A FIVE YEARS (1973 - 1977) RETROSPECTIVE STUDY AND A TWO YEARS EXPERIENCE IN THE TREATMENT OF ADULT (OVER 15 YEARS) HODGKINS DISEASE IN KENYATTA NATIONAL HOSPITAL

BY

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This thesis is my original work and has not been presented for a degree in any other University

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CONTENTS

SUMMARY :-

Literature on Hodgkin's disease is briefly reviewed under the following headings : (a) Aetiology (b) Clinical Presentation and Staging (c) Histipathological diagnosis and Classification (d) Treatment (e) Relapse Survival and Cure (f) Immunology.

Records of 49 adult (> 15 years) patients diagnosed and treated in Kenyatta National Hospital between January 1973 and December 1977 were analysed. The mean age was 31 years and the male-female ratio was 3:1. All the patients had Lymphadenopathy as a main presenting feature, and 94.5% complained of fever at the time of presentation. The mean duration of illness before presentation was 11 months. 70% of the patients were clinically in stage III and IV at the time of presentation. Histological classification showed a predominance of the more malignant mixed cellularity (37%) and Lymphocyte depleted (23%).

Multiple drug chemotherapy achieved a complete remission rate of 76% while the complete remission rate in the group treated with radiotherapy was 71%. Side effects in both groups were minimal.

INTRODUCTION :

Malignant Lymphomas form 8.5% of all malignancies in Kenya (1). Hodgkin's disease as one of the malignant lymphomas has been studied widely. It is no surprise therefore that a lot of epidemiological work has been done. A lot of literature has been published on aetiology (2-15) ; presentation and spread (16-19) ; clinical staging (20-40) ; histopathological classification (41-49) ; treatment (50-63) ; relapse, survival and cure (64-67) and most recently immunology of the disease (68-78).

Kenyatta National Hospital is the referal hospital for the whole of Kenya. Within the hospital complex are the departments of Surgery, Medicine, Paedriatrics, Pathology, Radiology and Radiotherapy. It will be obvious after all the literature is reviewed, that malignant lymphomas, particularly Hodgkin's disease will require the cooperation of the afore mentioned departments. It was noted before by Ogada in 1974 (1), "There is a great need for an integrated Centre in Nairobi to treat malignant lymphomas, as at the moment being treated by Surgeons, Paedriatricians and Physicians independently.

It is the aim of this paper therefore to : -

(a) assess the size of the problem of Hodgkin's disease in Kenyatta National Hospital.

(b) determine the stage of presentation and histopathological features as seen in Kenyatta National Hospital and compare this to

experiences elsewhere.

(c) determine the extent to which investigations necessary for accurate clinical staging are done in Kenyatta National Hospital.

(d) to assess the efficacy of administration of multiple drug chemotherapy on outpatient basis.

To achieve the above aims, the review of relevant literature will be done first and then the retrospective study will be presented.

REVIEW OF LITERATURE

AETIOLOGY

Like most malignant tumours, the aetiology of Hodgkin's disease remains unknown. Epidemiological studies have shown both community and familial clustering (2, 3). It has also been reported in married couples (4). The incidence is three times greater in close relatives (5) and seven times in siblings (6).

An infectious agent, environment and genetics have all been incriminated in the pathogenesis of Hodgkin's disease (7, 8). Immune dysfunction has recently been added to the above three (9). MacMahon suggested that familial association was more likely due to environment than genetics (10).

The presentation with fever, chills and sweating tend to point to possible infectious agent. Vianna suggested that Hodgkin's disease may be due to a virus of low virulence and infectivity which is acquired through oral-respiratory tract during birth. He further postulates that the virus is barrier held by intact noninvoluted lymphoid tissue and that the characteristic lymphnode changes are as a result of immune complexes (11). The same author advances that nodular sclerosing histological form is the most likely to be caused by "infectious agent (12)". He provides a possible evidence of transmission by a 10 year study of cases of Hodgkin's disease occuring in students from schools where a case of the disease (either in student or teacher) had been reported (13).

So far, a viral aetiology has been speculated but not demonstrated.

Elevated antibody titres to herpes type virus has been reported, but Goldman in 1970 demonstrated that the evidence of antibodies to E - B virus, herpes simplex and cytomegalic virus in Case of Hodgkin's disease was not statistically higher than in the general population (14).

An attractive theory on pathogenesis was advanced by Order and Hellmann in 1972 (15) :-

(I) T - cells or thymus derived lymphocytes are infected by an oncogenic (or tumour inducing) virus. This causes a change in the cell surface antigen.

(II) Normal T - cells interact with virus transformed cells.

(III) This interaction is protracted and leads to the production of neoplastic reticulum cells.

EVIDENCE FOR THE HYPOTHESIS :-

(I) T - cells are distributed in thymus, lymphnodes and spleen cells all primary sites of early Hodgkin's disease.

(II) Viruses are known to alter antigenic surfaces of cells leading to auto-immune phenomena.

(III) T-cell involvement in immune reaction together with viral infection of T-cells causes a T- cell depletion with a consequential loss of delayed hypersensitivity - a phenomenon seen in Hodgkin's disease.

(Iv) In thymectomised animals there is a T - cell depletion and plasma cell populate the thymus dependent areas. Plasma cell infiltrate

is a histologic feature of Hodgkin's disease.

(v) Experimental T-cell depletion leads to increased incidence of lymphoma.

At this stage therefore the aetiology of Hodgkin's disease remains unknown but the search still continues.

PRESENTATION AND STAGING OF HODGKIN'S DISEASE

The major presenting feature of Hodgkin's disease is painless lymphadenopathy. Kasili (16) analysed 117 cases of Hodgkin's disease ; 113 patients (a 97%) presented with lymphnode enlargement and only 4 (3%) patients presented with extranodal involvement. The lymphadenopathy may or may not be accompanied by systemic symptoms which include fever, weight loss, night sweats and pruritus. The significance of these will be discussed later.

There is evidence that Hodgkin's disease spreads from a primary site to contigous chain of lymph nodes (17, 18). Non-contigous distribution has also been reported and is attributed to vascular invasion and spread (19).

STAGING :

There are two major reasons why proper staging in Hodgkin's disease should be done :-

(a) to facilitate communication and exchange of information.

(b) to provide guidance on prognosis and assist in the therapeutic decision.

CLINICAL STAGING :

The commonly used clinical staging is that adopted at the Rye Symposium in New York in 1965 and reported by Rosenberg (20).

CLINICAL STAGING ADOPTED AT THE RYE SYMPOSIUM

STAGE	DEFINITION
I	Single node region (i.e. one anatomic site).
II	Disease limited to 2 contigous or non-contigous regions but on the same side of the diaphragm.
III	Disease on both sides of the diaphragm but limited to spleen, nodes and Walderyers ring.
IV	Involvement of any tissue or organ other than nodes, spleen and Walderyers ring.

NOTE : All stages are subclassified 'A' or 'B' to indicate absence or presence of systemic symptoms respectively.

Since the Rye meeting however, 2 things happened that necessitated further modification (21, 22).

(a) Extra lymphatic localised disease and/or involvement of tissues adjacent to involved lymphnodes did not adversely affect survival and patients do as well as patients with same stage without extra lymphatic spread.

(b) Exploratory laparotomy and splenectomy became widely used for staging.

Hence at the Ann Arbor Conference in Michigan, 1971, the following modifications were introduced (23).

CLINICAL STAGING IN HODGKIN'S DISEASE (Ann Arbar).

STAGE	DEFINITION
I	Involvement of a single lymphnode region (I) or of a single extralymphatic organ or site (I_E).
II	Involvement of two or more lymphnode regions on same side of diaphragm (II) or localised involvement of an extralymphatic organ or site and of one or more lymphnode region on same side of diaphragm (II_E)
III	Involvement of lymphnode regions on both sides of diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localised involvement of extralymphatic organ or site (III_E) or both (III_{SE}).
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, or tissues with or without associated lymphnode involvement.

NOTE : (a) All stages are again subclassified to 'A' and 'B' to indicate the absence or presence of systemic symptoms respectively.

(b) The subcategory 'E' denotes extralymphatic involvement.

In the same Symposium, the significant systemic ('B') Symptoms were accepted as :-

(I) Unexplained fever with temperature upto 38°C

(II) Unexplained weight loss (10% within 6 months)

(III) Unexplained night sweats.

(iv) 'Pruritus' - alone does not constitute sufficient evidence to place a

patient in category 'B'. It occurs in ⅓ of the patients and is not seen in children (24, 25).

The studies necessary for accurate clinical staging include :-

(a) Complete history with emphasis on 'B' systemic symptoms

(b) Thorough clinical examination including all peripheral lymphnode groups and any palpable abdominal masses. The sizes of all enlarged glands should be carefully recorded for this will be used as a therapeutic maker.

(c) Staging laparatomy and splenectomy. Multiple biopsies should be taken from the liver and all accessible suspicious lymphglands.

(d) Laparascopy plus biopsies from the liver

(e) Percutaneous liver biopsy.

(f) Bipedal lymphangiography.

(g) Bone Marrow examination

(h) Haematological work up inducing complete haemogram with differential white cell counts and ESR.

(i) Liver function tests especially alkaline phosphatase.

(j) X-rays of chest and skeletal survey

(k) Intravenous Pyelogram

(l) Mediastinoscopy.

It is always not necessary to do all the above investigations. In patients who present with advanced disease (Stage III or IV) and a decision is made, to use multiple drug chemotherapy, baseline investigations may be the only

investigation required. However in patients with stage I and II disease, and Radiotherapy is contemplated, then further investigations to ascertain the staging is very important.

Total white cell counts with differentials, and alkaline phosphatase are nonspecific and therefore not enough evidence of involvement of bone marrow or the liver (respectively) by Hodgkin's disease (26). Bone marrow and liver (percutaneous) biopsies are therefore necessary procedures. But as it will be seen later, biopsies from these sites are quite difficult to interpret and if negative, involvement by Hodgkin's disease is not altogether ruled out.

Mediastinoscopy (27), and peritonioscopy (28), have also been used for staging of Hodgkin's disease. However they do not appear to be as helpful as exploratory laparotomy and splenectomy if used routinely.
In some centres, they have found bipedal lymphangiography as a simple accurate informative technique with a minimum amount of complications; and of value in clinical staging and planning of Radiotherapy fields. Stage I and II of Hodgkin's disease may prove to be extensive after lymphangiography. The incidence of retroperitoneal nodeinvolvement has been stated to be from 0 - 36% in Stage I and from 14-51% in Stage II (30). The accuracy of lymphangiography for identification of pelvic and para-aortic node involvement is greater than that of intravenous urography and inferior cavography (31).

The use of exploratory laparotomy and splenectomy has been widely accepted and adopted as the most accurate method for the evaluation and clinical staging of patients with Hodgkin's disease. Its major value is to provide better diagnostic information primarily concerning the spleen. Only one-half of the patients who are assessed to have involvement of the spleen based on its enlargement clinically, will have involvement on histopathological examination. Conversely one patient in four will have demonstrable Hodgkin's disease of the spleen without pre-operative suspicion (33).

The non-operative clinical assessment of Hodgkin's disease involvement of the liver (i.e. liver size, liver function tests) is unreliable and cannot be dependent upon. As liver involvement would alter the form of treatment, histopathological verification is required. This can be obtained by percutaneous liver biopsy but better still at laparotomy. Since the entire liver cannot be studied at histology as can be the spleen, false positives clinical evaluations are more difficult to determine. However this occurred in 29 of 32 patients in Ultmann's review. False-negatives occurred in 8 of 33 instances in a group of patients at Stanford (34).

Laparotomy has been found to be superior to lymphangiography in the diagnosis of intra-abdominal lymphnode involvement. 20% to 25% of lymphangiograms cannot be interpreted as definitely positive or negative for Hodgkin's disease involvement. Therefore laparotomy with biopsy sampling of all suspicious nodes yield a more accurate evaluation.

Splenectomy has a direct advantage in the subsequent management of the patient especially when the treatment is radiotherapy. The fields which are required to encompass the spleen adequately include the left lower lung and pleura, and portions of the left kidney. When splenectomy has been done the radiotherapist limits his field to the splenic pedicles and hence eliminates the risk of radiation pneumonitis and pleuritis of left lung base and radiation damage to the left kidney.

The acute morbidity and mortality from laparatomy and splenectomy is now well described and is minimal (< 1%) (35). It is still not accurately known to what degree patients with Hodgkin's disease who have been splenectomised will have an increased incidence of infections, well described in other patients both children and adults who have had splenectomy (36, 37). However, Schimmff described infections in 92 splenectomised patients with Hodgkin's disease (38). Ravry (39) also reported two cases of serious pneumoccocal and H. influenza infection after splenectomy for Hodgkin's disease. Assigning the cause of this complication to splenectomy is particularly difficult in Hodgkin's disease because a number of other factors that predispose to infection are always present. These patients have a defect in delayed hypersensitivity and therapy with irradiation or intensive chemotherapy depresses their immune mechanisms even further (40).

Exploratory laparatomy and splenectomy therefore remains the method of choice in staging and deciding the form of therapy in Hodgkin's disease.

HISTOPATHOLOGICAL DIAGNOSIS AND CLASSIFICATION OF HODGKIN'S DISEASE

REED-STERNBERG (R-S) CELLS IN THE DIAGNOSIS AND CLASSIFICATION OF HODGKIN'S DISEASE (41)

The diagnostic type of R-S cell is a large cell which may be lobated, binucleated, or multinucleated and has a huge, inclusion-like nucleoli frequently with perinuclear halos (fig. 1). The cytoplasm is abundant and acidophilic to amphophilic and both the nucleoli and cytoplasm are vividly pyroninophilic. Recent studies by Peckham and Cooper (42) have shown that the diagnostic cell is a nonproliferating end-stage cell in which the huge nucleolus and amphophilic cytoplasm are a reflection of derangement of RNA synthesis with accumulation of cytoplasmic RNA. The intense pyroninophilia of the cytoplasm in methyl gree pyronin-stained sections is useful for this reason in the search for diagnostic R-S cells. The majority of large abnormal cells found in Hodgkin's disease are the nondiagnostic variants of the R-S cell since they lack the huge inclusion-like nucleolus and the abundant amphophilic cytoplasm.

The important proliferating cell in Hodgkin's disease according to the work of Peckham and Cooper (42) is a large abnormal mononuclear cell apparently related to the non-diagnostic variants of R-S cells. The frequency of diagnostic R-S cells with huge nucleoli is however of a primary prognostic significance, while the remaining R-S cell variants are useful only as indicators of the histological type of Hodgkin's disease.

There are three primary variants of R-S cell other than the diagnostic

type :-

(a) The lacunae type of nodular sclerosis. This cell has 2 distinctive features :-

(I) the abundant pale to water-clear appearing cytoplasm with a sharply demarcated peripheral margin.

(II) Hyperlobulated with small nuclei. The latter feature is common but not consistently found in all cells.

The most distinctive feature, the low-density or water-clear cytoplasm presenting a halo-like effect appears to be partly attributed to the artifact of fixation (Fig. 2). In well-fixed tissue with Zenker's Solution the cytoplasm is abundant, finely granular and acidophilic and usually only relatively narrow peripheral space is apparent (Fig. 3). The lacunar cells vary widely in frequency and occur singly or in cohesive clusters.

(b) The distinctive polypoid type of the lymphocytic and/or histiocytic (L & H) type. This variant has a large polypoid nucleus that is often twisted and overlapping, the nuclear chromatin is extremely fine and the nucleoli are small or inapparent (Fig. 4). The cytoplasm is pale staining and moderate in amount. The L & H variant of R-S cell may be extremely numerous and constitute 10% to 20% of the cellular population.

(c) The pleomorphic variant of R-S cell or the Sarcomatous type exhibits a wide range of bizzarre morphological expressions of the diagnostic type. They usually dominate the cellular proliferation

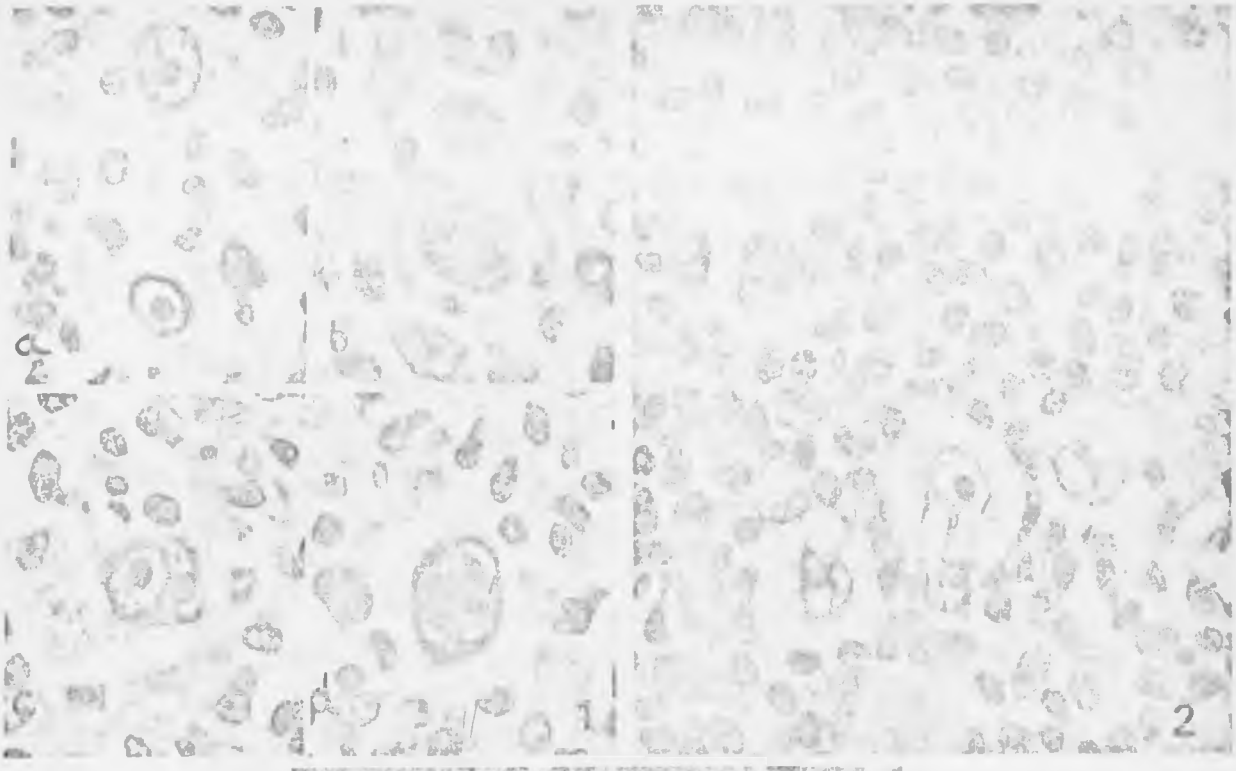
or aggregate in almost tumour nodules.

HISTOPATHOLOGICAL EVIDENCE OF HODGKIN'S DISEASE IN THE LIVER :

In patients with Hodgkin's disease elsewhere, if no R-S cells are seen, the presence of mononuclear cells with nuclear features of R-S cell in one of the characteristic cellular environment of Hodgkin's disease should be regarded as evidence of hepatic involvement(41) Atypical histiocytes or reticulum cells which fall almost short of these criteria but present in cellular environment should be reported as suggestive of Hodgkin's disease.

HISTOPATHOLOGICAL EVIDENCE OF HODGKIN'S DISEASE IN THE BONE MARROW :

In the presence of disease elsewhere the finding of focal or diffuse areas of fibrosis which contain only inflammatory cells characteristics of Hodgkin's disease with no R-S cells should be regarded as strongly suggestive.



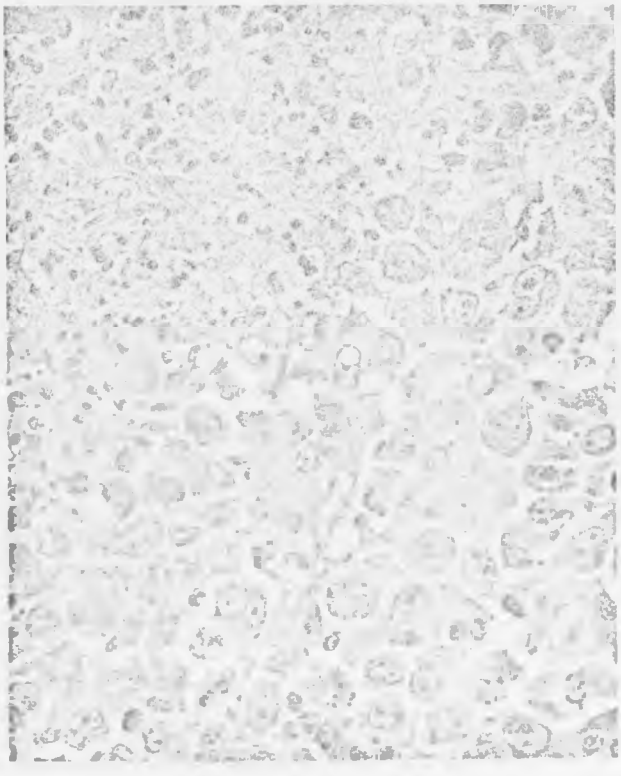


Fig. 1. The typical binucleated and multinucleated cells with inclusion-like nucleoli and deeply staining cytoplasm (*b*, *c*, and *d*) present the features of the diagnostic R-S cell and are compared with the diagnostically unreliable mononuclear form (*a*). LACH S-65 13924. H & E. × 850.

Fig. 2. These lacunar type R-S cells exhibit the pale cytoplasm with artifactual vacuolization and retraction, typically found in tissue fixed in formaldehyde. RJL 197-68 H & E. × 800.

Fig. 3. An aggregate of lacunar type R-S cells in tissue fixed in Zenker's solution have a narrow peripheral, clear zone; prominent granular cytoplasm; and a variable number of nuclei. The distinctive cytoplasmic character of lacunar cells may be lost with Zenker's fixation. RJL 93-71 H & E, × 800.

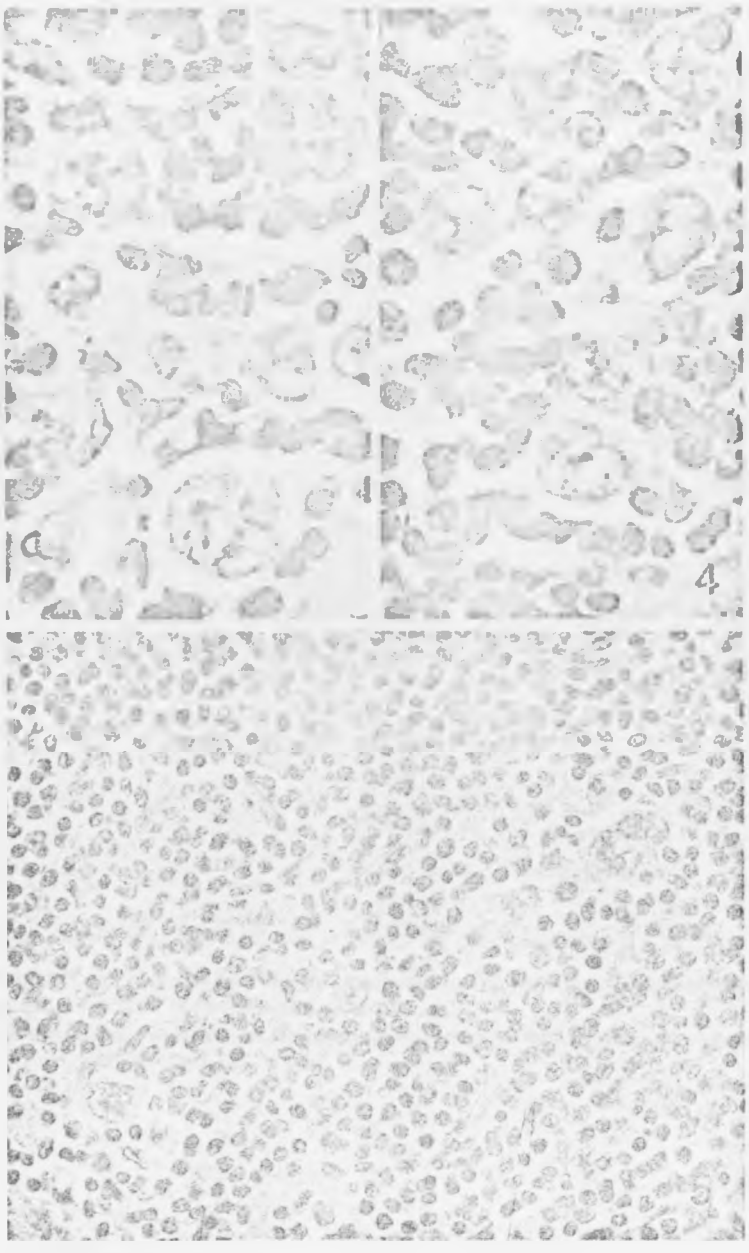


Fig. 4. L & H variant of R-S cell. These fragile polyploid cells have large, convoluted, twisted, overlapping nuclei with finely distributed chromatin, small nucleoli, and a small amount of pale, indistinct cytoplasm. RJL 165-71. H & E, × 800.

Fig. 5. Spleen. A minimal focus of involvement in the white pulp. Several multinucleated cells resembling R-S cells are found in a slightly enlarged Malpighian body in association with slight increase in reticulum. RJL 237-67. H & E, × 400.

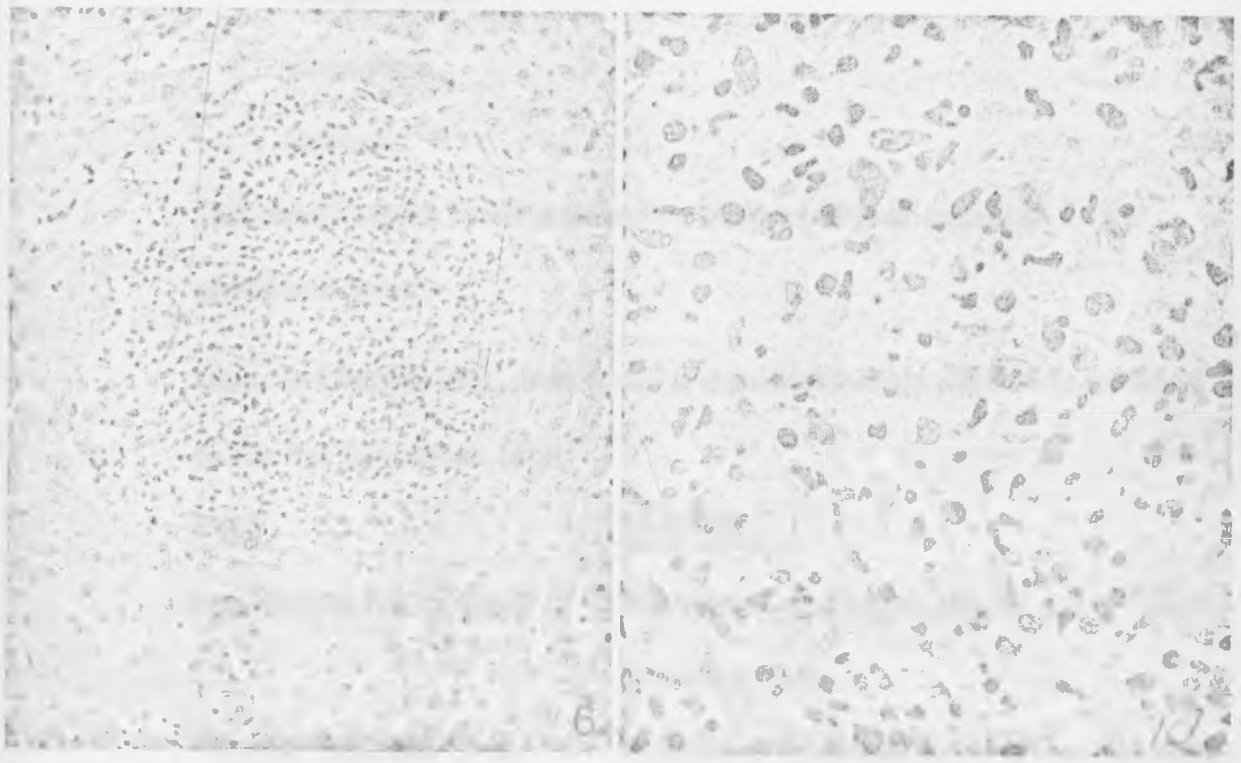


Fig. 6. A small focus of Hodgkin's disease in the liver. Scattered lobated and multinucleated cells are found in a discrete cellular focus exhibiting a prominent increase in connective tissue. LACH 70-5264. H & E, × 160.

Fig. 7. A focus of diffuse fibrosis in the bone marrow. The distinctive abnormal "precollagenous" character of the fibrosis typical of this type is seen in association with R-S variants. RJL 79-71. H & E, × 500.

HISTOLOGICAL CLASSIFICATION :

The original classification is that of Jackson and Parker (43) into :-

Paragranuloma

Granuloma

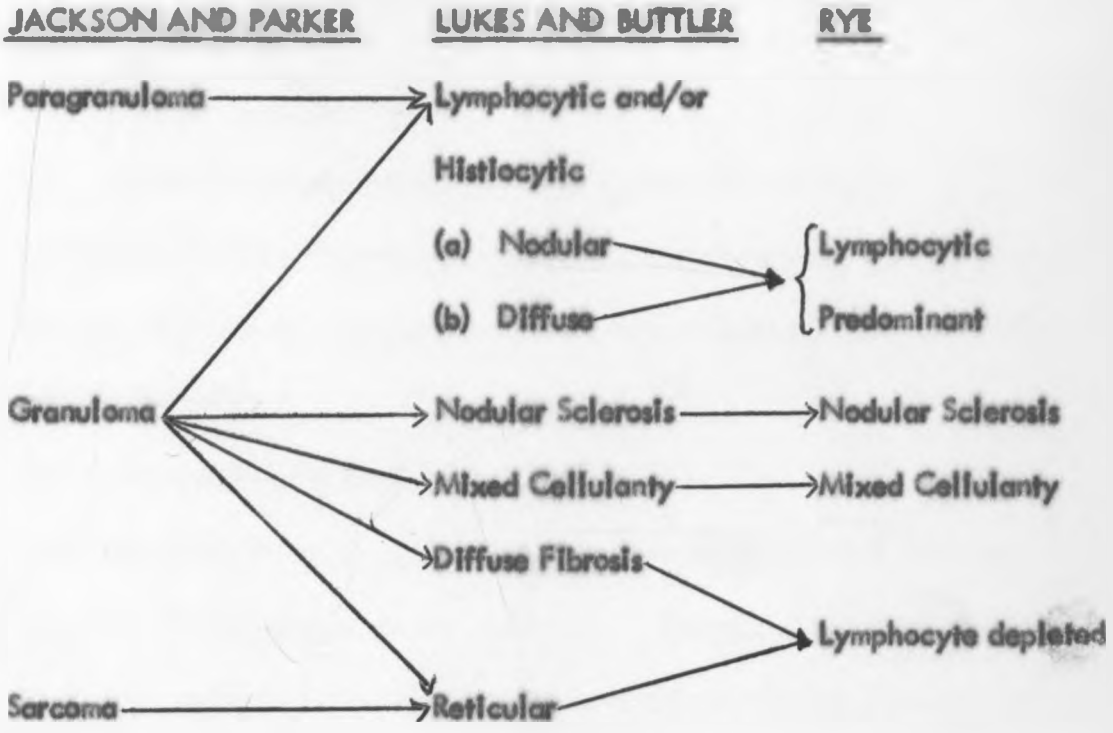
Sarcoma

This classification is not satisfactory because 90% of cases fell in the granuloma group.

Lukes and Butler (44), introduced a subclassification which was modified at the Rye Symposium (45).

TYPE	FEATURES
Lymphocyte Predominant -	Abundant Lymphocytic stroma sparse Reed-Sternberg Cells.
Nodular Sclerosis (NS) -	Nodules of Lymphoid tissue of varying sizes, separated by bands of collagen and containing lacunar cells variant of R-S Cells.
Mixed Cellularity (MC) -	More numerous R-S cells with pleomorphic stroma rich in eosinophils, plasma cells, fibroblasts and Lymphocytes.
Lymphocyte depleted (LD) -	Paucity of Lymphocytes, diffuse irregular fibrosis in some instances bizarre anaplastic R-S cells usually numerous.

TABLE COMPARISON OF JACKSON AND PARKER (43), LUKES AND BUTTLER (44) AND RYE CLASSIFICATION (45) OF HODGKIN'S DISEASE



Progression of disease tends to occur from Lymphocyte predominant to Lymphocyte depleted. Nodular Sclerosis may represent arrest of the progression related to host defence mechanism.

Lymphocyte predominance is strongly associated with clinical stage I and II while lymphocyte depleted is seen primarily with clinical stages III and IV. Mixed Cellularity occurs in all clinical stages without any strong associations. Nodular Sclerosis is associated predominantly with stage II and involves mainly lower cervical nodes, mediastinum and contigous structures. It occurs primarily in females and also has a younger age distribution (46).

Best prognosis is in lymphocyte predominant, nodular sclerosis, mixed

cellularity and lymphocyte depleted in that order (47). Absence of 'B' clinical symptoms especially weight loss and fever is also of better prognostic value (49).

TREATMENT :

There are three established forms of treatment for Hodgkin's disease :-

(a) Radiotherapy

(b) Multiple drug Chemotherapy

(c) Combined Radiotherapy and Multiple drug Chemotherapy.

As discussed before, accurate staging is absolutely important for deciding the form of treatment especially in centres where Radiotherapy is available.

RADIOTHERAPY

This is the treatment of choice for stages I, II and IIIA. Previous studies have established the tumoricidal dose to be between 3,500 to 4,000 rads (50, 51). This dose was usually given over 3-4 weeks ; but recent studies have shown administration over 6-8 weeks is not only highly effective but has markedly attenuated the acute and delayed normal tissue reactions to irradiation (52).

Radiation therapy is often guided by and limited to the apparent extent of involvement clinically, followed by prophylactic extension to the contigous areas (53). However relapses often occurs on non-contigous areas. The necessity for elective irradiation of clinically uninvolved contigous and non-contigous regions was demonstrated by a prospective clinical trial performed by the National Cancer Institute (54). The major advantage of prophylactic total nodal irradiation was the consequence of treating unsuspected disease in retroperitonial lymphnodes (which can even be missed at laparatomy). In the absence of prophylactic abdominal irradiation, extension of disease has been documented in one third of cases (55).

Extensive prophylactic irradiation also improves survival for patients with histology other than nodular sclerosis (54).

Total nodal irradiation is however not required for every clinical presentation, but factors such as primary site(s), presence or absence of systemic symptoms, and histological classification should be considered before a decision is made. Patients tolerance to intensive irradiation (56) has prompted treatment of patients with stage IIIA and extranodal involvement without evidence of generalised disease, with Radiotherapy. 70% 5 year survival rates for stage IIIA have been reported from the National Cancer Institute and in Stanford (54). Patients with localised extranodal involvement provided it can be included to its full extent in the curative radiation treatment, have same survival and cure rate as those with lymphnode involvement of the same extent (57).

CHEMOTHERAPY

In Hodgkin's disease, chemotherapy is used for the treatment of the more advanced stage IIIB and stage IV. However in centres where radiotherapy is not available, it is used for all stages including I and II.

Upto until 1963 chemotherapy consisted of single agents (either an alkylating agent or a vinca alkaloid) complete remission however rarely exceeded 20% (58).

A pilot study with combination chemotherapy started in 1963 at the National Cancer Institute showed that of the first 43 patients treated, all responded but 35/43 (81%) achieved complete remission (59). The pro-

gramme was modified slightly and began its present form of combination of Mustine hydrochloride (or Cyclophosphamide), oncovine, procarbazine and prednisone MOPP or COPP (59). The rationale for using combination chemotherapy is that :-

(a) All agents used should have activity against the tumour.

(b) All agents should have different mechanisms of action so as to delay emergence of drug resistant clone.

(c) Toxicity should be dispersed among different organs and thus obviate cumulative toxicity.

Details of the administration and toxicity are well documented (60). Table I shows a single cycle of the combination drug program. Each cycle is given over 2 weeks followed by a 2 week rest interval before institution of the next cycle. The therapy therefore consists of 6 cycles in 6 months. Haematological status of the patient especially the white blood cells and thrombocytes should be assessed before each cycle is started.

TABLE I.

DRUG	DOSE	ROUTE	SCHEDULE
Nitrogen Mustard*	6 mg/m^2	I.V	Day 1 and Day 7
Vinaristine (oncovine)	1.4mg/m^2	I.V	Day 1 and Day 7
Procarbazine	100mg/m^2	P.O	14 days
Prednisone	40 mg/m^2	P.O	14 days

*Can be substituted for Cyclophisphamide at 650 mg/m^2 especially in patients who develop thrombocytopenia.

The limiting factors in this form of treatment is usually leukopenia and/or thrombocytopenia (i.e. Bone Marrow depression). This occurred in 20% in De Vitas (60) series. Nausea and vomiting alopecia, and neurotoxity are never severe enough to warrant stoppage of treatment. Alopecia and neurotoxicity are always reversible after the patient finishes treatment.

Patients who relapse after treatment are successfully treated with the same regimen.

Some centres have used the same regimen but substituting Vinblastine (which is more neurotoxic) for Vincristine. In one such study, Nicholson (61) obtained a complete remission rate of 86%. It is no doubt therefore combination chemotherapy has greatly improved the outcome of patients with advanced Hodgkin's disease.

COMBINED RADIOTHERAPY AND CHEMOTHERAPY

The indications for combination of radiotherapy and chemotherapy are (52) :-

(a) Potentiation of radiation effect for better tumour shrinkage in certain resistant tumour or for those recurring within a former therapy port.

(b) To allow lower radiation dosage during therapy of tumour in organ easily damaged by x-rays e.g. lungs or kidneys.

(c) During initial therapy to stage IV patient with a dominant tumour mass in one area which can be treated locally followed by chemotherapy for the smaller disseminated foci.

(d) Before radiotherapy to shrink huge masses to allow more reasonable X-ray port size e.g. mediastinal tumours.

(e) As medical decompression on an emergency bases for obstructure syndromes of venae cava, spinal cord or airways prior to radiation.

(f) To control systemic symptoms e.g. fever prior to radiation.

Moore (63) randomised 102 untreated patients with Hodgkin's disease stages IB – IIIB ; one group received total - lymphoid radiation, and the second group received total-nodal radiation followed by 6 courses MOPP. Over 4 years the group which had received radiation alone had 10 relapses while the combined radiation and chemotherapy group had one relapse. The probability of disease free survival was also significantly improved ($p < 0.01$) in the combination group ; however actual survival was not significantly improved ($p = 0.10$). The MOPP was well tolerated by the patients who had recently received total lymphoid radiation.

RELAPSE RATE, SURVIVAL AND CURE OF HODGKIN'S DISEASE (64)

The risk of relapse of patients with stage I and II is approximately 20% in the first year. 15% the second year and 5 - 10% in the third year. For patients with stage III and IV, there is a similar sharp decrease in the risk of relapse from the first to the third year. For patients treated with radiotherapy, relapse if it occurs, invariably occurs in non-irradiated site(s). In contrast relapse following chemotherapy occurs in tumour that has been treated.

The relapse free interval (in radiotherapy treated patients), may be influenced by the histopathological type of Hodgkin's disease. Thus Fuller (65) found lymphocyte predominant Hodgkin's disease is cytokinetically slow moving, and late relapses is more common than for mixed and nodular sclerosis.

Information on survival is largely obtained from End Results Section of National Cancer Institute (66). The risk of death from Hodgkin's disease is about 15% in the first five years after treatment and 10 - 5% after 6 years. No death occured from Hodgkin's disease after the 20th year. There is therefore a decreasing risk of death from Hodgkin's disease with time, but cure (as defined by Easson and Russel (67) "We can speak of cure when in time - probably a decade or so after treatment there remains a group of disease-free survivors whose progressive death rate from all causes is similar to that of a normal population of the same sex and age constitution") by our defination does not occur until after the 20th year.

IMMUNOLOGY OF HODGKIN'S DISEASE :-

In 1902 Reed (68) noted tuberculin was given in five (out of eight) cases without reaction. It was not however until 1932 when Parker (69) suggested the negative tuberculin tests even in the presence of tuberculosis was as a result of an abnormal immune response. It has since been shown that patients with active Hodgkin's disease have impaired delayed cell mediated immunity (70). Further it has been shown peripheral blood lymphocytes from untreated patients are deficient in their vivo function as measured by their capacity to form E rosettes with sheep erythrocytes (71). Babrove (72) showed that the impaired immune response in patients with untreated Hodgkin's disease could not be attributed to a quantitative depletion of circulating T Lymphocytes and that the impaired E rosette formation could be restored to normal levels by incubating overnight the peripheral blood lymphocytes in tissue-culture medium containing foetal serum (73).

When the restored lymphocytes were incubated in serum of patients with untreated Hodgkin's disease, their E rosette forming capacity was suppressed, but when incubated in serum from normal subjects, no suppression was observed. This finding therefore suggested that there was a specific interaction between serum factors and the surface of peripheral blood T lymphocytes in Hodgkin's disease (74).

Grifoni (75) stated that antlymphocyte auto-antibodies present in serum and lymphnode extracts obtained from patients with Hodgkin's disease, could be detected on the surface of peripheral blood lymphocytes. He further obser-

ved that the antibodies inhibited the response of the lymphocytes to phytohemoagglutinin (76).

Chisari and Edgington (77) isolated a low density lipoprotein from the serum of patients with hepatitis B virus infection that reduced the capacity of peripheral blood lymphocytes from normal donors to form E rosettes. Hodgkin's disease rosette inhibiting factors also has been found to be a component of the low-density lipoprotein fraction (74) other than in the purified immunoglobulins fraction of the serum as found by Longmire et al (78). This field of investigation is new and further research is still going on.

A FIVE YEAR (JANUARY 1973 - DECEMBER 1977) RETROSPECTIVE STUDY AND TWO YEAR (JANUARY 1976 - DECEMBER 1977) EXPERIENCE IN THE TREATMENT OF ADULT (15 YEARS) HODGKIN'S DISEASE IN KENYATTA NATIONAL HOSPITAL

MATERIALS AND PATIENTS

The Kenya Cancer Registry (kept by the Department of Pathology of the University of Nairobi) was scrutinised. The number of all patients with histological confirmation of Hodgkin's disease was obtained. This was divided into patients below and above 15 years of age. The available case notes of patients treated initially at Kenyatta National Hospital were obtained from the Records Office and the following parameters analysed : age, sex, presenting symptoms, duration of symptoms prior to hospitalisation, site(s) of presumed tumour involvement, treatment given and subsequent response.

For the clinical staging, the modified Peters Criteria (20) was used. Lukes and Butler classification as modified at the Rye Symposium (45), was used for the histopathological classification.

During the period January 1976 and December 1977 I personally participated in the treatment of patients who still were attending the haematology clinic on outpatient basis. The side effects and response to combined drug chemotherapy noted during that period will be discussed later.

RESULTS

Histology reports of the period between January 1973 and December 1976

were complete. These reports represent biopsies taken from all over Kenya and sent to Kenyatta National Hospital. All biopsies sent from abroad were not included.

Approximately 39 patients are diagnosed every year and 69% of these are above 15 years of age (table I).

TABLE I

YEAR	1973		1974		1975		1976		Average %
Age/Yrs.	No.	%	No.	%	No.	%	No.	%	
< 15	11	29.8	7	18.4	13	30.9	17	44.7	30.9
> 15	26	70.2	31	81.6	29	69.1	21	55.3	69.1
TOTAL :	37	100	38	100	42	100	38	100	100

Files of 49 patients were available in Kenyatta National Hospital records for detailed analysis. There was varying degrees of non-uniformity in the patients' records, but most parameters were recorded and available for analysis.

Mean age of the patients was 31 years and the range was 15 - 74 years. There were 37 male cases and 12 female cases. Similar type of male preponderence is found both in African (79) and European communities (60). The mean duration of symptoms before presentation to hospital was 11 months. The range was 2 - 60 months.

TABLE II (Shows a Summary of Presumed Tumour Involvement)

LYMPHADENOPATHY :

SITE	NO. PATIENT	% OF TOTAL
NECK*	40	82
INGUINAL	23	47
AXILLA	27	55
EPITROCLEAR	2	4
MEDIASTINUM	5	10
INTRA-ABDOMINAL+	5	10
EXRANODAL		
BONE(STERNUM)	1	2
LUNG	1	2
LIVER=	10	20
SPLEEN=	14	28

NECK* - Includes cervical, submandibular, supraclavicular each alone or in combination

INTRA-ABDOMINAL+ - Two patients had masses of glands around the caecum with involvement of intestinal mucosa

- Three had retroperitonial lymphadenopathy

LIVER=) SPLEEN=) - These sites were just presumed to be involved without histological proof.

Among the 'B' symptoms, fever and loss of weight were the two commonest complains as shown below in table III. Five of the 49 patients had no

comment made on the B symptoms and therefore are not included in the table.

TABLE III. (Analysis of the B Symptoms in 44 patients)

SYMPTOM	NO.	%
Fever	35	94.5
Weight loss	19	43
Diaphoresis (night sweats)	9	20
Pruritus	4	9

Note : Anaemia of less than 10 gm% occurred in 36% of the patients at the time of presentation to Hospital. In most cases this was not investigated. It is likely therefore that it was either part of the disease or due to underlying parasitic infestation.

Table IV shows the clinical stages in 47 of the 49 patients. Records of two patients did not show enough information for staging. This staging is strictly based on a thorough clinical examination and thorough history from the patient. Enlarged Liver or Spleen was presumed to be part of the disease. Only 6 patients (12%) underwent diagnostic laparatomy. This is an inadequate way for accurate clinical staging as was discussed in the review of literature

TABLE IV (Clinical Staging)

STAGE	NO.	%
I	10	21.3
II	4	8.5
III	21	44.7
IV	12	25.5

All the patients with stage III and IV had 'B' symptoms ; while only two patients had 'B' symptoms in stages I and II.

TABLE V (Shows the Histological Classification of Adult Hodgkin's Disease in Kenyatta National Hospital compared with some Results from Uganda and U.S.A.)

	Kenyatta National Hospital 39 cases › 15 yrs.		Uganda 18 cases › 15 yrs.	U.S.A. Review of 377 cases by Lukes & Butler (44)
Histological Type	No.	%	%	%
Lymphocyte Predominant	8	20	0	16
Nodular Sclerosis	8	20	11	40
Mixed Cellularity	14	37	50	26
Lymphocyte Depleted	9	23	39	18

Note : 10 patients in this series (20% of the original 49 patients) were not classified in any of the four classes above.

All patients with H.D stage I and II were treated with Radiotherapy while those in stages III and IV were treated with either MOPP or COPP (59).

Table VI shows the drugs, dosages, route of administraion and schedule used for chemotherapy. The therapeutic aim was to administer 6 courses at 4 week intervals.

TABLE VI.

DRUG	DOSE	ROUTE	SCHEDULE
Nitrogen Mustard^{+}	6mg/m^2	I.V	Day 1 and Day 8*
Vincristine (oncovine)	1.4mg/m^2	I.V.	Day 1 and Day 8
Procarbazine (Methylhydrazine)	100 mg/m^2	P.O	14 days
Prednisone$^{=}$	40 mg/m^2	P.O	14 days

+When Nitrogen mustard was not available, cyclophisphamide (650 mg/m^2) was given.

*Second doses of Nitrogen mustard and oncovine where given on the 7th day because haematology clinic is run once in a week (on Mondays)

=Prednisone was given with courses one and four.

The patients who received radiotherapy had 4,000 rads to the tumour site plus the contigous site(s).

In all, 33 patients received chemotherapy and 14 Radiotherapy. The results of treatment are shown in Table VII.

TABLE VII

MODE OF TREATMENT	COMPLETE REMISSION		PARTIAL REMISSION		DIED*	
	No.	%	No.	%	No.	%
Chemotherapy	25	76	4	12	4	12
Radiotherapy	10	71.4	2	14.3	2	14.3

*4 patients died while on chemotherapy. 2 died of tuberculosis; 1 of pyogenic meningitis and 1 of disseminated disease.

2 patients diedwhile on Radiotherapy. 1 patient had mediastinal lung involvement and died following thoracotomy after airway obstruction. The other had recurrence of disease on non-irradiated areas and died despite being put on Chemotherapy afterwards.

The summary of the clinical data of the patient whom I treated between January 1976 - December 1977 is shown in appendix I. Most of the clinical data except the complication has been analysed with the other

patients studied. Table VIII shows a summary of the complications in the 11 patients

TABLE VIII

LEUKOPENIA*		ALOPECIA+		PARASTHESIAS + REDUCED+ REFLEXES		VOMITING+	
No.	%	No.	%	No.	%	No.	%
1	9	3	27	8	73	3	27

*The leukopenia was so severe that the treatment had to be discontinued and patient admitted for blood transfusions.

+These side effects were minor and treatment was continued to completion. Patients who were vomiting were given 5 mg of stemetil 30 - 60 minutes before drugs were administered and 5 mg eight hourly for 24 hours thereafter. No vomiting was recorded with this regimen. Alopecia always recovered after the end of treatment.

DISCUSSION AND CONCLUSIONS

The commonest mode of presentation in Hodgkin's disease is painless lymphadenopathy. This has been supported by a study in Ugandan patients (79); and an earlier study in Kenyan patients in Kenyatta National Hospital (16). The commonest site of involvement as shown in this study (Table II) is the neck (82% of the cases).

Patients in Kenya tend to present late with wide spread disease. The average duration of disease before presentation in this study is 11 months. This is similar to what Olweny (79) found in Ugandan patients. In the Ugandan series, 83% of the patients were stage IV while in this study the percentage of stage IV is low (Table IV). This discrepancy is likely due to the fact that more investigations (skeletal survey, intravenous pyelography, cavagraphy, percutaneus liver biopsies, bone marrow examination) were done for clinical staging than in this series. Exploratory laparatomy was done in 6 (42.8%) out of the 14 patients in stages I and II.

Histopathological analysis reveals an excess of the more malignant mixed cellularity and lymphocyte depleted type (Table V) unlike the experience reported from U.S.A.(44). Though, the pattern is similar to that found in Uganda (79), this series show 20% of the lymphocyte predominant type (Table V) while there was 0% in the Ugandan series.

The results of both multiple drug chemotherapy (76% complete remission rate) and Radiotherapy (71% complete remission rate) are encouraging. The results are similar to the overall 76% complete remission rate obtained in

Ugandan patients using multiple drug chemotherapy alone ; and comparable to the results (86%) of De Vita and his colleagues (60). It is to be remembered however that accurate staging leading to the correct choice of treatment is important in determining the type of results one will get. Therefore with careful staging our results in Kenyatta National Hospital can be definitely improved.

The toxicity encountered in this study is similar to that described by De Vita (60) but bone marrow depression was less common 9% than in De Vita's series (20%).

To determine survival and cure rate as described in the review of literature, protracted and careful follow up is necessary. The follow up of patients in this study was short, but if continued long enough survival and cure rates may be determined later.

In conclusion I would like to point out that we have all the facilities required to start an integrated centre for the treatment of all malignancies (including Hodgkin's disease). A department of Oncology (though it might seem an ambitious idea) should be seriously considered. It is my belief that, if we pool all our resources and skills together better results in the treatment of all forms of malignancies will be realised.

APPENDIX 1

No.	Age/ Sex	Clinical Stage	Systemic Symptoms	Site(s) of Presumed Tumour	Duration before Presentation in Months	Histology Type	Laparatomy	Response to COPP/ MOPP	Thiazina Steptomycin	Relapse	HAEMATOLOGICAL STATUS				Survival Months	COMPLICATIONS			
											Beginning of β		End of β						
											HB gms %	WBCx10^3	HB gms %	WBCx10^3		Anaemia or/and Leukapema	Alopecia	Parasthesthesia Diminished Reflexes	Neusea Vomitting
1.	19M	IIIB	F,NSW,WL	C,AX,Sp.	7	MC	YES	CR	NO	-	14.4	14.0	14.8	7.9	18	NO	NO	YES	NO
2.	24F	IIIB	F,NSW,WL	C,AX,Ing	12	NS	NO	CR	YES	-	12.0	13.6	13.0	7.0	22	NO	NO	NO	NO
3.	40M	IVB	F,Pru	C,AX,Ing, BM	12	NS	NO	CR	NO	-	12.8	10.2	11.6	7.7	14	NO	NO	YES	NO
4.	16F	IIIB	F	C,AX,Sp.	4	NS	YES	CR	NO	-	12.8	4.3	13.4	7.7	30	NO	NO	NO	NO
5.	23F	IIIB	F	C,I	24	LD	NO	CR	NO	-	10.0	7.1	13.2	9.1	21	NO	NO	YES	NO
6.	22M	IIIA	-	AX,I,RP	7	MC	YES	CR	NO	Yes after 9 months	14.9	10.4	14.8	5.5	21	NO	NO	YES	NO
7.	28M	IIIA	-	C,AX,RP	3	LP	YES*	CR	NO	-	11.9	5.7	14.9	3.8	6	NO	YES	YES	YES
8.	48M	IIIB	F,NSW,WL	C,AX,I	240	LP	NO	CR	YES	-	10.1	4.4	13.7	7.5	31	NO	NO	YES	NO
9.	15F	IIIB	F	C,I,MD	10	LP	NO	PR*	NO	-	11.4	7.4	-		2*	NO	NO	NO	NO
10.	18F	IVB	F,WL	C,AX,Ing LI, Sp	11	LP	YES	PR+	NO	-	8.1	2.5	-		4+	YES	YES	YES	YES
11.	15F	IVB	F,WL,Pru	C,AX,Li, Sternum	2	LD	NO	CR	YES	Yes after 5 weeks	14.0	8.6	3.3	5.2	12	NO	YES	YES	YES
Average	24				14						12.4	8.1	11.4	6.8	16.5				

F = Fever
NSW = Night Sweats
WL = Weight Loss
Pru = Pruritus
C = Cervical
AX = Axillary
Sp. = Spleen
LI = Liver
Ing = Inguinal
MD = Mediastinum
NS = Nodular Sclorosis
LP = Lymphocyte Predominant
LD = Lymphocyte Depleted
CR = Complete Remission
PR = Partial Remission

F : Female
M : Male

*This patient has not completed the six courses.

+Patient very sensitive to MOPP/COPP. Had frequent transfussions. Last seen 4 months ago. Presumed dead.

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REFERENCES :

1. Ogada, T. Malignant Lymphoreticular Disease at Kenyatta National Hospital in 1973.
   E. Afr. Med. J 51 : 824, 1974.
2. De Vore, J.W. Studies in Hodgkin's Disease XII, Heredity and Epidemiological aspects
   Ann Intern. Med. 47 : 300 - 316 1957.
3. Rezis, D.V., Diamond, H.D., Craver, L.F. Familial Aggregation of Hodgkin's Disease
   Ann Intern. Med. 51 : 933 - 971, 1959.
4. Berliner, A. Hodgkin's Disease in Married Couple.
   JAMA 221 : 703 - 704, 1972.
5. Dworsky, R.C. Hodgkin's Disease Clustering Families and Communities
   Cancer.Res . 34 : 1161 - 1163, 1974.
6. Grufferman, S., Cole, P., Smith, P.G., Lukes, R.J. Hodgkin's Disease in Siblings New Eng. J. Med. 296 (5) : 248 Feb. 1977.
7. Alsenberg, A.C. Hodgkin's Disease : Prognosis, Treatment and Aetiologic and Immunologic Consideration New Eng. J. Med. 270 : 508, 617. 1964.
8. Mazar, S.A., Straus, B., Mantal Hodgkin's Disease : A Review of the Familial Incidence and Aetiological Factors in Hodgkin's Disease Arch Inten. Med 88 : 819 - 830. 1951.
9. Edwond T. Creagan : Familial Hodgkin's Disease
   Lancet 2 : 547 September 9, 1972.

10. MacMahon, B. Epidemiology of Hodgkin's Disease Cancer Res. 26 : 1189 - 1200. 1966

11. Vianna, N.J. Greenwald, P., Danes, J.N.P: Nature of Hodgkin's Disease Agent. Lancet 1 : 733 - 735. 1971.

12. Vianna, N.J. : Ann Intern Med. 77 : 169 - 180. 1972.

13. Vianna, N.J., Polan, A.K. : Epidemiological Evidence for Transmission of Hodgkin's Disease New Eng. J. Med. 289 : 499 - 502.1973.

14. Goldman : Incidence of Antibodies to EB-Virus, Herpes Simplex and Cytomegalic virus in Hodgkin's Disease Cancer 26 : 327 - 331 Aug. 1970.

15. Order and Hellman : Lancet 1 : 571. 11th March 1972.

16. Kasili, E.G., Bowry, T.R. Malignant Lymphoma in Kenya : Pattern and Pathology E. Afr. Med. J. 54 : 480 - 490. September 1977.

17. Kaplan, H.S., Contiguity and Progression in Hodgkin's. Disease Cancer Res. 31 : 1811 - 1813 Nov. 1971.

18. Rosenberg, D.A., Kaplan, H.S. Evidence of an Orderly Progression in the Spread of Hodgkin's Disease Cancer Res. 26 (part I) : 1225 - 1231 1966.

19. Rappaport, H., Strum., Vascular Invasion in Hodgkin's Disease. Its Incidence and Relationship to the Spread of the Disease. Cancer 25 : 1304 - 1313. 1970.

20. Report of the Committee on the Staging of Hodgkin's Disease Cancer Res. 26 : 1310 1966.

21. Peters, M.V., The Need for a New Clinical Classification in

Hodgkin's Disease Cancer Res. 31 : 1713 - 1722 Nov. 1971.

22. Kaplan, H.S. Report of the Committee on Hodgkin's Disease Staging Classification Cancer Res. 31 : 1860 - 1861 Nov. 1971.

23. Symposium in Staging of Hodgkin's Disease Cancer Res 31 : 1708 - 1870. 1971.

24. Strum, S.B., Rappaport, H. Hodgkin's Disease in the First Decade of Life Paediatrics 46 : 748 - 759. 1970.

25. Teillet, F. Hodgkin's Disease in Children Clin. Paediat. Philadelphia 8 : 698 - 704. 1969.

26. Kaplan, H.S. Hodgkin's Disease Cancer Res. 31 : 1730 . 1971.

27. Marshall, E.R., Constantine, E.A. Ultman, J.E. The Possible Value of Mediastinoscopy in Staging Hodgkin's Disease Cancer Res. 31 : 1740 - 1745, 1971.

28. De Vita, V.T. JR. Bagley, C.M.JR., Goodall, B.O., O'Kieffe, D.A. Trujillo, N.P. Cancer Res. 31 : 1746 - 1750. 1971.

29. Manuel Viamonte JR., Current Status of Lymphangiography Cancer Res. 31 : 1731 - 1971.

30. Brickner, T.J., JR., BOYER, C.W., Perry, R.H. Limited Value of Lymphangiography in Hodgkin's Disease Radiology 90 : 52 - 56 1968.

31. Lee, B.J., Nelson, J.H., Schwarz, G. Evaluation of Lymphangiography, Inferior Venacavography and Intravenous Pyelogram in the Clinical Staging and Management of Hodgkin's Disease and Lymphosarcoma New Eng. J. Med. 271 : 327 - 336. 1964.

33. Rosenberg, S.A., A Critique of the Value of Laparotomy and Splenectomy in the Evaluation of Patients with Hodgkin's Disease. Cancer Res. 31 : 1737 - 1740. 1971.

34. Gladstein : The Value of Laparotomy and Splenectomy in the Staging of Hodgkin's Disease Cancer 24 : 709 - 718. 1969.

35. Enright, L.P., Trueblood, H.W. and Nelsen, T.S.. The Surgical Diagnosis of Abdominal Hodgkin's Disease. Surg Gynecol. Obstet. 130 : 853 - 858. 1970.

36. Erskills, A.J., Kevy, S.V., Diamond, L.K., and Gross, R.E. Hazard of Overwhelming Infection After Splenectomy in Childhood. New Eng. J. Med. 276 : 1225 - 1229. 1967.

37. Whittier, A.N. Infections and the Spleen: Association between hypoplenism, Pneumococcal Sepsis and Disseminated Intravascular Coagulation Med. J. Australia 1 : 1213 - 1219. 1969.

38. Schlumff, Infections in 92 Splenectomized patients with Hodgkin's Disease - Clinical Review. Am - J. Surg. 62(11) : 853 - 62 1975.

39. Revry, M., Maldonado, N., Velez-Garcia, E. Montalvo, J., Santiago, P.J. Serious Infection After Splenectomy for the Staging of Hodgkin's Disease. Ann Int. Med. 77. 11 - 14 July 1972.

40. Editorial - Risk of Severe Infection in Patient with Lymphoma After Diagnostic Laparotomy and Splenectomy. Ann Int. Med. 77 : 143 - 145 July 1972.

41. Lukes, R.J. Criteria for Involvement of Lymphnode, Bone Marrow,

Spleen, and Liver in Hodgkin's Disease.Cancer Res. 31 : 1755 - 1767 1971.

42. Peckham, M.J., and Cooper, E.H. Proliferation Characteristics of the Various Cells in Hodgkin's Disease.Cancer 24 : 135 - 146 1969.

43. Jackson and Parker. Hodgkin's Disease. New Eng. J. Med 231 : 35 - 44 1944.

44. Lukes, R.J., Butler, J.J. The Pathology and Nomenclature of Hodgkin's Disease. Cancer Res. 26 : 1063 - 1081. 1966.

45. Lukes R.J., Craver, L.F., Hall, T.C.? Rappaport, H., and Rubin P. Report of the Nomenclature Committee.Cancer Res. 26 (part I) 1311. 1966.

46. Costan, W.B., Louis, B.J., Lillian, M.A., Mary Kruse, Guy Newell, and Robert Kagan. The Relationship of Histopathological Subtype to Clinical Stage of Hodgkin's Disease at Diagnosis. Cancer Res. 31 : 1776 - 1785. 1971.

47. Butler, J.J. Relationship of Histological Findings to Survival in Hodgkin's Disease. Cancer Res. 31 : 1770 - 1775. 1971.

49. Tubiana, M., Attie, E., Flamant, R. Gerard Marchant, R. Mayat, M. Prognostic Factors in 454 cases of Hodgkin's Disease. Cancer Res. 31 : 1801 , 1971.

50. Friedman, M., Pearlman, A.W., Turgeon. Hodgkin's Disease : Tumour Lethal Dose and Iso-Effects Am J. Roentgenol 99 : 843 - 850 1967.

51. Kaplan H.S. Evidence of Tumouricidal Dose Level in Radiotherapy of

Hodgkin's Disease Cancer Res. 26 (part I) 1221 - 1224. 1966.

52. Landberg, T. and Forsle, H. Radiosensitivity of Mediastinal Lymph-nodes in Hodgkin's Disease Treated with Split-Course Radiotherapy Acta Radiol 9 : 77 - 189. 1970.

53. Peters, M.V. Prophylactic Treatment of Adjacent Areas in Hodgkin's Disease. Cancer Res. 26 (part I) 1232 - 1243. 1966.

54. Johnson, R.E., Thomas, L.B., Schneiderman, M., Glenn, D.W. Faw, F. and Haferman. Preliminary Experience with Total Nodal Irradiation in Hodgkin's Disease.

55. Ralph E.J., Marilyn, K.G., and Sandra, K.M. Results of Radiation therapy and Implications for Clinical Staging. Cancer Res. 31 : 1834 - 1837. 1971.

56. Johnson, R.E,, Kagan, A. R., Haferman, M.D. and Keyes, J.W. Patient Tolerance to Extended Irradiation in Hodgkin's Disease Ann Int. Med. 70 : 1-6 . 1969.

57. Karl Mishaff. Prognostic and Therapeutic Implications of Staging in Extranodal Hodgkin's Disease. Cancer Res. 31 : 1814 - 1820 -1971.

58. Carbonne, P.P. and Spurr, C. Management of Patients with Malignant Lymphoma : A Comparative Study with Cyclophosphamide and Vinca alkaloids.Cancer Res. 28 : 811 - 822. 1968.

59. De Vita, V.T. Chemotherapy in the Treatment Advanced Hodgkin's Disease. Cancer Res. 8 : 13. 1967.

60. De Vita V.T., Serpick, A. and Carbonne, P.P. Combination Chemotherapy in the Treatment of Advanced Hodgkin's Disease

Ann. Int. Med. 73 : 881 - 895, 1970.

61. Nicholson, W.M., Beard, M.E.J., Crowthe, D., Stansfeld, A.G., Vartan, G.P., Malpas, J.S., Fairly, G. H. and SCOH R.B. Combitation Chemotherapy in Generalised Hodgkin's Disease. Brit. Med. J. 3 : 7 - 10. 1970

62. Gamble, J. F., Fuller, L. M. and Shullenberger, C.C. Combined Use of Chemotherapy and Radiation Therapy in the Treatment for Generalised Hodgkin's Disease. Leukaemic - Lymphoma pp 285 - 295. Chicago : Year Book Medical Publishers Inc. 1970.

63. Moore, M.R., Bull, J. M., Jone, S.E., Rosenberg, S.A. and Kaplan, H.S. Sequential Radiotherapy and Chemotherapy in Treatment of Hodgkin's Disease. Ann Int. Med. 77 : 1 - 97. 1972.

64. Emil Frei, Gehan, E.A. Definition of Cure for Hodgkin's Disease Cancer Res. 31 : 1828 - 1833. 1971.

65. Fuller, L.M., Gamble, J.F., Shullenberger, C.C., Buttler, J.J. and Gehan, E.A. Prognostic Factors in Localised Hodgkin's Disease Treated with Reginal Radiation. Radiology 98 : 641 - 654. 1971.

66. Cutler, S.L. and Heise, H.W. Long Term End Results of Treatment of Cancer J. Am. Med. Assoc. 216 : 293 - 297. 1971.

67. Easson, E.C. and Russel, M.H. The Cure of Hodgkin's Disease. Brit. Med. J. 1 : 1704 - 1707, 1963.

68. Reed, D. M. The Pathological Changes in Hodgkin's Disease with Special Reference to Its Relation to Tuberculosis. John Hopkins Hosp. Rep. 10 : 133 - 196, 1902.

69. Parker, F. Jr., Jackson, H. Jr., Fitzhugh, G. et al : Studies of Diseases of the Lymphoid and Myeloid Tissue. Iv. Skin Reactions to Human and Arian Tuberculin. J. Immunol. 22 : 277 - 282, 1932.

70. Young, R.C., Corder, M.P., Haynes, H. A. et al : Delayed Hypersensitivity in Hodgkin's Disease : A Study of 103 Patients. Am. J. Med 52 : 63 - 72. 1973.

71. Cohnen, G. Augener, W., Brittinger, J. et al : Rosette - Forming Lymphocytes in Hodgkin's Disease : N. Eng. J. Med. 289 - 863, 1973.

72. Bobrove, A.M., Fuks, Z., Strober, S., et al : Quantitation of T and B Lymphocytes and Cellular Immune Function in Hodgkin's Disease.

73. Fuks, Z., Strober, S., King, D.P., et al : Reversal of Surface Abnormalities of T Lymphocytes in Hodgkin's Disease After in vitro Incubation in Foetal Sera, J. Immunol (in press)

74. Fuks, Z., Strober, S., Kaplan, H.S. Interaction Between Serum Factors and T Lymphocytes in Hodgkin's Disease.

75. Grifoni, V., Recent Immunological Finding in Hodgkin's Disease : Tumori 59 : 363 - 373. 1973.

76. Tognella, S. Mantovani, G., Del Giacco, G.S., et al : Effecto del Siero Citotossico di panzienti con Malattia di Hodgkin's sulla PHA-responsivita in vitro di linfociti periferici umani. Tumori 61 : 53 - 62 1975.

77. Chisari, F. V., Edgington, T.S. : Lymphocyte E-rosette Inhibitory Factor : a Regulatory Serum Lipoprotein J. Exp. Med 142 : 1092 - 1107, 1975.

78. Longmire, R. L., McMillen, R. , Yelenosky, R. et al :
In vitro Splenic Ig G Synthesis in Hodgkin's Disease. N. Engl.
J. Med 289 : 763 - 767, 1963.

79. Olweny et al. Cancer Res. 27 : 1295 - 1301.