CHRONIC LYMPHOCYTIC LEUKAEMIA

AT KENYATTA NATIONAL HOSPITAL

WITH A REVIEW OP LITERATURE

BY

AGGREY JAMES OLOO, MB ChB (Nairobi).

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

I declare that this dissertation is my own original work, and has not been published elsewhere. And I submit it to the University of Nairobi, as Part fullfilment for the degree of Master of Medicine (Medicine) of the University of Nairobi.

AGGREY JAMES 0L00, (MBChB, Nairobi)

I certify that this dissertation has been submitted to the Univeristy of Nairobi, with my approval as University supervisor.

PROFESSOR THOMAS A. OGADA, MB, FRCP
PROFESSOR OF MEDICINE AND
UNIVERSITY SUPERVISOR

(frills

CONTENTS

SUMMARY;

A study to find out the main clinical features of presentation, the clinical course, and laboratory findings for patients with chronic lymphocytic leukemia (CLL), as seen at Kenyatta National Hospital (KNH), Nairobi was carried out during the calender year 1981. Also done, was a review of literature on this disorder. The study period covered the years 1976 to 1981 both inclusive.

A total of 42 patients were studied, 29 of them retrospectively and 13 prospectively. There were 29 males and 13 females providing a sex ratio of 1:2.2 (F:M). The age range was 17 to 78, with a mean of 54±14 (1 SD). All the patients were of African origin.

The most frequent clinical sign was splenomegally - present in 80% of the patients. Hepatomegally and lymphadenopathy was noted in 76% and 64% respectively. Abdominal pains and discomfort was the most frequent symptom and was recorded in 52% of the patients.

Concurrent infections was conmon. 81% had detectable-respiratory infections; among whom 23% had pulmonary tuberculosis.

Hemoglobin values below 12 Gm/dl was recorded in 72% of the patients. Nearly 1/3 had absolute lymphocyte count above 100,000 per Mm^3

Disease staging (according to Rai, 1975) revealed no patient in stage 0, 26% in stages I and II, and 73% in stages III and IV combined.

35% of the patients were seen within six months of the onset of symptoms, while 42% presented after 6 months. Patient compliance was poor with a default rate of 69% noted in this study. 21% were still being followed up at the clinic by the close of the study. 4 deaths, constituting 9% of the patients were noted. Chest infections and anemia were the main terminal events.

Remission was observed in 66% of 18 patients of whom there was adequate data to enable labelling as remission. Most patients were treated with Chlorambucil and Prednisone. The study is concluded with a resume of a case report of a patient who had very severe disease and multiple complications.

A STUDY OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AT KENYATTA NATIONAL HOSPITAL, (KNH) NAIROBI, FOR THE PERIOD 1975 - 1981 (BOTH INCLUSIVE), AND A REVIEW OF LITERATURE ON THIS DISORDER.

INTRODUCTION:

The Disease:

Chronic lymphocytic leukemia (CLL), has been described as an accumulative disease of immunologically incompetent lymphocytes (1). The small 'mature' looking lymphocytes show decreased functional capacity 'in vitro'. There is also a definite but variable association with autoimmune manifestations (2).

The Lymphocyte:

95% of lymphocytes in CLL have surface immunoglobulins (slg) detectable by imnunofluorescence (3). The slgs so far detected, have been slgM, slgD, slgG and very rarely slgA (3,4). Hie inference is then that CLL is largely of B lymphocytes. But T (CLL) have been described (5,6).

The small lymphocyte, is a round cell with a diameter of less than 10 um, densely staining nuclear chromatin and a thin rim of non-granular, pale staining cytoplasms.

lymphocytosis:

The absolute numbers of lymphocytes in the peripheral blood of an adult is in the range of 1,000 to 3,000 per ran^{3} -constituting 20 to 40 per cent of 5,000 to 10,000 leucocytes per mm^{3} in the peripheral blood. Children have higher absolute numbers till the

age of 5-7 years, when they may have 50 to 70% of 10,000 or more leucocytes per mm^3, being lymphocytes (7). In the peripheral blood most of the lymphocytes are the small type. Lymphoblasts are rare in normal peripheral blood. Lymphocytosis may occur as a result of viral, fungal or mycobacterium infections. Chronic lymphocytosis in otherwise normal individuals is seen but rarely.

Etiology:

The etiology of CLL is unknown. Neither viral nor ionising radiation has been firmly incriminated. Familial CLL with a defect in slgs have been described and probably suggests an inherited defect at molecular level. CLL is rare among orientals but whether this suggests the absence of an inheritable defect is not certain. Familial cases of CLL are however very rare, and no blood groups association has been demonstrated (3,8,9).

Summary of Hematological Features:

There is a rising leucocyte count in the peripheral blood, reaching 200,000 to 500,000 cells per mm^3 in the final stages of the disease. Lymphocytosis is an essential feature. Small 'mature' lymphocytes predominate while occasional 'blasts' may be present. Bone marrow reveals lymphocyte infiltration, often to complete replacement. The bone marrow may be so 'packed' that aspiration becomes impossible.

Anemia and thrombocytopenia are features of advanced disease. They may be the result of increasing marrow infiltration or autoimmune disturbances (9).

Biochemistry and Metabolism:

Some patients will present in a hypermetabolic state with; weight loss, sense of warmth and sweating. These have tendency to improve with therapy. Hyperuricaemia, otherwise cannon in lymphomas and other leukemic states, may be present in CLL. Increased urinary excretion of pseudouridine have been described, and imply increased pyrimidine production, - a result of rapidly dividing precursor cells. The serum levels of enzyme lactic dehydrogenase may be increased (10).

About 50% of CLL patients have reduction in circulating gamma globulins, this is particularly so with advanced disease. A few patients will have hypergammaglobulinemia, especially of macroglobulins (1,11).

Immunological Abnormalities:

Patients with CLL may ^ present with 'anergy' and, through a spectrum, to severe immune reactions. A range of 20 to 70% of CLL patients have low gammaglobulins. IgM is most affected, followed by IgA and very little reduction .in IgGs. The leukemic lymphocytes have defective Igs synthesis. These patients are plagued with infections (11,12).

There is frequent association with autoimmune disorders. And, as many as 20% of patients will show some autoimmune disorders (AID) at various times. Hemolytic anemia is the commonest of these. The latter often lacking the usual indices - spleen size may be insignificant, reticulocytes may be normal in distribution, there may be no hyperbilirubinaemia, and anti-globulin tests (direct and indirect) are often negative. However, cytokinetic studies reveal significant shortening of the red cells

survival times with decreasing haemoglobin levels. Sometimes chemotherapy or radiation triggers on very severe hemolytic process (9,10).

While delayed skin reactions appear normal, there does occur impairment of rejection of skin homograft. Neoplasms tend to be more malignant in CLL patients. Association with macroglobulins, cryoglobulins and Heavy Chains disease have been described (10).

Clinical Features:

CLL. is an insidious disease. Nearly one out of every four patients with CLL is asymptomatic (1,10). But often as the disease advances, so does the symptoms become more and more severe. Patients with moderate affection may present with fever (not due to infections), pruritus and weight loss. Pruritus may be non-specific or a result of cutaneous infiltration by leukemia, or from non-specific dermatitis (13).

Features of advanced disease include shortness of breath, bruising and bleeding tendency; dragging abdominal discomfort or pain; and exfoliative dermatitis.

Massive lymphadenopathy in the neck or axillae may be present. Hie asymptomatic patient may have no overt clinical signs. Chest roentogenograph may suggest hilar lymphadenopathy. Hepatomegally and/or splencmegally occur with advanced disease. The spleen may be palpable below the umbilicus. Pallor resulting from autoimmune hemolysis, or bone marrow replacement by 'malignant' lymphocytes, or a result of bone marrow suppression by cytotoxic therapy - occur often in very advanced disease.

Patients presenting with elevated temperatures - especially if persistent - will most likely have an infection, bu c verv rarely due to de-differentialion of CLL into a difuse histiocytic lymphoma - 'the Ritcher's syndrome' - the latter having a very rapid downward clinical course (2,14).

Pathology:

CLL can involve virtually any organ in the body. Infiltration of the lymph nodes, liver and spleen, besides the bone marrow are the most frequent. These organs may enlarge to enormous sizes.

The Lymph Glands:

Are usually discrete, firm and painless. On section, they are firm, and in colour pinkish-grey. Microscopically the normal gland structure has disappeared and gem centres cannot be found, the whole substance consists of a mass of lymphocytes. The lymphatic tissue in the tongue, tonsils, and nasopharynx is hypertrophic and germ follicles are absent. It is unusual for the nodules to ulcerate or bleed, although this may occur. GIT shows enlargement of lymphoid tissues.

The Spleen:

Often enlarged and palpable. Previously reported to be of moderate size as compared to the huge spleens of CML, but in Africans the splenic size can be very large, (15,16). Infarcts, perisplenitis and adhesions occur, but probably less frequently "than in CML, Fibrosis is common. In late disease, the whole tissue consists of densely packed lymphocytes, so that smears obtained by splenic punctures may consist of up to 99% lymphocytes, infact,

unless excessively diluted with blood if a smear has less than 90% lymphocytes then CLL can be excluded. Erythroblasts are often present in the smears. Subcapsular hemorrhage are cormmon and spontaneous rupture of the spleen may occur (17).

The Liver:

Often enlarged with lymphocytes accumulation in portal areas.

The Bone Marrow:

Is infiltrated with lymphocytes. Most of the yellow marrow of long bones is greyish or red in colour - partly due to infiltration and partly due to hyperplasia of the eiythropoietic tissue. The normal red marrow of the ribs and sternum are altered and replaced by lymphocytes, indeed in early stages, a foci of lymphocytes may be surrounded by myeloid cells as in secondary carcinoma. Megakaryocytes are usually diminished (9).

CLL. and the Nervous System: (CNS)

Hemorrhages and infiltration in the CNS may occur in terminal stages. A syndrome similar to myasthenia gravis has been described (9).

CLL and the Kidneys:

CLL may affect the whole column of the urinary tract, while the pathology will range fran acute UTI to an asymptomatic infiltration. UTI is common, and can be chronic. Hematuria as a symptom may result from UTI, thrombocytopenia, cyclophosphamide therapy or Uric Acid Nephropathy. Some patients may present with frank nephrotic syndrome with immune complexes demonstrable on the basement membrane as in the nephrotic syndromes which complicate

Hodgkin's disease and other malignancies. Infiltration of the kidneys may be demonstrable only for the first time at autopsy (9).

CLL and the Gastrointestinal Tract (GIT):

Infiltration of the GIT is often without symptoms and only noted at autopsy. Occasional lymphomatous polps have been described (9).

CLL and Acropachy:

If sub-ungal infiltration occur, they result in bullous digits. Radiography of the bones, may reveal translucent cysts in the hands and feet, and other bones. Some reversion of these lesions have been noted with treatment (9).

CLL and the Skin:

Infiltration of the skin may present as papules or larger nodules. However, non specific vesico-bullous lesions may occur and probably have a less favourable prognosis. 'Honme rouge' - generalised leukemic erythroderma with thickened, leathery and intensely itchy skin is a severe presentation. The 'orange man[1] - haematodermia is however rare. It is noteworthy to remember that itching without infiltration is a frequent cutaneous manifestation (9,10,17).

CLL and Other Neoplasms:

No definite evidence has been advanced so far. But the incidence of skin neoplasms and colonic tumors is probably higher in patients with CLL (18).

CLL and Pregnancy:

Pregnancy is a little rare with CLL, probably because the disease occurs late in life. Occasional cases have been described. Chlorambucil may well be teratogenic - as it has been shown to cause chromosomal damage (9) .

Unusual Associations:

Association of Hodgkin's disease in the same patient has been recorded (8,9).

Note on Cytogenetic studies:

As Dameshek (1) has described, CLL is an accumulative disease; and cell division is infrequent. The Christchurch chromosome which is a deletion of the short arm of chromosome No. 21(G2 autosome) 21-p deletion was described in a family in which 2 sibs had CLL, but unaffected sib also had chromosomal defect. It has not been described again (19). Chlorambucil may however induce chromosomal damage.

Treatment:

The diagnosis of chronic lymphocytic leukemia does not automatically imply need for treatment of the leukemic state (13). Though recently opinion have been variably expressed that it may be worthwhile to treat those asymptomatic patients, in particular when the lymphocyte count is very high (4,15). It must be appreciated however, that the disease is incurable with the methods of treatment available (4).

Indications for Treatment of the Leukemia:

Patients with massive lymphadenopathy require treatment for cosmetic purposes or otherwise if they are symptomatic. In the same line, massive splenomegally with dragging discomfort need treatment.

Those who develop autoimmune complications are necessarily treated, as are those patients who have impending Bone Marrow failure.

Patients with constitutional symptoms like those with very high lymphocyte count should be treated (4,10).

Treatment of Infections:

Antibiotics are administered when indicated by the presence of an infection, though there is probably a place for prophylactic antibiotics, e.g. in winters in the temperate world. The administration of human imxiunogarrmaglobulins in severe infections can be life saving (10).

Blood Transfusions:

Are essential in Bone marrow failure not responding to treatment as well as in those with acute bleeding if they occur.

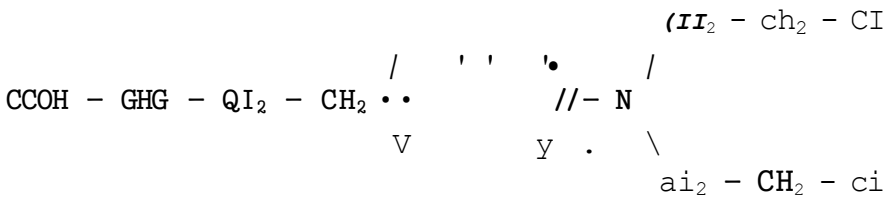
Treatment, of Hyperuricemia:

This is rarely indicated. But Allopurinol can be given to patients with very large* lymph nodes or very high leucocyte counts, in particular at initiation of cytotoxic therapy (10).

Methods of Treatment of CLL:

1. Chemotherapy: Alkylating agents are effective in reducing the lymphocyte mass in CLL. Chlorambucil arid Cyclophosphamide are used in the treatment of CLL. The former is administered orally in doses of 0.1 to 0.3 mg/kg/day - often as a single daily dose. Some patients are unusually sensitive to chlorambucil - hence it is preferable to start therapy with lower dosage. Cutaneous allergic reactions may occur. In advanced centres, 'in vitro' sensitivity testing has been devised.

The lymphocyte count will fall in nearly \ of patients treated. Lymph-node regression may be noted in about \ of the patients, while splenomegally is not usually much altered. Similarly, bone marrow infiltration, anemia and thrombocytopenia do not improve substantially, and increasing the dose of chlorambucil will only further depress the marrow.



P (di-2-chloroethylamino) phenylbutyric acid = CHLORAMBUCIL.

Cyclophosphamide by oral administration is used in the dosage of 100-200 rog/day (50 mg tablets). It probably will complicate less often with thrombocytopenia than chlorambucil, but other side effects can be more troublesome (10).

RADIOTHERAPY:

Local Radiation Therapy:

This can be applied to:

i) Large lymph node masses not suitable for chemotherapy or resistant to chemotherapy,

ii) Skin infiltration which may also respond.

iii) Troublesome lymph node masses with only a moderate rise in leucocyte count.

iv) Splenic area when spleen is very large and splenectomy is inadvisable. Remission may be induced.

External Whole Body Irradiation:

Has been used to induce both symptomatic and haematological remissions. There is probably a subsequent increased risk to develop acute myelogenous leukemia (AML) (20).

Radiophosphorus:

Administration of radiophosphorus has met with satisfactory results in the centres where these have been tried, but like external whole body irradiation, there is the risk of developing AML (20).

Extracorporeal Irradiation of Blood (ECIB)

The method does not appeal to many as a treatment procedure. Blood is irradiated outside the body as it passes through a coil (20).

Steroids:

Steroids are useful in hemolytic anemias and autoimmune thrombocytopenia. Many patients with anemia have negative

antiglobulin tests and evidence for hemolysis is often unimpressive, more so if the anemia is mild to moderate in severity. Although thrombocytopenia may be due to B.M. failure, a trial of steroids is often worthwhile for it may raise the level of thrombocytes count * to values when alkylating agents may be used with greater safety (4,20).

Androstanes: '

Are worth a trial in Bone marrow failure, when they may raise the level of Red blood cells (RBC) and possibly neutrophils. Gxymstholone is given orally (50-200mg/day). Testosterone enanthate or fluoxymestrone may be given, but by parenteral route (9).

Anti-Lymphocyte Serum (ALS):

The use of ALS is still experimental. Isoantibodies and xenogeneic serum have been used with resultant transient lymphopenia. Lymph nodes and other organ enlargements have shown very poor response (9).

Leucapheresis:

This method which uses cell separators is relatively effective in reducing lymphocyte count and even lymph nodes, spleen and B.M. infiltration may decrease (4,9,10,20).

Splenectomy:

Is beneficial in large spleens which are causing intolerable discomfort or pain. Also when splenomegally is associated with anemia and thrombocytopenia, and very high doses of drugs and steroids necessary may bo too high to vise safely, it may be advisable to consider the operation (17).

Prognosis:

CLL has variable progression after diagnosis. Survival is however influenced by the stage of disease at diagnosis. A paucity of symptoms, clinical signs, and hematological statistics augur well for the patient. Survival does appreciably decrease with advancing age (4,11). Acute termination is rare in OIL, unlike CML. Rare instances of acute myelomonocytic leukemia and acute plasma cell leukemia have followed chlorambucil therapy, while AML may follow radiation treatment. Infections is the corrmonest cause of death in CLL.

OBJECTIVES OF STUDY:

1. To find out the pattern of clinical presentation of patients with CLL as seen at KNH with respect to the following:
   i) age and sex;
   ii) main symptoms and signs of presentation;
   iii) complications of the disease: INFECTIONS;
   iv) levels of Hb, lymphocyte counts and platelet counts;
   v) duration of symptoms before diagnosis and fate of patients at close of the study;
   vi) in fatal cases, to document the terminal clinical events, stage at diagnosis, therapy administered, and duration of follow up from diagnosis to death.

2. In the prospective study: to record the hematological pattern at diagnosis; viz:
   the frequency and type of anemias;
   the frequency of thrombocytopenia.

3. To study the pattern of remissions viz:
   the duration of treatment before remission;
   the type of therapy administered.

PATIENTS AND METHODS:

Selection of Patients:

Patients in this study had been seen, or were still being followed up at KNH, Nairobi. Patients in the retrospective study were documented and reappraised by the vise of hospital case notes obtained from the medical records department at KNH. The period covered was from 1976 to 1980, both years inclusive.

Patients seen during 1981, belonged to the prospective study. They were seen at the Hematology clinic, KNH. This clinic was held every Monday mornings. This figure was augmented by a surveillance over the medical units at KNH. This was done every Monday after the Hematology clinic, when every ward was visited. As a check, a comparison was maintained with the medical records to ensure all patients registered as having (or probable) CLL were traced and reappraised.

Tne purpose and intent of the study was explained to the patients and their consent obtained.

Methodology:

All patients had a complete medical history obtained. Specific symptoms were enquired into if not volunteered by the patient; and a note on the patients previous health recorded. This was followed by a full clinical examination.

The following routine laboratory investigations were done on all patients, unless otherwise stated:

(V.I.) 1. Stools for parasitic infestations, and occult blood tests.

2. Urine for urinalysis, microscopy and culture.

3. Blood for urea and electrolytes.

4. Chest radiographs were requested for those patients with symptoms or signs referrable to the chest.

The following specific investigations were carried out for the prospective patients or results retrieved from the case notes for the retrospective study; viz:

i) Full Hemogram (V.i)

ii) Liver function tests (serum bilirubin in particular) (V.i).

iii) Serum uric acid,

iv) Antiglobulins tests (Direct and Indirect).

Surrtnary of Laboratory Procedures:

1. Hemogram: Venous blood collected from main veins in antecubital fossa was utilised. 2 blood films were prepared on clean glass slides before adding the blood to the anticoagulated containers.

Ethylene diamino tetraethyl acetic acid (EDTA) containers were used. With minimal squarting force and the needles detached from the syringes, the blood was collected and gently mixed with the anticoagulants. Whenever films could not be made immediately, these were prepared from the anti-coagulated blood at least within one hour of their collection.

Electronic Coulter S was used to obtain most of the parameters of the Haemogram viz: the Hemoglobin (lib), the Hematocrit (Hct), Mean Corpuscular Volume (MO/), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular HerrDglobin

concentration (MCHC) and the total white blood cell count (WBC).

The Erythrocyte Sedimentation Rate (ESR) was estimated by the method of Westergren (7).

Thrombocyte counts were done by direct visual method using a diluent ammonium oxalate. Brilliant Cresyl Blue was used as a vital stain for the reticulocyte count. Films of peripheral blood were stained by May Grunwald Giemsa Stain (7).

Serum Uric acid levels were estimated by spectrophotometric method using phosphotungstic acid (21).

The serum bilirubin estimation was obtained from auto-analyser result sheet for liver function tests.
Machine: Automated SMA II.

Antiglobulin tests (direct and indirect) and blood group and Rhesus were performed as outlined in Dacie and Lewis (7).

RESULTS:

42 patients were studied for the period 1976-1981. 69% were introspective cases and 31% prospective case studies. There were 29 males and 13 female patients. This distribution is represented in Table 1 below.

Table 1: Patient Distribution in Study:

Portion of Study	No. of Patients	M	F	%
Retrospective	29	20	9	69
Prospect ive	13	9	4	31
% and Totals	42	29(69)	13 (31)	100

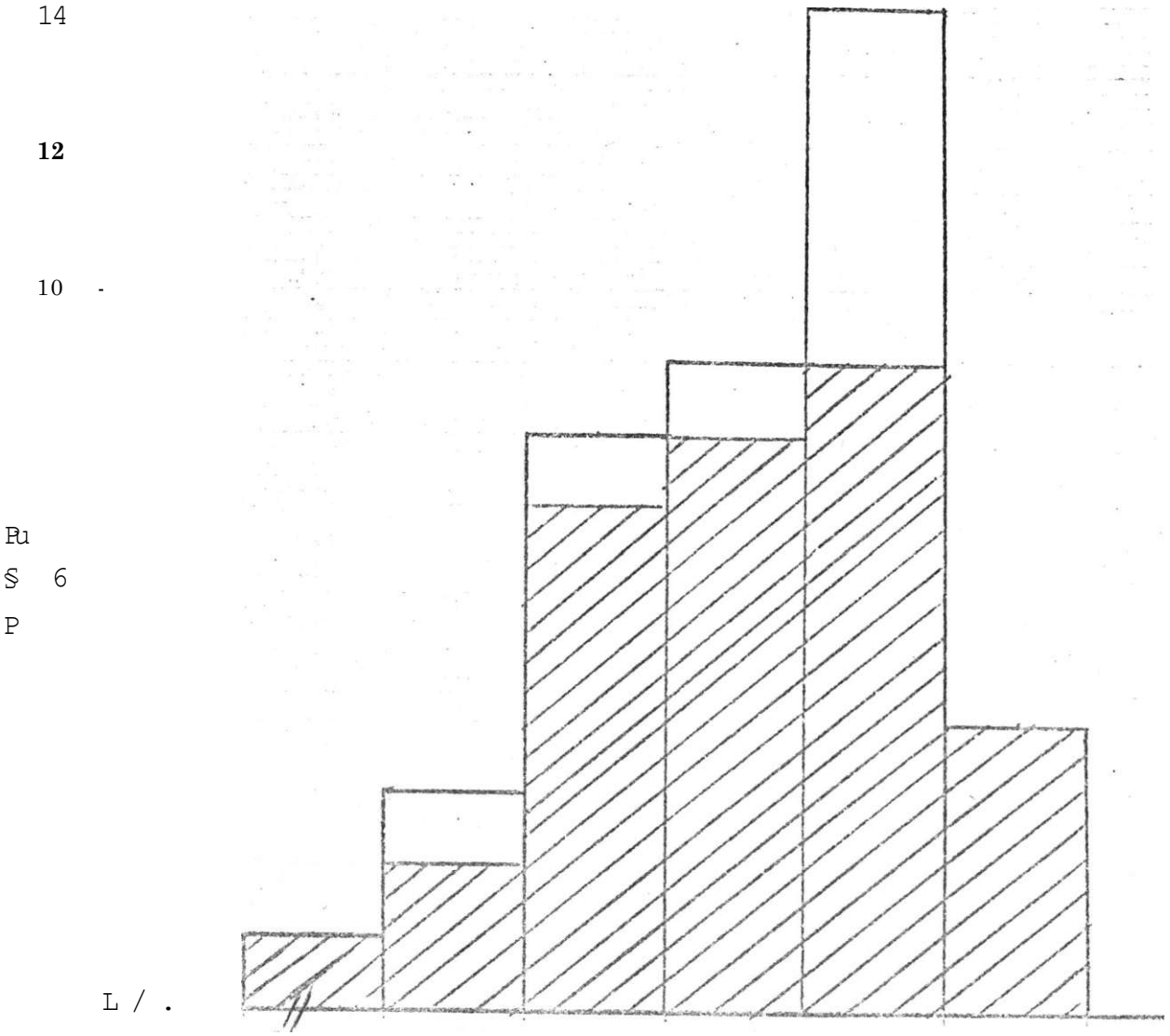
N = 42

F:M = 1:2.2

The age-group distribution is depicted in Figure 1. The mean age was 54+14 (ISD). The age range from 17 to 78 years. Males outnumbered females at all age-groups studied.

FIGURE I: AGE AND SEX DISTRIBUTION' AMONG CLL PATIENTS

A



The frequency of main presenting symptoms are outlined in Table II below, 52% of the patients complained of abdominal pains or discomfort.

Table II: Presenting Symptoms of Patients with CLL

(N = 42)

Symptoms	No. of Pts.	%
Abdominal pains & discomfort	22	52.4
Chest pains and cough	12	28.6
Weight loss	12	28.6
Generalised weakness	11	26.2
Swelling of feet	8	19.0
Epistaxis	4	9.5
Cutaneous manifestations	4	9.5
Diarrhoeas	4	9.5
Headaches	3	7.1
Dysphagia *	1	2.4
Swelling of glands	8	19.0

* The one patient who had dysphagia had carcinoma of esophagus.

The frequency of main clinical signs were calculated and recorded. Splenomegally was present in nearly 80% of the patients. Palpable lymph nodes were recorded as such without recourse to their sizes. About 60% of the patients had pallor .

Table III: Main Clinical Signs for Patients with CLL

(N = 42)

Clinical Signs	No. of patients	%
Splenomegal l'y	34	80.9
Lymphadenopathy	27	64.3
Hepat omegally	32	76.2
Pallor	25	59.5

Patients with CLL have frequent infections. 4 patients had pulmonary tuberculosis proven by sputum studies. Respiratory infections were suspected and/or diagnosed in 17 patients. 81% of all infections were referrable to respiratory system. 9.5% of infections were those of the urinary tract. One patient had fulminant oropharyngeal candidiasis. Recurrent otitis media was recorded in one patient. The frequency of infections is presented in Table IV.

Table IV: Frequency of Infections in CLL Patients

Infections	No.of. patients	%
Respiratory Infections	17	81
(Tuberculosis*)	(4)	(19)
Urinary Infections	2	9.5
Skin Infections	0	0
Otitis Media	1	4.8
Candidiasis	1	4.8
Totals	21	100

*The 17 patients who had respiratory infections also included the four with tuberculsosis. The absence of overt skin infections is remarkable.

Hematological Parameters: More than one half of the patients had hemoglobin less than 12 g/dl. Only 36% of the patients scored Hb more than 12 g/dl. Hemoglobin distribution is presented in Table V. 7% of the patients were severely anemic.

Table V: Hemoglobin Distribution among patients with CLL at Diagnosis.

Hb in g/dl	< 4	4 - 7	8 - 1 2	> 12	Totals
No. of patients	3	9	15	15	42
Percentage	7	21	36	36	100%

N = 42

The absolute lymphocyte counts presented a very wide range. 28.6% of patients had total lymphocyte count more than 100,000/irm^3. 33.3% had a count between 50,000 to 100,000/nm^3, while 28.6% had count between 15,000 to 50,000/rmi^3, Only 9.5% had lymphocyte count below 15,000/nm^3 (see Table vi)•

Table VI: Distribution of Lymphocyte Counts among CLL Patients

Absolute Lymphocyte counts X1000	•C 15	15-50	50-100	>100	Totals
No. of patients	4	12	14	12	42
%	9.5	28.6	33.3	28.6	100%

Thrombocyte counts: This was not done in a uniform fashion especially for the retrospective study. 22 patients had platelet count above 100,000/mn^3 or reported as 'adequate' (5). The other 20 patients either had a count below 100,000/mn^3 or reported as 'reduced' in numbers. The platelet counts at diagnosis for the prospective study patients is given in Table VII.

Platelet count amoung 13 patients studied prospectively at diagnosis

Patient No.*	i	9	7	8	16	17	18	19	20	21	22	23	33
Platelet counts Xl,000/irm^3	55	197	90	119	92	150	225	142	150	145	90	156	146
Distribution	R	NR	R	NR	R	NR	NR	NR	NR	NR	R	NR	NR

4 patients out of the 13, had platelet counts below 100,000/nm and are marked 'R' (R = Reduced platelet count). The other 9 patients had their counts above 100,000/rmi^3 and are makred 'NR' (Not reduced platelet counts) in Table VII.

•patients numbers in this table refer to those numbers allocated to the study patients in the order in which either their files were first studied or they were first interviewed and entered into the study.

Staging of CLL Patients: (after Rai). The criteria for staging patients with CLL as defined by Rai et al in 1975 was used in this study. 31 patients belonged to either stage III or IV. There were eleven patients in stages I and II. There was ho patient grouped into stage 0. In TableVI11 the proportion of patients in each stage and their sex distribution is presented.

Table yin.Staging of Patients with CLL (after Rai et al 1975)

Stage	No. of patients	%	Sex	
			F	'M
0	0	0	-	-
I	2	4.8	1	1
II	9	21.4	3	6
III	15	35.7	6	9
IV	16	38.1	2	14
Totals	42	100%	12	30

Data on duration of symptoms before patients presented themselves for medical treatment and therefore for diagnosis were collected. An attempt was made to correlate this duration with the fate of the patient at the end of this study period. Only 2 patients presented within the first three months of onset of symptoms. For 10 patients it was 'unknown for how long they had had problems - these were all retrospective study patients. 18 patients came in after more than 6 months of symptoms. This distribution is expressed in Fig. 2. A further analysis of these findings which include the fate of the patients is shown in Table IX.

FIGURE 2: DURATION OF SYMPTOMS BEFORE DIAGNOSIS FOR CLL PATIENTS.

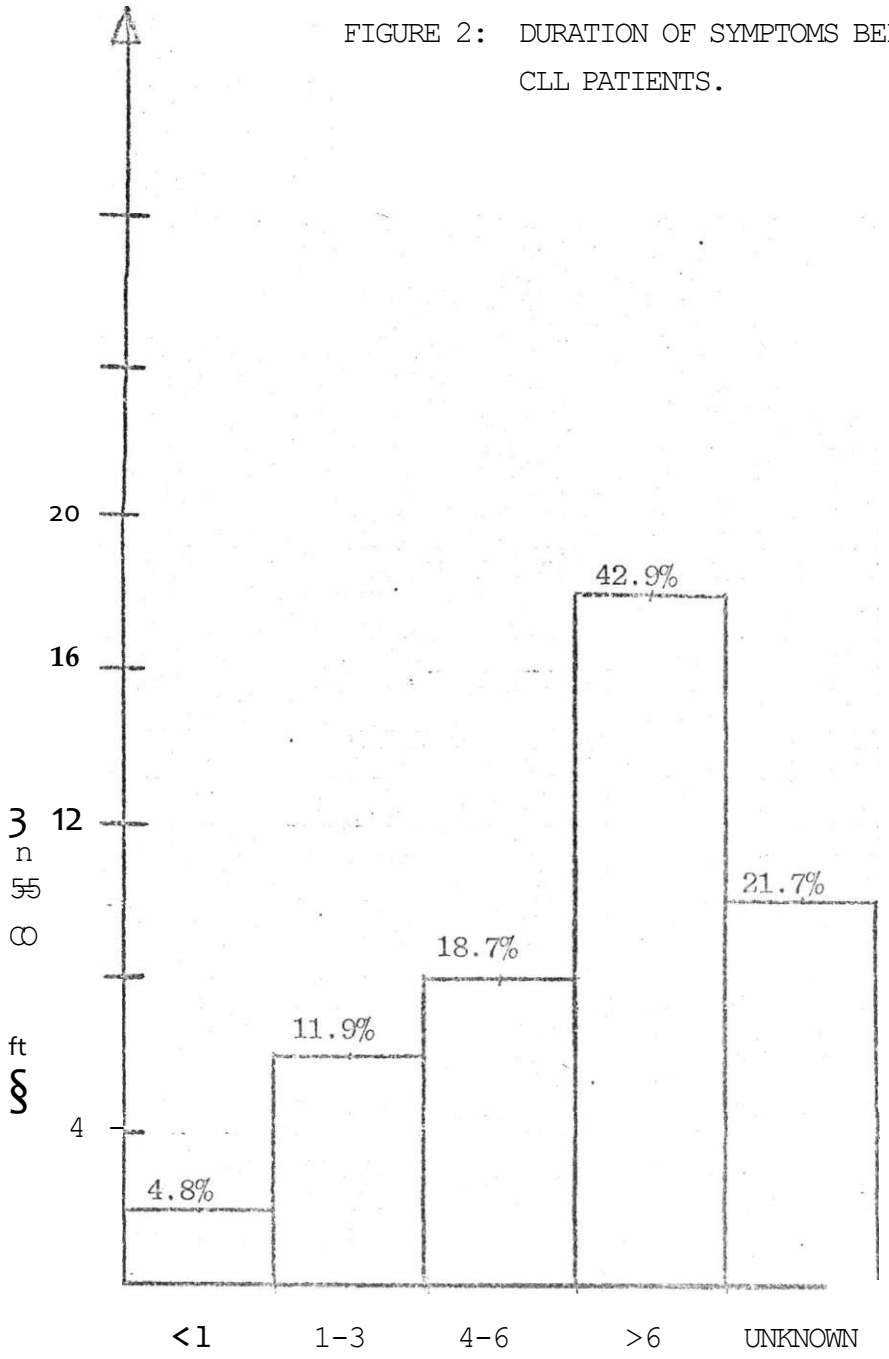


Table ix: Distribution of Patients According to Duration ox' Symptoms before Presentation and fate of patients by December, 1981.

Duration of symptoms before A in months	No. alive at end of study	No. lost to follow up	No. dead by end of study	Totals and %
< 1	1	-	1	2(4.8)
1 - 3	3	2	-	5(11.9)
.4 - 6	1	5	1	7(16.7)
> 6	4	13	1	18(42.9)
Unknown		9	1	10(23.7)
Totals	9 (21.4)	29 (69.0)	4 (9.6)	42 (100%)

Patients lost from the followup clinic constituted 69% of the whole patients group. 9 patients out of the 42 were still alive (= attending followup clinic at the end of this study). 4 patients had died - (the particulars of these 4 patients, including therapy administered and terminal clinical events are presented in Table No. X below).

Table X: Data on Patients who died with CLL

Patient No.	Sex & Age*	Duration from to -J'	Therapy Drug/ duration	Rai Stag- ing	Terminal events
39	M(40)	21 MO	Oral E[1] OOP x 6[2] CBL[3]	IV	Liver Failure
32	M(17)	8 MO	CBL Pred	III	Anemia Hemoptysis Chest Infections
41	M(65)	13.9(MD)	COP x 6 CBL STH[5]	IV	Anemia Chest Infections
12	M(65)	1.4 MO	NO Specific BP	III	Renal Failure Chr. G.N.[7]

* Ages are in parentheses

1. E = Oral cyclophosphamide
2. COP = Cyclophosphamide, vincristine and Prednisone
3. CBL = Chlorambucil
4. Pred = Prednisone
5. STH = Streptanycin/Thiazina
6. No antileukemic treatment
7. Chronic Glomerulonephritis.
8. = Date of diagnosis
9. j" = Date of death.

Data for the pat ients in the prospective study summarising their initial hematological statistics at diagnosis is given in Table No. XI.

Table XI: Hematological data for the Prospective study patients at diagnosis

Patient No.	Hb G%	MCV FL	Retics %	Bilirubin Umol/L	Uric acid Mg%	Cocmb's Test D	Cocmb's Test I	xlOOO WBC/ MM^3	PBF Conment
1	12.7	84	3	0.3	6.9	-ve	-ve	18.3	Normocyt ic/Normochromic
8	14.0	82	2	3.0	3.5	-ve	-ve	30.1	it
9	8.1	107	2	3.0	4.0	-ve	-ve	23.3	Macrocytosis
16	9.7	96	1	10	4.0	-ve	-ve	30.0	Normocyt ic/Normochromic
17	13.3	89	2	8	4.5	. -ve	-ve	469	11
18	12.0	80	2	4	3.5	-ve	-ve	355	Polychromasia N/N
19	9.4	103	2	3	3.5	-ve	-ve	297	Blasts 14%, N/N
20	.10.1	101	2	4	5.0	-ve	-ve	103	Polychromasia, A/P
21	11.4	80	1	9	4.1	-ve	-ve	31	Isolated blasts, N/N
23	6.9	81	2	8	3.6	-ve	-ve	24.2	Normocytic/Normochromic
33	10.7	73	2	6	4.0	-ve	-ve	28.7	Hypochromia
34	7.4	98	1	8	10.0	-ve	-ve	59.2	Anisopoikilocytosis
22	12.0	80	2	8	6.4	-ve	-ve	160.0	Normocyt ic/Normochromic

Hemoglobin for the 13 prospective patients ranged from 6.1 G/dl to 14.0 G/dl. Mean Hb was 10.4 + 2.5 (ISD). 6 patients had lib above 11.0 G/dl, while the other 7 had Hb below 11.0 G/dl. 3 patients had MCV above 100 FL; one had MCV below 80 FL, the rCTft3.iriirig O Ho-d MCV bttrnon SO 1.CO 1TL. Orvcs poAiotA Kt^a ^ reticulocyte count of 3 per cent the rest had reticulocyte ***count of 2 or less. Mean retics count was 1.9 + 0.5 (ISD).***

Nil the 13 patients bad scram bilirubin levels below 17 umol/1, which is the upper limits of normal. The lowest value was 0.3 umol per litre, and the highest value was 10 umol/litre. Mean = 6.2 + 2.5 (ISD).

Serum uric acid levels ranged from 3.5 mg% up to 10.0mg%. Only one patient had serum uric acid levels above 7 rng%. Mean = 4.8 + 1.8 (ISD).

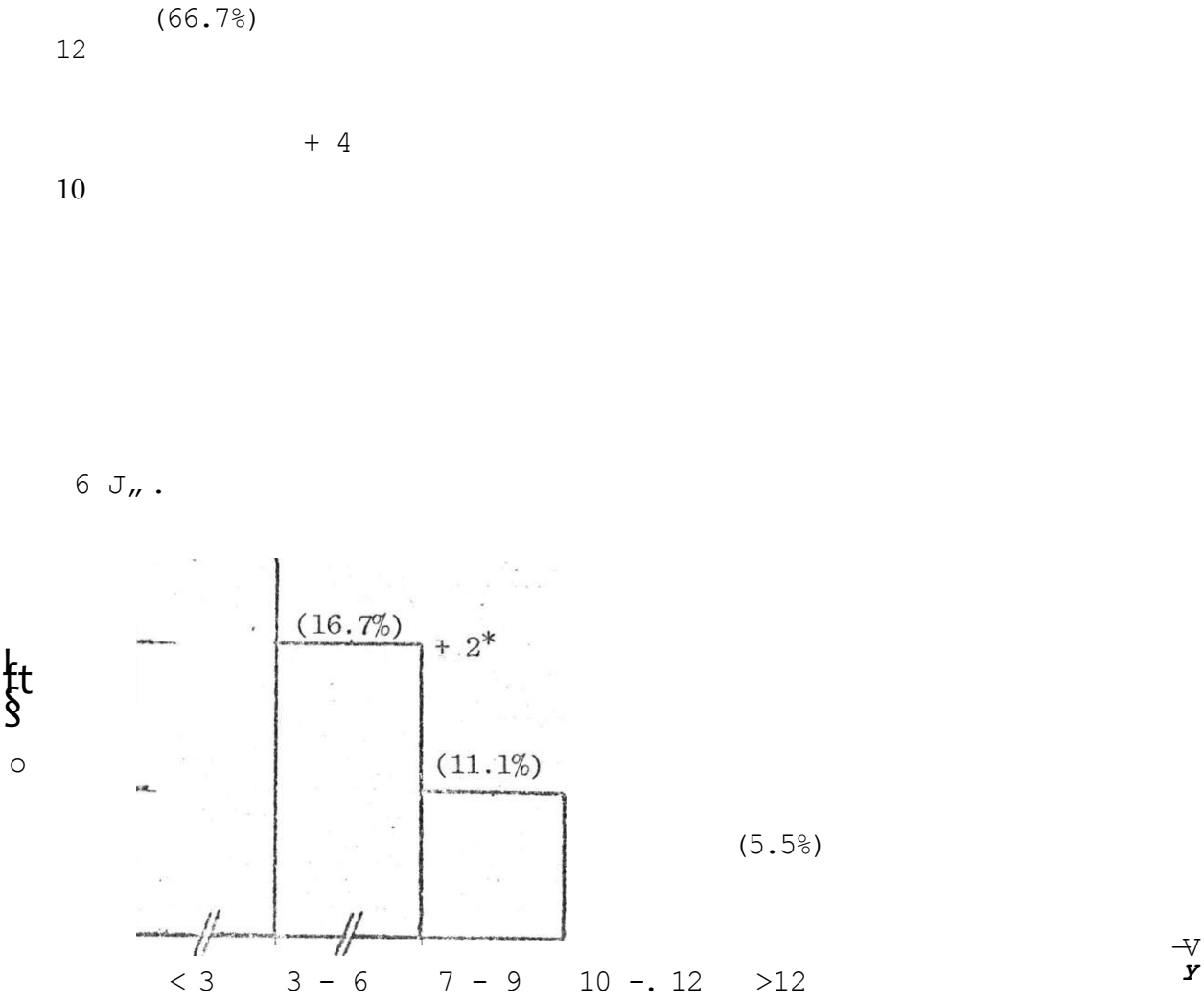
None of the prospective patients, anemic or not, had positive antiglobulin test - (direct or indirect). In fact only one patient in the retrospective study group had a positive Direct antiglobulin test.

The absolute lymphocyte values ranged from 18,300 cells per ran^{3}" to 469,000 cells per mm^{3}.

Nine patients had a nomiochromic normocytic film. One had overt macrocytosis and another had hypochromia. Two had poly-chromasia. The patient with hypochromia also had hookworm infestation. Remissions study was handicapped by the high default rate already noted. At least information for 18 patient was obtainable. 66.7% of these 18 patients had sufficient cytoreduction to consider as remission, within the first three

months. 5.5% required more than 12 months for remission. At least 27.8% required between 3 and 9 months. This pattern is presented in Figure 3.

FIGURE 3: DURATION OF THERAPY BEFORE REMISSION FOR 18 PATIENTS



* No. OF PATIENTS FROM PROSPECTIVE STUDY

CASE REPORT No. 1:

Patient No. 32

X.Y. was a 17 year old, male patient who was a Luhya by tribe from Western Kenya. He was first admitted at KNH in March, 1976 on referral from a District Hospital in the Western region. His complaints consisted of increasing generalised weakness, swelling of the glands in the neck and axillae, and epistaxis on and off - the latter for a period of 2 years. Objective assessment revealed moderate pallor, generalized lymphadenopathy and splenic enlargement. He had a hemoglobin of 6.8 G/dl; WBC of 85,000/mm^3; MCV 101 FL; and a blood film: RBC - normochromic normocytic, lymphocytosis of 99% - small mature lymphocytes and a platelet count of 106,000 p.cu.mm. Bone marrow aspiration BM 3/B53/76 - did show almost complete replacement of the marrow with small lymphocytes. Antiglobulin tests (direct and indirect) were reported negative. He was placed on chlorambucil and prednisone. His leukocyte count fell to 13,300 cells p.MM^3 within one month. His general status was described as improved and he was discharged home in April (of the same year) without cytotoxic therapy.

He ***was readmitted in August, 1976 with a two weeks history of cough and icterus. He was then found to be*** quite pale. His Hb was 4.0 G/dl, MCV 105 FL, WBC = 3,100 cells p.MM^3, a reticulocytosis of 2% and a platelet count of 168,000/mm^3. His serum bilirubin was estimated as 6mg% (with unconjugated bilirubin of 5mg%). Direct antiglobulin test was positive (indirect test reported negative). He had supportive trans-

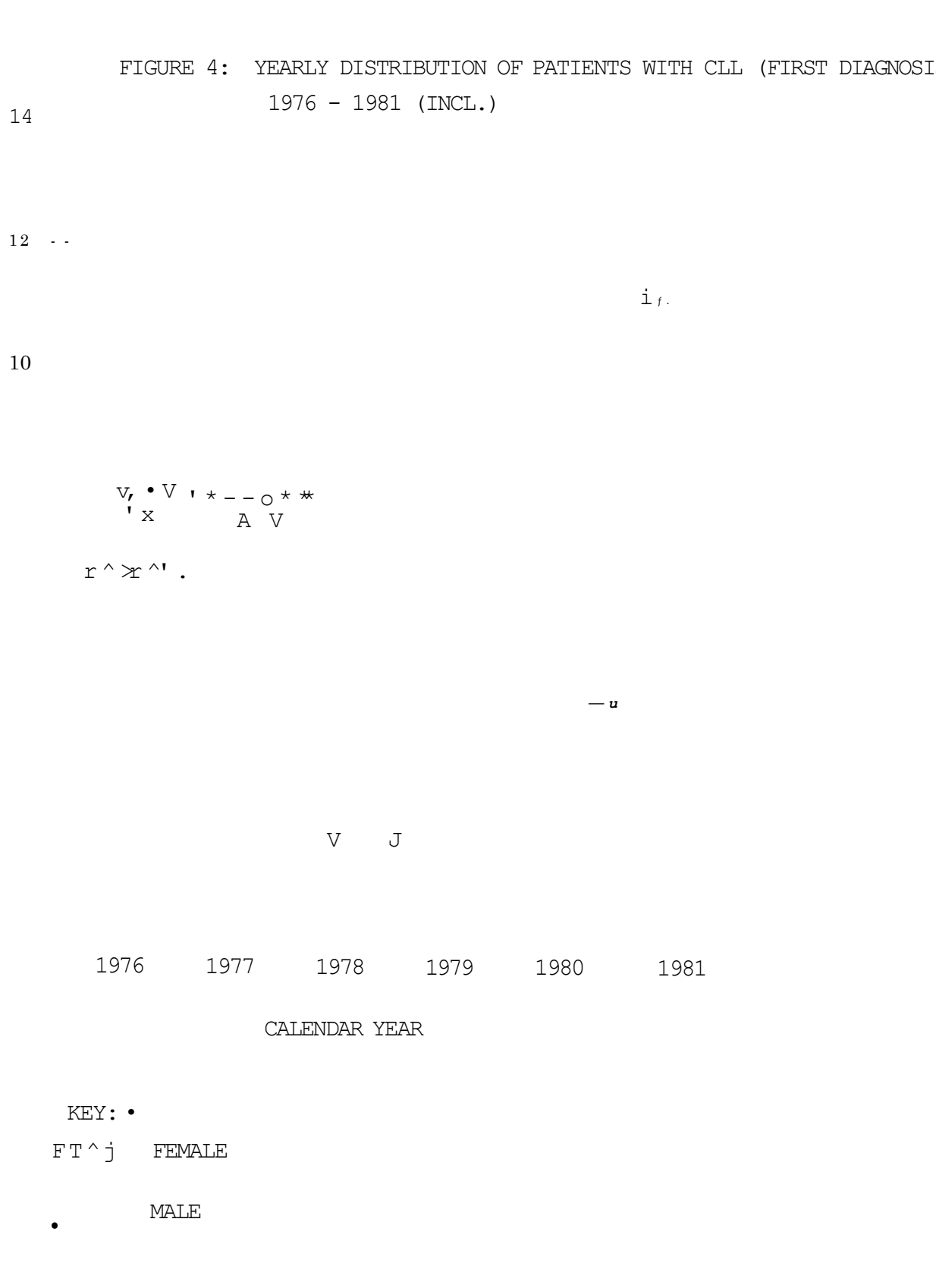
fusions, placed on prednisolone and folic acid, and discharged in early September, 1976.

He was again readmitted a week later with hemoptysis and pallor. His chest radiograph was consistent with a pneumonic process and he was placed on Ampicillins. He also developed severe oropharyngeal candidiasis and was prescribed rnycostatin. He had rapidly rising total leukocyte count and had a count of 150,000 wbc p. mm^3 by October of the same year. He was put back on chlorambucil. He succumbed to severe chest infections in November, 1976.

SUMMARY: A young patient presenting at Stage III CLL (according to Rai classification), with hemorrhagic tendency; hemolytic autoimmune anemia, florid chest infection and opportunistic fungal affections of the oropharynx. He succumbed to severe chest infections. His bone marrow smear photomicrograph is presented in Plate I.

Figure 4 depicts the distribution of the study patients over the 6 .years study. Most patients were seen in 1981 (the year[1] of prospective study). Only 3 patients were recorded to have been diagnosed in 1979, and this was the lowest figure. The average of figure for the the 6 years is 7. Fewer female patients were seen in each year except in 1978 - (there is no obvious explanation ***for this variation).***

FIGURE 4: YEARLY DISTRIBUTION OF PATIENTS WITH CLL (FIRST DIAGNOSIS' 1976 - 1981 (INCL.)



DISCUSSIONS:

It has been said, before that (XL was uncommon among Africans, but recent work since the seventies have disproved this belief (16,22,23,24,25,26,27,29). Indeed it has been shown in this hospital that although CLL did not occur as frequently as CML, its incidence was not as rare as among the Asiatics (29). In this study a total of 42 patients were seen from 1976 to 1981, both years inclusive. This figure is almost double on earlier report of a study which covered the years 1969 to 1975. It seems to me that there has been an increase in the availability of both hematological services and expertise over the years. The hematology clinic at KNH is currently the prototype of this proficient organisation. A total of 13 patients were diagnosed and followed up at the clinic in 1981. While this was the highest number of patients diagnosed in one given year, it probably did reflect an active effort to identify and document the cases.

The sex-ratio of 1:2.2 (F:M), appears to conform well with results of previous work here and elsewhere. The male preponderance has been reported among Nigerians in Africa and is the general trend among the Caucasians (24,26,29,30). In Papua New Guinea, a ratio of 1:2.3 (F:M) was reported in an 8 year study (28).

CLL appears to be uncommon among young patients here. This has been reported as the trend from other parts of the world. In this study only 4 patients were under the age of 40, from a total of 42 patients. The mean age was 54 + 14 (1 SD). This is close to the figure of 58 reported by the Americans (13) and compares well with the Nigerian study which reported only 7 patients under the age of 25 in a study of 85 patients (15).

CLINICAL SIGNS:

In 1967, it was reported from Rhodesia (now Zimbabwe) that lymphadenopathy was not as prominent in the African with CLL, as it was amongst the Caucasians. The same study also noted the very large spleens that resembled those otherwise only seen in patients with CML (16). In an analysis of medical admissions at Mulago hospital, Kampala in the late fifties, splenomegally of very large sizes were reported with a paucity of lymphadenopathy (31). From Nigeria in 1976, out of 85 patients with CLL, 92% had splenomegally while 66% showed lymph node enlargement. The findings in this study reveal splenic enlargement in 80% of the 42 patients and lymphadenopathy in 64%. This trend generally agrees with the pattern as already described in other parts of Africa, in contradistinction to the already documented pattern in Caucasians (V.S., 16, 30). No other explanation seems as yet more appropriate other than that the frequent infections, e.g. malaria, so rampant in the tropics alter the RES of the spleen so that a disease like CLL will cause its enlargement to enoxmous sizes (30}.

Hepatomegally was recorded in 76% of the patients in this study. This appears also to be an important feature of CLL in the African. This finding is similar to the reported series from Nigeria, but perhaps unlike the Caucasians frequency often given to be about 50% (15,20).

60% of the patients seen in this study had pallor of seme degree (-further discussed below). This was the fourth most frequent of clinical signs noted.

CLINICAL SYMPTOMS;

Abdominal pains and discomfort, followed by generalised weakness and fatigue were not surprisingly the most frequent symptans - (as already mentioned - V.S. - intra-abdominal organomegally and pallor are very frequent). This pattern agrees with that already described from elsewhere in Africa (15,16). Less than 20% of the patients complained of lymph gland enlargement - although palpable lymphadenopathy was recorded in 60% of the cases. It seems to me that many patients did not take the enlargement of lymph nodes seriously as some glandular enlargement is comron, may be as a result of frequent tropical infections, and certainly as a result of trauma where people walk on their bare feet. 20% of the patients complained of swelling of their feet - most likely as a result of lymphatic obstruction with enlarged lymph nodes. Severe anemia with lib 4 Qn/dl was present in only 7% of the patients, hence severe anemia alone would not explain the occurrence of swelling of the feet. Neither was a decreased total serum proteins noted in the prospective patients; in fact albumin was unaffected in all the samples analysed. The patients with edema were therefore unlikely to have been hypoproteinaemic.

Only 4 patients gave history of bleeding tendency at one time or other. This contrasts with a figure of 38% who had

platelet counts below 100,000/tim . 3 of these 4 cases, belonged to stage IV by Rai classification. The 4th patient who is further described in this dissertation as a case report, did not at any early time have a platelet count below 100,000/inn''. Bleeding tendency was therefore uncorrmon in this study group.

Similar findings have been reported from Nigeria (15).

There was marked absence of dermatological features. Only 4 patients presented with or gave a past history of seme skin problem. They either had or had had non-specific pruritus or erruptions that were vesicular or bullous. In Western countries pruritus without actual leukemic infiltration is a frequent manifestation (9). The vesico-bullous lesions have been said to have a less favourable prognosis. The number of patients with any cutaneous features in this study is small and so no prognostication is attempted. It does however appear that cutaneous manifestations is uncommon among CLL patients at KNH.

Dysphagia: Only one patient had this symptom. He had carcinoma of the esophagus for which esophagectomy had been done. In the following six months he was diagnosed to have CLL. Evidence on 'second' neoplasms on patients with CLL is scanty, though colonic and skin tumors are probably more frequent (18). In this study no other patient had any evidence of second neoplasm. But it should be mentioned that where no differentiation is made between well differentiated lymphocytic lymphoma (WDLL) with bone marrow, and peripheral blood involvement, and 'pure' chronic lymphocytic leukemia, it remains a probability that one is dealing with one or two separate disorders, WDLL does convert into CLL and then cellular studies are indistinguishable (10). In this study a few patients who had lymph node biopsies taken and showed WDLL could be said to have had one malignancy converted into another when their blood and bone marrow studies suggested CLL.

Infections: Patients with CLL are prone to infections, often due to low irrmunoglobulins levels, or as a result of cortico-steroids or inraunosuppresant therapy (11,12). In this study, respiratory infections were the most frequent, and constituted 81% of all infection incidents. These were either lobar-pneumonias, bronchopneumonias or pharyngitis. Some of these patients were on therapy and hence reasons referred to above could predispose to infections. 4 cases of pulmonary tuberculo-sis were identified among these patients.

It has been previously reported from here that respiratory tract infections were the most frequent in CLL patients. This appears to be the case even in this study (26).

Urinary tract infections and recurrent otitis media were recorded in two and one patients respectively. These were therefore uncoronon complications.

Fulminant oropharyngeal candidiasis was noted in one patient who had very severe disease (= case report Mo. 1). This was obviously an example of opportunistic infections - expected as it were - in a patient with a disorder known to depress iniriune functions.

There was marked absence of skin infections.

Anaemias; 72% of the patients in this study had an Hb below 12Gm/dl. 7% had severe anemias with Hb below 4Gn/dl. Most of the patients had normocytic normochromic anemia. And where accurate analysis was possible as in the prospective study group, out of the 8 patients with Hb below 12 Gm/dl, 4 had normochromic normocytic picture, microcytosis in one and macrocytosis in three.

In this latter group also, no evidence of hemolytic process was obtained either biochemically or immunologically. Coomb's tests were negative in all the 13 patients and no significant reticulocytosis was recorded. The cause of the anemias was therefore more likely to be a result of bone.marrow replacement with lymphocytes.

Staging:

70% of the patients had lymphocyte counts above 50,000 p.mm^3. This implies that peripheral blood films should be striking and suggest the diagnosis. It is however a curious finding that no patient was diagnosed in stage 0. It may be that fewer films are made routinely, or that lymphocytosis in patients without other clinical features of disease is ignored. It is worthwhile to suggest a serious need to document and follow up patients who may fall into this category.

Most patients in this study belonged to either stage III or IV (= 74%). These are advanced stages of the disease. The reasons why majority of patients should present so late may have a relationship to both cultural and economic conditions obtaining locally. Many patients may not seek medical attention until the weakness of anemias or discomfort of a dragging splenomegally become unbearable. The hospitals are often few and scanty, they are congested, and the staff and facilities often overworked. There may be sane hardships also with means to and mode of corrmunication. As the Rai classification still does conform fairly well with survival, increased medical awareness and interest in follow up of patients may lead to diagnosis in early stages.

It is also perhaps appropriate to mention as a reminder that not all patients with splenomegally and lymphocytosis in malarial areas have Tropical splenomegally syndrome (30).

PATIENT DYNAMICS:

A reappraisal of the duration of symptoms before the patient presented for diagnosis and the fate of the 42 patients at the end of the study are presented in Table IX and Figure No. 2. Majority of the patients were seen after having symptoms for more than 6 months. This statement takes into account that the disease CLL may actually exist for quite a long time while patient remains asymptomatic. What is discussed here, is however, the symptomatic stage. A trifle 4.8% were seen within the first month of symptoms. The trend appears generally that it is uncarmon for the patients to present themselves early. The reasons for this behaviour may be similar to those already discussed under the 'staging' in chapter.

Analysis for the fate of patients is equally interesting. 69% of the patients were lost to follow up by the end of the study. Their fate was unknown. They had merely ceased to attend the clinics. It is probably noteworthy that the majority of the patients who were lost to follow up had earlier presented after more than 6 months duration of symptoms. It may be relevant that for the same reasons they come so late, they similarly cannot continue coming to the clinics.

Only 4 patients had their deaths noted in the case notes. One had been symptomatic for unknown time, the second for more than six months, the other two for less than one month and for

six months respectively. They all belong to either stage III or IV (table X). This already implies the very advanced stage of the disease. The longest survivor was observed for 21 months (from diagnosis to death). American figures give values of 3.5 years survival times for stage IV patients, and 5 years for stage I to stage III (13). It would not be statistically viable to attempt an analysis of survival times for four patients. Three of these patients were already on cytotoxic therapy. It is uncertain the role these drugs could have played either to accelerate or decelerate survival time. One patient did not get any cytotoxic treatment. He lived for only 1.4 months from diagnosis to death. He did infact have chronic glomerulonephritis.

An analysis of the terminal events in this study revealed no patient with blast transfoimations. Neither was the de-differentiation of 'Ritcher's type' noted. Two of the 4 patients who died had severe anemia and chest infections as terminal events. Two other patients had major organ failures viz: liver failure for one and renal failure for the other. The role played by chemotherapeutic agents (if any) in the possible induction of these last stages are uncertain. Remissions study was attenpted but could not be expected to be an easy task, noting the multiplicity of prognostic factors in CLL. When there was evidence of restoration of normal bone marrow function, and return of some hematological parameters towards or to normal values, and reduction in organ or lymph node sizes (13), then it was assumed patients had attained a remission.

Figure No. 3 shows the duration of treatment before remission was achieved. In fact 83% of the 18 patients had achieved remissions. This is a large figure and implies chlorambucil 'sensitivity'. This has been described to be another prognostic factor and resistance to therapy by 6 months does not augar well for patients (32). Of the patients in the prospective study, 6 did enter into remissions. All of than within the first six months. Their values are marked with asterix in figure No. 3. The 6 patients were all treated with chlorambucil, and two of them had additional prednisone. These numbers are extremely small and treatments were not necessarily standardized, hence a detailed analysis of these ranission patterns may not be representative of the larger samples which may be derived from this population. Suffice to say that the patients tended to do well with treatment, in terms of improvement on hematological parameters and general well being.

CONCLUSIONS:

CLL is not uncoirmon at KNH, but most patients are diagnosed in advanced stages of the disease.

The pattern of clinical presentation and laboratory findings do not differ with those already documented from other parts of Africa.

Patients response to chemotherapy with chlorambucil with or without steroids is generally impressive.

Occasionally the patients require energetic supportive care to combat anemias and infections.

Follow up of patients is seriously curtailed by the very high default rate. It is doubtful if most patients understand the gravity of their illness.

SUGGESTIONS:

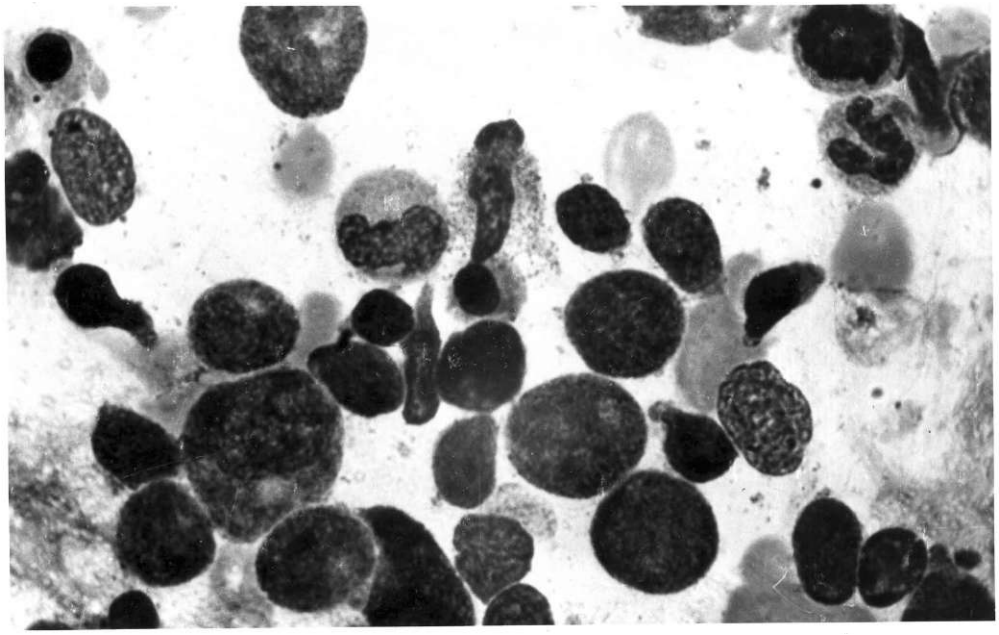
It is apparent that increased awareness among medical personnel to take seriously the cases of patients seen occasionally with significant lymphocytosis without other apparent cause, would go along way to enhance early diagnosis.

The education of the patients on their disease, stressing the need for regular review in the clinics, together with improving the general socio-economic status of the people - may alter favourably the as yet, very poor patient compliance.

A coordinated work, involving the medical personnel in the peripheral hospitals - increased alertness on leukemias, appropriate referral of these patients to suitable centres - may enhance early diagnosis and proper treatment.

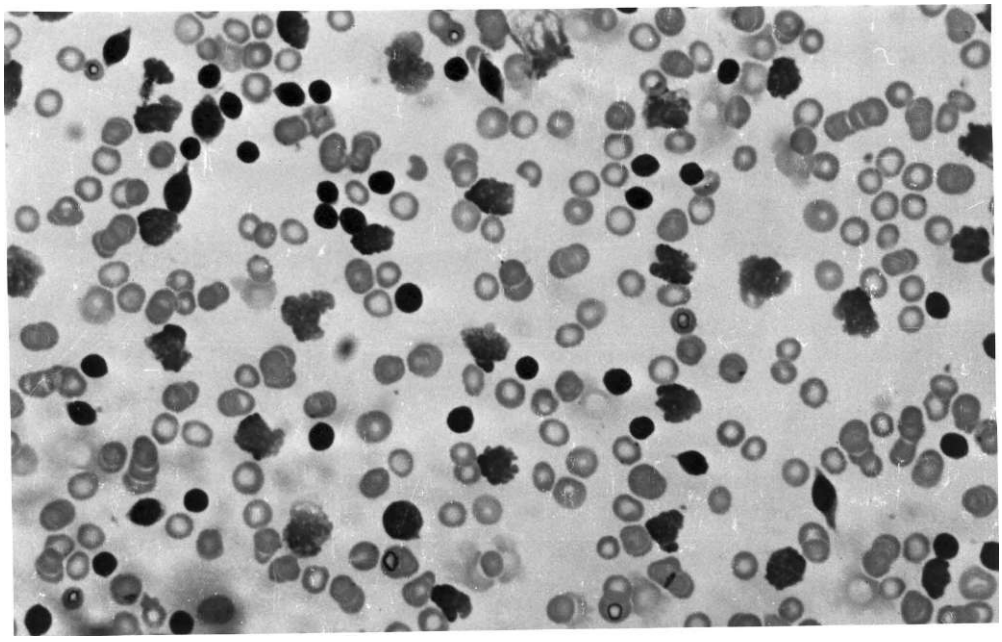
The availability for immunological studies will not only help open up more knowledge on this disorder but may assist to select those patients who may be having benign lymphocytosis with splenomegally and spare than cytotoxic therapy.

PLATE 1,



Photomicrograph of Bone Marrow Film: BM No. 8/3160/76 of patient

PLATE 2.



Photomicrograph of PBF No. 3/A145/77 for patient No. 17 in study.

Note: The small lymphocytes and 'smear' cells.

r

ACKNOWLEDGEMENTS:

I wish to record in writing, my indebtedness to my supervisor, Professor Thomas Ogada, FRCP, Professor of Medicine, University of Nairobi, for his constant encouragement and invaluable criticism in the course of preparation of this dissertation.

I also wish to acknowledge with thanks the assistance obtained from Mr. John Kyobe, HILT, and the technical staff, Department of Medicine, on laboratory procedures and interpretation.

Last but not least to Mrs. Veronica W, Macharia who tirelessly went through the manuscript and prepared this print.

REFERENCES:

No. TITLES AND AUTHORS

1. DAMESHEK, W.: CLL - An accumulative disease of immunologically incompetent lymphocytes. Blood 29; 566, 1967.

2. Diagnosis of CLL. Medical Clinics of N.A. July 80, 64: (4). **pp.** 705-727.

3. AINSBERG, AC, KURT, J, LONG, JC: Cell surface Igs in CLL and allied disorders. Amer.J.Med. 55: 184-191, 1973.

4. GOLDMAN, JM: Medicine International, 2nd series, Blood and Reticuloendothelial disorders pp. 908-912.

5. KAY EN, JOHNSON, JD, STANECK, R. , DOUGLAS, SD: T-cell subpopulation in CLL. Blood 54 : 540-544, 1979."

6. LILLE, I., DESPLACES, A., MEEUS, L., SERNANCINO, Iff: CLL of T cell origin. Lancet 2: 263-4, 1973.

7. DACIE JV and LEWIS, SM: In practical Hematology, 4th edition, Churchill Livingstone.

8. BLATTER, WA: Familial CLL; Ann.Int.Med. 84: 554, 1976.

9. THOMPSON, RB: In a short textbook of Hematology. 5th Edition. Pitman Medical, 1979.

10. LINMAN, JW: In Hematology: Physiologic, pathophysiologic and clinical principles. MacMillan Publishers, pp. 611-624, 1975.

PANGALIS, GA. , BHARAT, NN, RAPPAPORT, H: WDLL and CLL and Macroglobulinemia. Cancer 39: 999-1010, 1977.

MYERS, JT, RODGERS, JW: Infections in CLL; Cancer 1980, August 1, 46(3); 619-20.

RAI, KR, SAWITSKY, A., CRCNKITE, EP, CHANANA, AD, LEVY, RN, PASTERNACK, BS: Clinical staging of CLL. Blood 46: 219, 1975.

POUCAR, K., RYDELL, RE: Ritcher's Syndrome in CLL. Cancer July 1, 1980; 46(1): 118-134.

EISSEN, EM: Leukemia among Nigerians. E.A.M.J. 53: 96-103, 1976.

GELFAND, M: Leukemia in the African, In Trop. & Geog. Med.Hyg. 70: 85: 1967.

HARDISTY, RM and WETHERAL, DJ: In blood and its disorders. Blackwell scientific publications 1974 pp 976-989.

MOERTEL, GC, HAGEDORN, AB: Leukemia or lymphcma and co-existent primary malignancies. Blood 12: 788: 1957.

JUBERG, RC and JONES, B. : The Christchurch chromosome (Gp-) NEJM 282: 292-97, 1970.

WINTROBE, MM: In clinical hematol6gy. 7th Edition.

KING, EJ and WOOTTON, IDP: In microanalysis in medical biochemistry. J & A Churchill Ltd. 1964.

22. LOIHE, F: Leukemia in Uganda. In Trap. & Geog. Med. 19: 163-70, 1967.

23. JEFFREY, C. and GELFAND, M: Leukemia among Rhodesian African. In Trop. Med. Hyg. 75: 176-179, 1972.

24. AHMED, MAN, SULEIMAN, GA, CMERA: Leukemia in Sudan. E.A.M.J. 54: 21-26, 1977.

25. KASILI, E.G., Taylor, JR: Leukemia in Kenya. E.A.M.J. 47: 622: 1970.

26. Kasili, EG: Management of leukemia in a developing country. E.A.M.J. 55: 417: 1978.

27. HADDOCK, DRW: Leukemia in Accra: Jn.Trop.Med.Hyg. 70: 60: 1967.

28. BOOTH, K. , AMATO, D. : Leukemia in Papua New Guinea. In Trop.& Goeg.Med.Hyg. 30: 343, 1978.

29. OGADA, TA, de LEEW, NMK: Incidence of CLL and CML in Kenya, 1976: pers. comm.

30. EDINGTON, GM, GILLES, UM: Pathology in the tropics 2nd edition 1976. Edward Arnold Publishers.

31. SHAPER, AG, SHAPER, L: Medical admissions to Mulago Hospital, 1957; EAMJ 35: 647, 1958.

32. MICHALLET, M., SOTTO, JJ, HOLLARD, D: Second staging of CLL after 6 months of chlorambucil. Eur.J.Can. 16: 511-517, 1980.