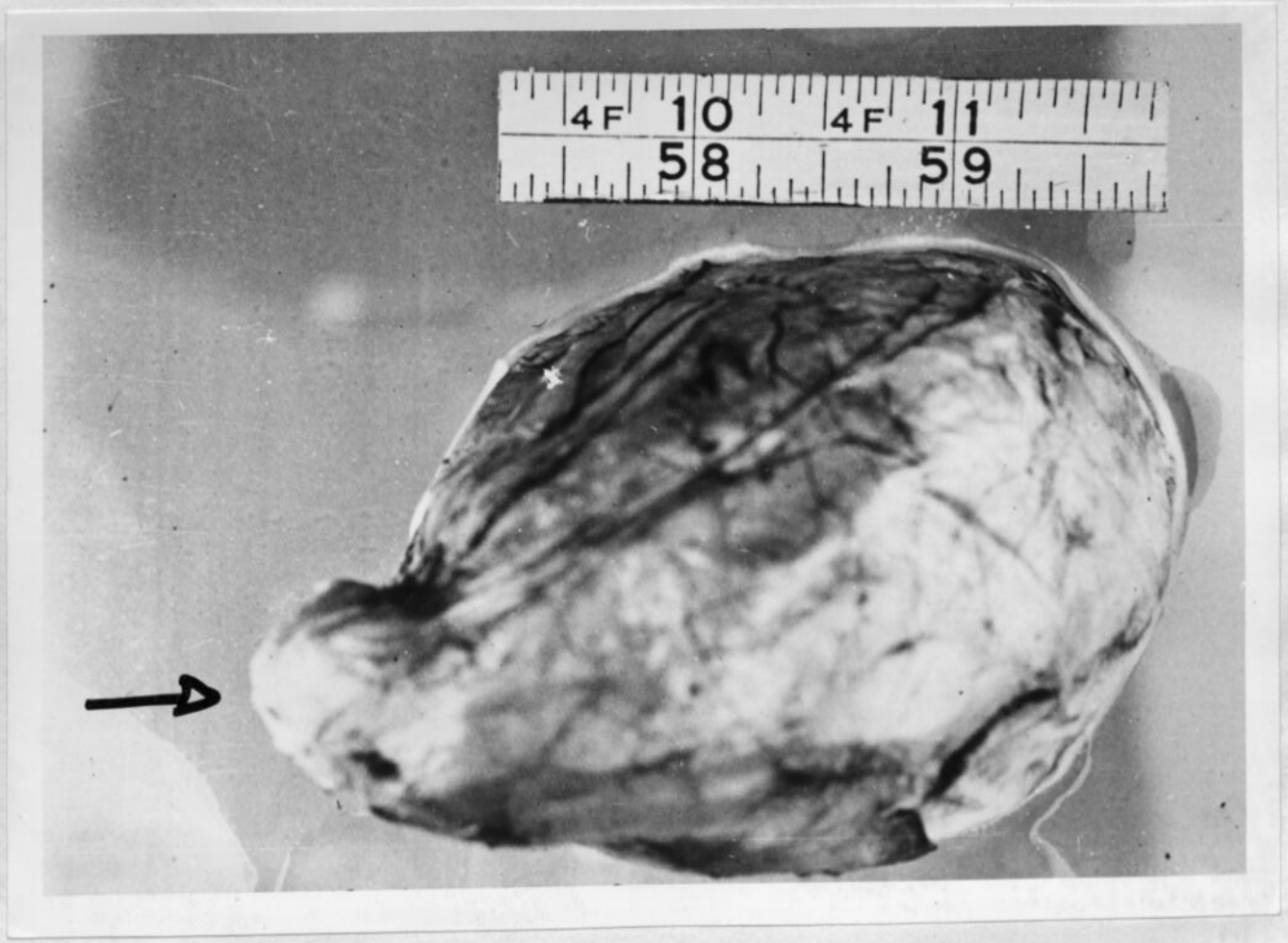


Fig. 24: Autopsy appearance of chloroma in the frontal lobe in one of the cases of AML who died of increased intracranial pressure. He was still in complete bone marrow remission.

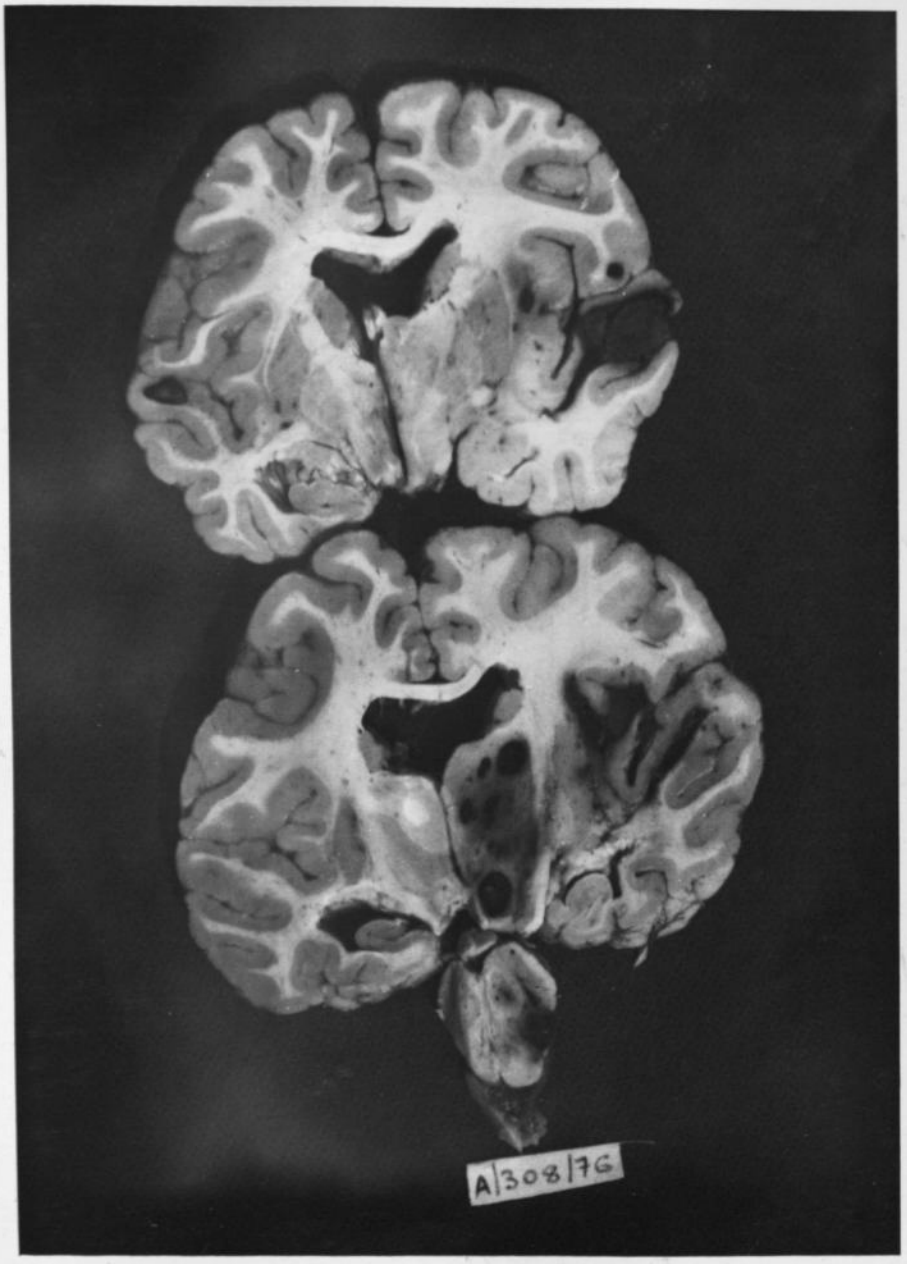


Fig. 25: An autopsy specimen of brain in AM-ML showing haemorrhagic leukaemic infiltrates in the right temporal area, the right internal capsule and brain stem. This picture is unusual in ALL.

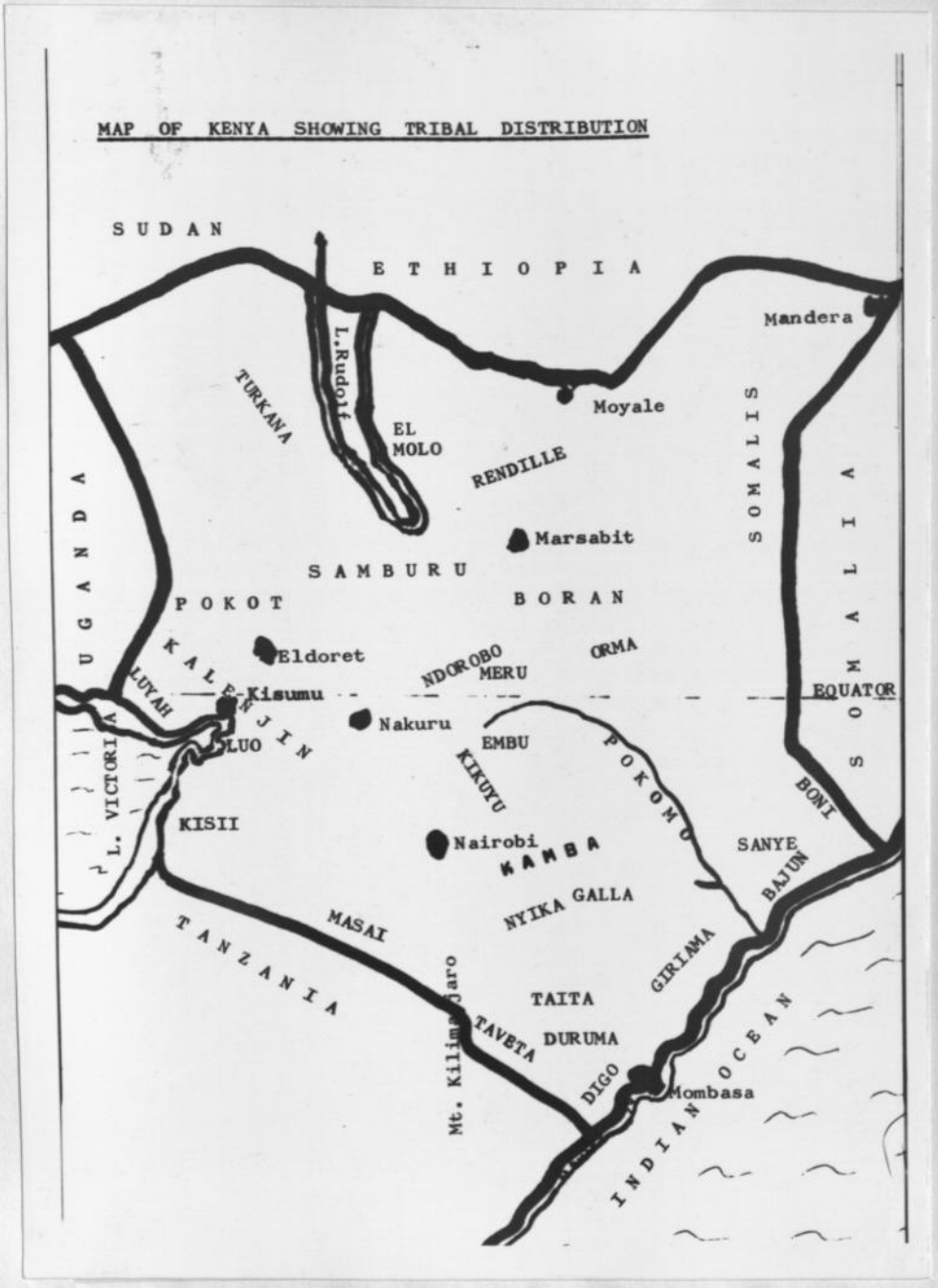


Fig. 26: A map of Kenya showing tribal distribution. Note the close proximity of the Kikuyu and the Kamba to Nairobi.

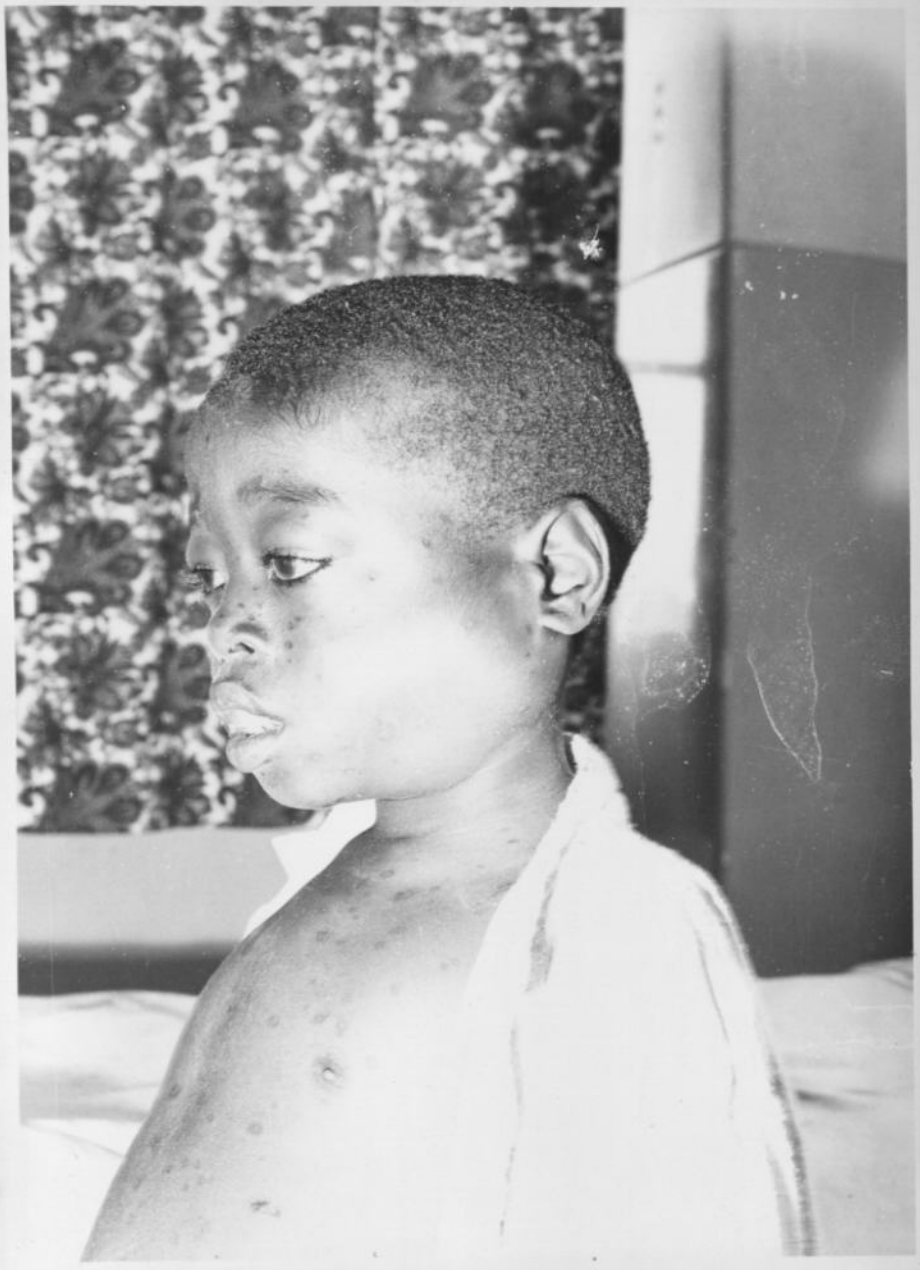

Fig. 27: Parotid and preauricular lymph node enlargement in ALSCL. This is the patient discussed as case 3, Appendix III, before commencement of therapy. Also note the post-varicella scarring, mainly on the trunk.

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