ASPECTS OF CANCER CHEMOTHERAPY

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By

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SECTION I

INTRODUCTION

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INTRODUCTION

"Although the physicians of all nations, from the time of Hippocrates to the present, have, by numberless researches and experiments, made trial of everything in nature, from the most innocent drug to the most virulent poison, both in the mineral and vegetable kingdoms; yet the disease still baffles the power of physic."

Burrows 1767.

In the management of malignant disease two major problems remain current and unsolved; the prevention of spread and recrudescence and the treatment of the advanced case.

The primary tumour may be eradicated by surgery or radiotherapy, but the patient dies, often after an interval of many years, from the effects of metastatic disease. The dissemination of viable malignant cells probably begins within a short period of the inception of a tumour. Many of these cells fail to survive but those which do may remain dormant for long periods before certain, little understood factors, operate to restore their activity. If cancer is to be controlled then means must be found for preventing dissemination, or for destroying cells which have successfully established themselves in secondary sites. The concept of cancer as a systemic disease requires the application of systemic therapy and this is implied in the use of chemotherapeutic agents. This same idea was expounded by Sir Astley Cooper in 1825 when he said:-[1]

> "It behoves medical men to direct their minds to the trial of the numerous agents which chemistry and botany have of late abundantly discovered and simplified . . . . . and if the operation be performed for this disease, the surgeon should never trust solely to the knife, but he must endeavour to alter the constitution which has not only led to the complaint, but will surely regenerate it, if it remain unchanged."

A few patients with advanced malignant disease may remain almost symptomless and require no special treatment; the terminal stage /

stage is short and pain and distress are absent or minimal. Others present an impelling need for treatment; pain is severe and unrelenting; ulceration, bleeding, discharge and other distressing symptoms produce the picture which to many is the epitome of "cancer". Between these two extremes are the patients in whom advancing disease results in progressive impairment of health, loss of appetite and weight, disturbances of normal function and inevitable death. When conventional means of treatment prove inadequate, or cannot be employed because of the extent of the disease, the need for effective agents, to control its progress and to relieve symptoms, becomes urgent.

Whether the treatment of cancer with the chemical agents at present available is effective, can be considered ethical and can be carried out without further jeopardising the patient's course, remains a matter of controversy. Some consider that cancer chemotherapy is unjustified,[2] on the basis that good results are only obtained in a small percentage of patients at the expense of producing severe toxic effects and often death in a large proportion of those treated. It has also been stated that the use of cytotoxic agents may speed the advance of certain tumours by reducing the effectiveness of the host response to the tumour.[3] The risk of producing overwhelming intercurrent infection from severe depression of the bone marrow is advanced as a further argument against the employment of chemical agents in the management of cancer. While it is accepted that the results of using

anti-cancer /

anti-cancer drugs are poor, a few dramatic and worthwhile responses are nevertheless obtained and, in many cases, symptomatic relief is afforded for at least a few months. The chemotherapy of cancer is very much where the chemotherapy of tuberculosis was twenty-five years ago; the agents available were crude, their side-effects severe and the outcome of treatment uncertain.

The problem of cancer is infinitely more complex than that of tuberculosis, but the steady conquest of this and other diseases by the advent and widespread use of effective chemotherapeutic agents is sufficient encouragement to continue the search for agents effective against cancer. Whether or not such agents will be discovered in the immediate future is uncertain, but as Walshe,[4] in 1846, said, "nothing can be more unphilosophical than to conclude that a cure does not exist because it has not yet been found." It, therefore, remains necessary for interested clinicians to explore the use of those drugs currently available and to obtain a detailed knowledge of their nature, range and duration of action, indications and toxic effects. The majority of human tumours cannot be cultured and since the laboratory animal can in no way substitute for the clinical problems that present in the management of human cancer, chemotherapy will remain a field in which clinical investigation must precede laboratory confirmation. The behaviour of two apparently identical tumours, in patients of the same age and sex, may be entirely different. Few observations in one patient can be directly translated to the management of a tumour in another patient. /

patient. Only by the careful collection and collation of information obtained from a number of patients, treated over protracted periods, is it likely that any advances in applied cancer themotherapy will be made.[5]

The management of advanced malignant disease by drugs is complicated by the intangible human problems associated with this disease. As William Osler[6] said "... the practice of medicine is an art, not a trade: a calling not a business: a calling in which your heart will be exercised equally with your head." It is easy for both doctor and patient to be biased in their assessment of response to any particular line of treatment and objective means of assessment are essential. The burden of uncertainty must be shared, often for many months, by patient, relatives and doctor alike, while the effort is made to stave off an inevitable death.

Those undertaking the management of malignant disease by chemotherapeutic agents require an optimistic outlook to overcome the disappointments which follow their use. It is believed, however, that worthwhile remission can be obtained in some cases and it is these which should prompt the continued use of cytotoxins. Their use requires selection, care, consideration, time and a sympathetic awareness of the human problems involved. This study is an attempt to illustrate these points.

ASPECTS OF CANCER CHEMOTHERAPY

SECTION II

AIMS OF INVESTIGATION

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AIMS OF INVESTIGATION

> "Mere numbers of cases, however, mean little. It is what is done with the few that actually counts, and numbers, even though they add to personal experience, may in reality prove a handicap to the advancement of knowledge by absorbing the time which might otherwise be spent in assuaging curiosity."
>
> Harvey Cushing. [7]

The aim of this investigation was to study, in depth, the application of chemotherapeutic agents to the management of cancer, in a small number of patients, carefully followed up to the time of death or for a minimum of six months from commencing treatment. The investigation was based on the following considerations:-

1. That the cytotoxic agents at present available have a definite part to play in the management of malignant disease.
2. That their clinical application and assessment must frequently precede laboratory investigation.
3. That their effects on the metabolism of normal and malignant cells are incompletely understood and require further elucidation.

4. /

4. That the toxic effects of the agents at present available can be minimised and need not contra-indicate their use.
5. That the present methods of assessing response to the cytotoxic agents are unsatisfactory.
6. That there are a number of problems, such as the effects on "immunity mechanisms" and red cell survival time which justify study in relation to the use of cytotoxic agents.

The results obtained form the basis of this thesis.

ASPECTS OF CANCER CHEMOTHERAPY

SECTION III

HISTORICAL REVIEW

a) Early Concepts: Arsenicals and Galenicals.

b) Cancer as a Systemic Disease: the Alkylating Agents.

c) Rational Research: the Anti-metabolites.

d) Serendipity and Empirical Research: the Antibiotics and Plant Products.

e) Present Position and Future Prospects.

HISTORICAL REVIEW

"In criticizing the ignorance of the dark ages or the middle ages, modern writers often forget how very ignorant we ourselves are, or how recent is our knowledge."

Sir Norman Moore
(1847-1922)

To understand the present position of cancer chemotherapy and to assess the effectiveness of the agents available, it is necessary to review briefly the steps leading up to their discovery and use.

a) Early Concepts: Arsenicals and Galenicals

The concept of treating cancer by chemicals is by no means new. The efficacy of lead and arsenic in the control of certain superficial cancers was known to Paracelsus, Hippocrates and Galen.[8,9,10,11,12] Many of the remedies employed at this time, such as dried lizard skins, coal and extracts of hemlock, deadly nightshade and other herbs, were entirely empirical and the results rarely justified the extravagant claims.[4,13,14,15] The use of pastes, ointments and escharotics, containing varying proportions of arsenic, lead or zinc, was vigorously pursued by "quacks" who toured Europe and this country proclaiming the wonders of their various cures. Few of their extravagant claims could ever be substantiated, but articles advising the /

the use of these preparations can be found in the literature as late as 1926.[16]

b) Cancer as a Systemic Disease: the Alkylating Agents

The treatment of superficial, accessible tumours was well established by the late 18th century, but the problems of managing internal cancer by chemicals had to await the acceptance of cancer as a systemic disease and the development of less toxic agents. Hunter,[17] Astley Cooper[1] and others supported the belief that "cancer is more than a local disease" and that its control or "cure" required the use of systemic remedies. It was not until the early 20th century, however, that systemic cancer chemotherapy became a possibility with Ehrlich's discovery of the sulphonamides and salvarsan and the incidental observations that these drugs possessed a cytotoxic effect.

The vesicant and haemopoietic effects of nitrogen mustard gas in man had been noted in the First World War. The possible application of mustard gas to the treatment of leukaemia and malignant disease was investigated, in the laboratory, by Adair[18] and others in the 1930's but this work was largely overlooked. Not until the Bari Harbour disaster in 1941, in which a troop ship, carrying one hundred tons of nitrogen mustard gas, was sunk, was further intensive study carried out. Many of the survivors of this incident demonstrated severe bone marrow depression particularly affecting the white cell series and platelets. This effect was attributed to the /

the absorption of nitrogen mustard through the skin or from the alimentary tract of those swallowing the contaminated sea water. As a result of the subsequent researches, largely carried out in secret by Gilman and Philips[19,20] and by Rhoads and others[21] in America, nitrogen mustard was introduced in 1945 in the management of leukaemia and malignant disorders of the reticulo-endothelial system.[22,23] It was immediately recognised as a powerful, but highly toxic agent which still has a part to play in the management of certain malignant conditions, such as Hodgkin's Disease and lymphosarcoma.

c) Rational Research: the Anti-metabolites

Some of the most exciting steps in the search for anti-cancer agents followed the observation by Faber,[24] in 1947, that the progress of acute leukaemia in children was accelerated by using the folic acid conjugate pteroyl diglutamic acid. That folic acid was present in large amounts in the cells of certain tumours, had been known for some years. Folic acid could also be antagonised in the laboratory and by further research anti-folic acid agents were isolated which could be used in clinical trials. The most effective of these was amethopterin (methotrexate) and in 1948 Faber published his first results in the management of acute leukaemia of childhood using this agent. From this has developed the most fruitful and most rational line of research in cancer chemotherapy. A number of "anti-metabolites" effective against a wide range of malignant /

malignant disorders has been discovered as a result of intensive search.[25] These agents, specifically designed to antagonise various essential components of cell metabolism include the anti-purine, 6-mercaptopurine, the anti-pyrimidine, 5-fluouracil and the anti-amino acid, azaserine. Although most effective in the management of the malignant disorders of the haemopoietic and reticulo-endothelial system, certain of the anti-metabolites are also of value in treating solid tumours.

d) Serendipity and Empirical Research: the Antibiotics and Plant Products

It has been known for sixty years that colchicine[14] produced depression of the bone marrow, but at clinically effective levels is highly toxic. Largely as a result of empirical research, a number of cytotoxic agents, derived from moulds and plants, have been discovered in recent years. The work of Waksman and Woodruff (1940)[26] on the identification and isolation of Actinomycin from soil micro-organisms, paved the way for the isolation of agents possessing cytotoxic activity of clinical value from other varieties of mould (Mithromycin; Mitomycin) and from plants such as the Periwinkle, Vinca Rosea[27,28] (Vinblastine sulphate; vincristine sulphate). These are most effective in malignant diseases of the haemopoietic and reticulo-endothelial systems, but a few are of value in the management of solid tumours.

e) Present Position and Future Prospects

Great strides have been made in the search for suitable cytotoxic agents /

agents and the early days of arsenic, lead and conium are now remote. Despite this progress the ideal agents have not been found and their immediate discovery cannot be anticipated.[29] Those at present available have a narrow range of activity, may produce severe and occasional fatal toxicity, are unpredictable in their effects and usually produce remissions which are incomplete and short-lived. A few dramatic and prolonged remissions, however, are obtained and in chorion carcinoma occasional "cures" are reported.[30] The use of drug combinations, prophylactic chemotherapy and intra-arterial administration require further study.

Extensive research continues in America, this and other countries for new agents. In the United States of America, the Cancer Chemotherapy National Service Center organises and co-ordinates research on a gigantic scale and it is estimated that fifty thousand chemical substances are screened each year for anti-tumour effect.[31] Of these, only a very few reach the stage of concentrated research and only one or two each year reach the stage of clinical trial. The likelihood of a new agent even then being more effective and less toxic than those already available is slight. This continued research, however, embodies the principle hope of these concerned in the management of malignant disease; its control and final eradication.[32]

In 1867, Langston Parker expressed the opinion that "we are at the eve of a discovery for the arrest or perhaps the cure of cancer." One hundred years later, this is still an overstatement, but the possibility exists that current research will validate this view.

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SECTION IV

METHODS AND MATERIALS

a) Nature and Source of Material.

b) Principal Agents Available.

c) Synopsis of Principal Agents Used.

d) Methods of Application of Anti-cancer Agents.

e) Routes of Administration.

f) Routine Investigations.

g) Laboratory-Research Investigations.

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TABLE I

THE CHEMOTHERAPY OF CANCER

SYNOPSIS OF CASES TREATED

TOTAL = 107 Female = 45 Male = 62

Case No.	Initials	Age	Sex	Primary Tumour	Group	Total Cases
1	J.G.	23	F	Hodgkins Disease	A	
2	P.O'S.	39	M	" "	A	
3	G.R.	26	M	" "	A	
4	J.B.	19	M	" "	A	7
5	W.McG.	50	M	" "	A	
6	G.C.	22	M	" "	A	
7	R.P.	17	M	" "	A	
8	A.A.W.	53	M	Carcinoma of Lung	B	
9	J.C.G.	39	M	Carcinoma of Larynx	B	
10	T.A.N.	43	M	Carcinoma of Lung	B	
11	L.W.T.	50	M	" " "	B	
12	H.S.	36	M	" " "	B	
13	J.P.	65	M	" " "	B	
14	A.M.	46	M	" " "	B	
15	A.H.P.	32	M	" " "	B	15
16	E.J.W.	49	M	" " "	B	
17	J.S.W.	50	M	" " "	B	
18	A.McL.	43	F	" " "	B	
19	A.L.F.	37	M	" " "	B	
20	R.J.C.	51	M	" " "	B	
21	M.W.	56	F	" " "	B	
22	J.M.	61	M	" " "	B	
23	T.W.	27	M	Lymphosarcoma	C	
24	T.H.W.	47	M	"	C	3
25	D.T.W.	47	M	"	C	
26	B.H.W.	38	M	Leukaemia	D	
27	T.M.P.	18	M	"	D	
28	M.C.C.	6	M	"	D	4
29	L.F.C.	21	M	"	D	
30	H.E.V.	50	M	Myeloma	E	1

TABLE I (continued)

Case No.	Initials	Age	Sex	Primary Tumour	Group	Total Cases
31	E.B.	48	F	Carcinoma of Breast	F	
32	M.C.	36	F	" " "	F	
33	D.B.	50	F	" " "	F	
34	F.M.P.	43	F	" " "	F	
35	M.G.	52	F	" " "	F	
36	D.N.	36	F	" " "	F	
37	F.H.	42	F	" " "	F	
38	M.M.D.	53	F	" " "	F	
39	M.P.	42	F	" " "	F	
40	F.S.	39	F	" " "	F	
41	B.S.	43	F	" " "	F	
42	I.F.	53	F	" " "	F	22
43	V.L.	67	F	" " "	F	
44	M.McD.	47	F	" " "	F	
45	L.B.	38	F	" " "	F	
46	B.K.	42	F	" " "	F	
47	M.G.	67	F	" " "	F	
48	A.W.	63	F	" " "	F	
49	M.O.	44	F	" " "	F	
50	M.S.	63	F	" " "	F	
51	M.K.	50	F	" " "	F	
52	S.O.	64	F	" " "	F	
53	J.M.H.	41	F	Carcinoma of Ovary	G	
54	A.E.	39	F	" " "	G	
55	D.M.	46	F	" " "	G	
56	S.G.	42	F	" " "	G	6
57	M.C.	70	F	" " "	G	
58	E.H.	60	F	" " "	G	
59	D.H.	30	M	Testicular Tumours	H	
60	T.T.	30	M	" "	H	
61	B.A.	49	M	" "	H	5
62	A.J.I.	22	M	" "	H	
63	M.W.F.	25	M	" "	H	
64	H.F.S.	40	M	Renal Carcinoma	I	
65	V.M.A.	49	F	" "	I	
66	J.W.	66	M	" "	I	5
67	J.C.	60	M	" "	I	
68	H.S.	53	F	" "	I	

TABLE I (continued)

Case No.	Initials	Age	Sex	Primary Tumour	Group	Total Cases
69	W.K.	70	M	Carcinoma of Bladder	J	1
70	T.P.	59	M	Carcinoma of Prostate	K	1
71	J.R.	43	M	Carcinoma of Adrenal Gland	L	2
72	O.M.	26	F	" " "	L	
73	A.A.C.	45	M	Carcinoma of Oesophagus	M	2
74	J.A.P.	33	M	" " "	M	
75	R.B.H.	42	M	Carcinoma of Stomach	N	8
76	T.H.	58	M	" " "	N	
77	W.M.	64	M	" " "	N	
78	I.M.	69	F	" " "	N	
79	R.C.	66	M	" " "	N	
80	E.C.	71	M	" " "	N	
81	P.D.	63	M	" " "	N	
82	A.W.	58	F	" " "	N	
83	J.N.S.	32	M	Carcinoma of Colon and Rectum	O	9
84	I.L.	22	F	" " " "	O	
85	A.M.T.	52	M	" " " "	O	
86	E.R.W.	50	M	" " " "	O	
87	A.W.S.	53	M	" " " "	O	
88	E.M.H.	39	F	" " " "	O	
89	E.D.	35	F	" " " "	O	
90	P.W.N.	44	M	" " " "	O	
91	R.G.	59	M	" " " "	O	
92	F.H.R.	62	F	Carcinoma of Pancreas	P	4
93	E.L.	48	F	" " "	P	
94	J.K.	65	M	" " "	P	
95	J.T.	59	M	" " "	P	

TABLE I (continued)

THE CHEMOTHERAPY OF CANCER

Case No.	Initials	Age	Sex	Primary Tumour	Group	Total Cases
96	R.G.C.	52	M	Malignant Melanoma	Q	3
97	M.S.	50	F	" "	Q	
98	J.S.	65	F	" "	Q	
99	C.J.B.	46	M	Carcinoma of Unknown Primary	R	4
100	J.A.	24	M	" " "	R	
101	J.McI.	54	F	" " "	R	
102	J.W.	35	M	" " "	R	
103	S.L.P.	37	M	Others	S	5
104	D.L.O.	42	M	"	S	
105	J.S.W.	53	M	"	S	
106	M.M.A.	45	F	"	S	
107	W.J.P.	39	M	"	S	

TABLE II

CHEMOTHERAPY OF CANCER

PRINCIPAL AGENTS USED

1. Alkylating Agents

   (a) Nitrogen Mustards

   (i) Nitrogen mustard (Mustine)
   (ii) Cyclophosphamide
   (iii) Phenyl-alanine mustard (Melphelan)
   (iv) Mannitol mustard (Degranol)
   (v) Uracil mustard
   (vi) Chlorambucil (Leukeran)

   (b) Ethylene Imines

   (i) Tri-ethylene-thiophosphoramide (Thiotepa)

   (c) Epoxides

   (i) Ethoglucid (Epodyl)

   (d) Sulphonic Acid Esters

   (i) Busulphan (Myleran)

2. Antimetabolites

   (a) Anti-Folic Acid

   (i) Methotrexate

   (b) Anti-Purine

   (i) 6-Mercaptopurine

   (c) Anti-Pyrimidine

   (i) 5-Fluorouracil

   (d) Anti-Amino Acid

   (i) Azaserine

3./

TABLE II PRINCIPAL AGENTS USED (continued)

3. Antibiotics and Plant Products

(a) Moulds

(i) Actinomycin D

(b) Plants

(i) Vinblastine sulphate (Velbe)
(ii) 2-ethyl-hydrazine (S.P.I.)

4. Hormones

(a) Sex Hormones

(i) Oestrogens
(ii) Testosterone

(b) Steroid Hormones

(i) Prednisone
(ii) Prednisolone
(iii) Durabolin

5. Others

(i) Thiocolciran
(ii) Imuran

TABLE III

CHEMOTHERAPY OF CANCER

METHODS OF APPLICATION USED

1. Prophylactic against spread or implantation
2. As an adjunct to radiotherapy or surgery
3. In advanced disease when other measures already tried or not applicable

In each case anti-cancer drugs were used:-

(a) Singly or in combination
(b) In intermittent or continuous courses

TABLE IV

CHEMOTHERAPY OF CANCER

ROUTES OF ADMINISTRATION USED

1. Topical application
2. By mouth
3. Intramuscular
4. Intravenous
   - (a) Intermittent injection
   - (b) Continuous infusion
5. Intra-arterial
   - (a) Intermittent injection
   - (b) Continuous infusion
   - (c) Perfusion
6. Intra-cavitary
7. Intra-muscular injection

TABLE V

CHEMOTHERAPY OF CANCER

ROUTINE INVESTIGATIONS

1. Haematology

   (a) Haemoglobin
   (b) Packed-cell volume
   (c) Erythrocyte sedimentation rate
   (d) Total white cell count
   (e) Differential white cell count
   (f) Platelet count
   (g) Bone marrow examination

2. Biochemistry

   (a) Liver function tests
      (i) Serum bilirubin
      (ii) Alkaline phosphatase
      (iii) Thymol turbidity
      (iv) Zinc sulphate turbidity
      (v) Serum glutamic oxalic transaminase
      (vi) Serum glutamic pyruvic transaminase
      (vii) Bromsulphthalein excretion
      (viii) Plasma proteins
   (b) Serum electrophoresis
   (c) Serum uric acid

3. Radiology

   (a) Routine diagnostic investigations
   (b) Chest
   (c) Pelvis and spine
   (d) Serial X-rays of metastatic sites
   (e) Follow-up X-rays of inoperable alimentary tract neoplasms

4./

TABLE V

ROUTINE INVESTIGATIONS (continued)

4. Bacteriology

   (a) Urine
   (b) Sputum
   (c) Wounds
   (d) Blood
   (e) Superficial tumours

5. Photography

6. Pathology

   (a) Histological
   (b) Macroscopic

TABLE VI

CHEMOTHERAPY OF CANCER

LABORATORY-RESEARCH INVESTIGATIONS

1. Lymphocyte transformation
2. Chromosome changes
3. Red-cell survival studies

METHODS AND MATERIALS

a) Nature and Source of Material.

b) Principal Agents Available.

c) Synopsis of Principal Agents Used.

d) Methods of Application of Anti-cancer Agents.

e) Routes of Administration.

f) Routine Investigations.

g) Laboratory-Research Investigations.

a) NATURE AND SOURCE OF MATERIAL

A total of 107 patients (62 male and 45 female) with histologically proven malignant disease and all receiving cytotoxic therapy, were studied. Details of distribution by age, sex and tumour groups are contained in Table 1.

These cases were studied in the period July 1962 to September 1965, first at the Royal Air Force Hospital, Uxbridge, Middlesex (July 1962-March 1964) and subsequently in the University Department of Clinical Surgery and Royal Infirmary of Edinburgh (April 1964-September 1965). They represent approximately half of the cases receiving cytotoxic therapy in the two centres during this total period. The remainder did not fulfil the necessary criteria for inclusion.

b) PRINCIPAL AGENTS AVAILABLE

Of the many chemical agents now available for treating cancer, only a very few are of real value. These may be classified in four main groups:

1. The Alkylating Agents,
2. The Antimetabolites,
3. The Antibiotic and Plant Products,
4. The Hormones.

A further group of drugs which do not fit into any of the above categories is of little importance and may be labelled "Miscellaneous".

1. Alkylating Agents [22,33]

The alkylating agents are distinguished by their ability to combine with reactive molecules, within the nuclei of cells, in such a manner as to destroy normal cellular metabolism. It is believed that this process of alkylation occurs through the medium of short carbon chains which form abnormal linkages between the various reactive sites, particularly those related to the nucleic acids of the cell nucleus. In view of the important role played by the nucleic acids in cell reproduction, it is reasonable to assume that interference with the formation of nucleic acids is the basic action of this group of drugs. Exactly how alkylation operates to interfere with cell growth and division is, however, a matter of

continued /

continued controversy.

The alkylating agents are among the oldest of the chemotherapeutic drugs in use in the treatment of malignant disease and many of the earlier agents are still of value. They, therefore, constitute the best-known group of anti-cancer drugs. The drugs in this group closely resemble each other in their action, side effects, and in the nature, degree and duration of response obtained. The four important sub-groups are:-

I. The nitrogen mustards, of which the best-known examples are nitrogen mustard itself (Mustine), cyclophosphamide and phenylalanine mustard (melphelan).

II. The ethyline amines, of which triethylenethiophosphoramide (thiotepa) is the prototype.

III. The sulphonic acid esters, represented by Busulphan (myleran).

IV. The epoxides, of which ethoglucid (epodyl) is the principal agent of clinical value.

These preparations are particularly toxic to the bone marrow, and, in varying degree, cause gastro-intestinal disturbances such as nausea, vomiting and diarrhoea. Apart from a few exceptions, for example myleran, which is much more toxic to granulocytic than to lymphocytic precursors, the concept of a specific agent for treating a specific tumour is not valid for this group as a whole. If a tumour does not respond to one alkylating agent, it is /

is unlikely that it will respond to another. If recrudescence of the tumour occurs after satisfactory response to one agent, it is unlikely that further remission will be obtained if another alkylating agent is used.

In that the alkylating agents are cytotoxic, mutagenic and most active against cells in the process of division, they may be described as radiomimetic. This is, however, a meaningless term, since those tumours most likely to be affected by radiotherapy, cryotherapy, or hormone therapy are also most likely to be affected by chemotherapy.

The duration of response to these agents is usually short and frequently incomplete. They nevertheless represent the most generally useful group of drugs for the treatment of solid tumours. Their toxicity to bone marrow and gastro-intestinal mucosa limits the extent of this usefulness.

2. Antimetabolites [5, 24, 34, 35, 36].

The antimetabolites constitute a group of anti-cancer agents with the common property of accurately substituting for a normal constituent of cell metabolism. By being incorporated in a counterfeit manner for normal constituents, they interfere with nucleoprotein synthesis and, therefore, with cell division, again leading to cell death. They may compete with a normal metabolite, either by a greater affinity for the reactive molecules, or by being present in greater amount. They may directly inhibit the activity /

activity of an enzyme essential to nucleo-protein synthesis or be incorporated into abnormal molecules which in turn will lead to interference with cell metabolism and death.

The antimetabolites represent the best example of rational thought and research applied to the development of chemical agents for the cure of cancer. Much ingenuity has been applied to the design of new antimetabolites with the result that this has been the most productive line of research. By various, often minor, chemical modifications, substances have now been made available which will compete with essential cellular metabolites, such as folic acid, the purines, pyrimidines, and amino acids. Many other specific antagonists are also available but they do not differentiate sufficiently between normal and tumour cells to be of clinical use. Each of the four main groups of the antimetabolites is represented by one better known agent. The anti-vitamins or anti-folic acid agents by methotrexate, the antipurines by 6-mercaptopurine, the antipyrimidines by 5-fluorouracil and the anti-amino acids by azaserine.

The antimetabolites are of greatest value in the treatment of the leukaemias and malignant disorders of the reticulo-endothelial system. With the exception of 5-fluorouracil, they are of very little value in the management of solid tumours. This drug is peculiar in its action on well-differentiated gastro-intestinal tumours, particularly those of the colon.

Apart /

Apart from their effects on the bone marrow, these agents, as a group, commonly give rise to severe oral ulceration and bleeding. They also cause nausea, vomiting, and skin rashes. The length of remission obtained by the use of antimetabolites varies from a few weeks to a few months but is seldom longer than six months. The degree of remission may, however, be remarkable and the rapidity of its onset dramatic.

26,27.

3. Antibiotics and Plant Products

In recent years, certain antibiotic and plant products have been shown to possess varying degrees of anti-tumour activity. A few of these agents have entered into clinical use and are of value in the management of a narrow range of malignant disorders.

Of the antibiotics, the Actinomycins, particularly Actinomycin 37
D, have proved of greatest value. This agent, in combination with radiotherapy, is effective in treating neuroblastoma of childhood and rapidly growing sarcomas, such as rhabdomyosarcoma. Since, however, these conditions are uncommon, the applications of this drug are limited.

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Of the plant products, the alkaloids of the Periwinkle such as Vinblastine sulphate (velbe) and Vincristine sulphate are the best-known. They are of most value in the management of the malignant reticuloses but also have a limited application in the treatment of solid tumours.

Gastro-intestinal and haematological side effects are common, despite /

despite the fact that certain of them are used in very small doses. Their mode of action is uncertain; they are grouped entirely on the basis of their origin, and not on any common mode of action. It is believed that they principally act as antimetabolites, again interfering with essential enzymatic processes within the cell. Their total place in the management of malignant disease remains uncertain.

4. Hormones [38]

The use of oestrogens and androgens in the treatment of advanced carcinoma of the breast and prostate is too well established to require emphasis. These agents are frequently employed as adjuncts to surgery or radiotherapy and if remission is obtained it is of greater duration, more complete and freer of side effects than the remission obtained with any of the other anti-cancer agents. Despite this unique position, it is generally accepted than the hormones are not included in the detailed discussions of cancer chemotherapy. While they will be discussed in context throughout this study, they are largely excluded from the analysis of the results obtained by treating cancer by chemical agents.

In a similar manner, the steroid hormones, of great value in the management of the leukaemias and malignant reticuloses will be discussed in context, but are not considered in detail.

5. Miscellaneous Agents /

5. Miscellaneous Agents

Many of the drugs in this group, such as arsenic, urethane and lead, belong essentially to the history of cancer chemotherapy. Colchicine, a powerful metaphase inhibitor, has been combined with an alkylating agent, similar to thiotepa, to form Thiocolciran. This agent is of value in treating certain gastro-intestinal tumours but causes considerable toxicity.

c) SYNOPSIS OF PRINCIPAL AGENTS USED [39]

1. ALKYLATING AGENTS

a) Nitrogen Mustard (methylbis(beta-chlorethyl)amine hydrochloride. HN_2 Mustine) [5,20,21,22]

Nature and mode of action.- One of the earliest available agents, nitrogen mustard, is a water-soluble, crystalline powder which rapidly deteriorates after going into solution and must be given immediately. It contains two active alkyl radicals which are able to react with many cell constituents, producing abnormal cross-linkages and preventing the chains of deoxyribonucleic acid from dividing.

Haemopoietic and other effects.- There is a progressive and sometimes severe fall in polymorph, lymphocyte and platelet count commencing within 24 to 36 hours of giving nitrogen mustard, reaching a maximum between 10 and 15 days. The haemoglobin falls by /

by 10 to 20 points within 8 to 16 days. If no further treatment is given, these effects persist for three to ten days and then slowly reverse. It has a powerful vesicant action on tissues, producing induration and indolent ulceration at sites of accidental, extravascular injection. Nausea and vomiting are common and occasionally severe.

Indications.- Of most value in the malignant disorders of the reticulo-endothelial system and blood-forming tissues, it is also effective against tumours of the breast, ovary and lung.

Doses and administration.- The recommended dose is 0.4 mg. per Kg. of body weight, given well-diluted by intravenous injection or continuous infusion. It can also be given by intra-cavitary instillation[40] to control serous effusions, when the dose used is between 15 and 30 mg. per Kg. of body weight. Treatment is best accompanied by an anti-emetic such as chlorpromazine or promazine.

b) Cyclophosphamide (N,N-bis(B-Chlorethyl)-N,O-propylene-phosphoric acid ester diamide monohydrate Endoxan)[5,41]

Nature and mode of action.- This agent, first synthesised in 1957, is presented in the form of a water-soluble white crystalline powder in 100 and 200 mg. vials and as 50 mg. oral tablets. Arnold and Bourseaux (1958)[42] first reported on the action of cyclophosphamide. This action depends on the attachment of a phosphorus atom to the alkylating groups so that these are liberated locally /

in the tumour cells, at the site of high phosphatase activity. The general effect on normal tissues is thereby reduced.

Haemopoietic and other effects.- With small doses the effects on the haemopoietic system are mild, while the platelets remain unaffected by even high dosage. Prolonged treatment results in progressive fall in white cell count and haemoglobin which may take weeks or months to reach a maximum. These effects can be dramatically produced, however, by the use of large dose infusions. On withdrawal of treatment the effects on the haemopoietic system are reversed within 10 to 20 days and bone marrow depression is seldom complete. Alopecia, a dry scaly skin, brittleness of the nails, nausea and anorexia are the most important additional effects. They usually disappear with dose reduction or withdrawal of the drug.

Indications.- Cyclophosphamide is of particular value in treating carcinomas of the breast, ovary and lung. It is also of benefit in certain other tumours, including those of the gastro-intestinal and genito-urinary tracts.

Dosage and administration.- An oral dose of 100 to 150 mg. daily is usually well tolerated. Single intravenous or intra-cavitary injections of 200 to 600 mg. produce little disturbance although the higher dosage should be combined with an anti-emetic such as chlorpromazine. When used by intravenous or intra-arterial infusion /

infusion a dose of 2,000 mg. over a period of 24 hours gives maximal benefit with minimal discomfort. The optimal maintenance dose must be established by continuous monitoring of peripheral blood count, but very large total doses may be given in some cases.

c) Phenyl-alanine Mustard (p-di(2 chloroethyl)amino-L-phenylalanine, Melphelan) [5,43]

Nature and mode of action.- This compound was first synthetised independently by Bergel and Stock [44] in 1953 in this country and by Larionov [45] in 1955 in Russia. It is presented in 5 mg. tablets for oral administration and more recently has become available as an oily solution for intramuscular injection, in 2 ml. ampoules. By combining phenylalanine with active alkylating groups, these are released within the malignant melanoma cell by the incorporation of phenylalanine in the production of melanin.

Haemopoietic and other effects.- The effects on the haemopoietic system are marked. A severe reduction in white cell count and haemoglobin occurs within 10 to 12 days of commencing treatment, persists for 14 to 21 days and only slowly reverses. Nausea, vomiting and bucco-labial ulceration are also common.

Indications.- By its chemical nature this agent is designed for the treatment of malignant melanoma and is the drug of choice for this condition. It also has some effect on lymphosarcoma and multiple myeloma.

Dosage /

Dosage and administration.- Five to 10 mg. should be administered by mouth daily to a total dose of 50 to 100 mg. For intravenous infusion or intra-arterial perfusion a dose of 25 to 50 mg. produces a good and occasionally dramatic response in a few cases, but leakage of drug into the general circulation may cause severe bone marrow and other effects.

d) Mannitol Mustard (Degranol)[46]

Nature and mode of action.- This substance is available in 100 mg. ampoules for intra-venous or intra-arterial injection and more recently has been produced in 100 mg. tablets for oral administration. It acts both as an alkylating agent and, by virtue of the mannitol fragment, as a metabolic blocking agent. This and uracil-mustard are examples of dual antagonists.

Haemopoietic and other effects.- The effects of Degranol on the haemopoietic system are similar to those of nitrogen mustard, but a marked, persistent and sometimes fatal marrow depression may develop as late as 30 to 100 days after commencing treatment and thus renders the use of this drug hazardous. Anorexia, nausea and vomiting are also marked but can usually be controlled with anti-emetics.

Indications.- The use of mannitol mustard is indicated in the treatment of chronic leukaemia, lymphosarcoma and Hodgkin's disease.

Dosage /

Dosage and administration.- The intravenous or intra-arterial dose is 2 to 3 mg. per Kg. of body weight to a maximum of 1,000 to 1,500 mg. This total dose may be given as a single intravenous infusion over a period of 24 to 36 hours, but should be accompanied by the use of sedatives or anti-emetics. An oral dose of 100 to 300 mg. per day may be continued for 10 to 30 days but constant attention must be paid to the peripheral blood count. This agent may also be administered by intra-cavitary instillation in a dose of 100 to 500 mg.

e) Chlorambucil (p-(di-2-chlorethyl)amino-phenylbutyric acid, Leukeran) [47]

Nature and mode of action.- This weak alkylating agent is available in 2 and 5 mg. tablets for oral administration. Chlorambucil was first synthesised by Everett, Roberts and Ross [48] in 1953.

Haemopoietic and other effects.- This agent is much less toxic than nitrogen mustard. Depression of white cell count and haemoglobin usually occurs within 14 to 30 days of commencing treatment with leukeran and are controlled by reduction or withdrawal of the drug; return to normal levels occurs within 10 to 20 days. Gastro-intestinal effects are minimal.

Indications.- The use of this agent is largely confined to malignant disorders of the blood-forming tissues and the malignant reticuloses. It is weakly effective in carcinomas of the genito-urinary tract.

Dosage /

Dosage and Administration.- The oral daily dose varies from 4 to 16 mg. per day and the total dose is controlled by regular blood count.

f) Tri-ethylene-thiophosphoramide (N-Triethylenethiophosphoramide. Thiotepa) [49]

Nature and mode of action.- Thiotepa is produced in 15 mg. ampoules as a white crystalline water-soluble powder, suitable for intravenous or intramuscular injection. It is the most effective of a group of closely related compounds and its clinical use was first reported by Shay and his colleagues in 1953. [50] Its mode of action is similar to that of nitrogen mustard and the other alkylating agents.

Haemopoietic and other effects.- The haemopoietic effects of thiotepa are again similar to those of nitrogen mustard but the gastro-intestinal disturbances are usually less marked.

Indications.- Thiotepa is of greatest value in the management of advanced carcinoma of breast and ovary particularly when these are complicated by serous effusions. Good results have occasionally been observed in tumours of the gastro-intestinal tract.

Dosage and administration.- An intravenous or intracavitary dose of 15 to 45 mg. may be given on two or three occasions at intervals of 7 to 14 days. A total dose of 90 to 120 mg. is usually sufficient to produce remission.

2. ANTIMETABOLITES

a) Methotrexate (4-amino-N^{10}-methyl pteroylglutamic acid. Amethopterin) [51]

Nature and mode of action.- The anti-folic acid agent, methotrexate, is available as 2.5 mg. tablets for oral administration. It is also available as a solution for intravenous, intra-arterial or intracavitary use. By blocking the conversion of folic acid to folinic acid it prevents D.N.A. synthesis and as such represents one of the earliest and still most effective anti-metabolic agents.

Haemopoietic and other effects.- The action of this agent is principally directed against the haemopoietic system and therefore bone marrow depression may be marked. The range between therapeutic and toxic levels is narrow so that toxicity is usually produced before evidence of remission is obtained. The most significant effects are, however, on the gastro-intestinal tract; nausea, vomiting, diarrhoea and buccal ulceration occurring commonly.

Indications.- The principal indication for use of this drug is chorion-carcinoma in the female and this is one of the few tumours in which chemotherapy may occasionally prove curative.[30,51] Methotrexate is also of value in the treatment of the acute leukaemias and has been used in certain gastro-intestinal tumours. In an attempt to reduce toxicity, methotrexate has been given together with its antagonist folinic acid.[52,53] It is doubtful, however, whether this technique /

technique offers any real advantage.

Dosage and administration.- A daily dose of 2.5 to 5 mg. may be continued until a total dose of 100 to 200 mg. has been administered. When used for intra-arterial or intravenous injection, infusion or perfusion, a single dose of 50 mg. has been found of most value. Alternatively, daily doses of 10 to 20 mg. may be infused over a period 3 to 5 days at intervals of 6 to 12 weeks.

b) 6-Mercapto-purine (6-M.P.)[5]

Nature and mode of action.- This agent acts as an anti-purine and is presented in 50 mg. oral tablets.

Haemopoietic and other effects.- The principal action of this drug is again on the haemopoietic system and the range between toxic and therapeutic levels narrow. Gastro-intestinal disturbances are, however, much less marked than with methotrexate.

Indications.- The principal indication for the use of 6-mercapto-purine is acute leukaemia. Remission usually begins within 10 to 20 days of commencing treatment and treatment may be continued for many months.

Dosage and administration.- An oral dose of 100 to 300 mg. per day may be tolerated for long periods before serious bone marrow depression necessitates reduction or withdrawal of treatment. /

treatment.

c) 5-Fluouracil (5.F.U.)[34,35,36]

This anti-pyrimidine is available in solution form in vials of 250 and 500 mg. It was first described by Heidelberger and his co-workers[34] in 1957 and is suitable for intravenous and intra-arterial use. It acts by blocking the methylation of deoxyurdylic acid to thymidylic acid which is an essential step in the formation of desoxy-ribonucleic acid.

Haemopoietic and other effects.- Marked depression of bone marrow function may develop within a short period of commencing treatment particularly if 5.FU. is used in combination with, or shortly after, another alkylating agent. Alopecia and skin pigmentation occur in a few patients and gastro-intestinal symptoms - nausea and vomiting, stomatitis and diarrhoea, may be moderate to severe.

Indications.- 5-Fluouracil is one of the few effective agents against adenocarcinomas of the gastro-intestinal tract. It is also valuable in the management of carcinoma of the breast and ovary, and of tumours of the head and neck.

Dosage and administration.- A recommended dose of 15 mg. per Kg. of body weight has been found, in practice, to be too high and 12 mg. per Kg. of body weight is more suitable. A total dose of 1 G. should not be exceeded in 24 hours. Treatment is best administered /

administered by intravenous injection or infusion in intermittent courses of 3 to 5 days at intervals of 6 to 12 weeks.

3. ANTIBIOTICS AND PLANT PRODUCTS

a) Vinblastine Sulphate (Velbe) [27]

Nature and mode of action.- This agent, obtained from the alkaloids of the Periwinkle (Vinca Rosea) is presented as a crystalline powder, readily soluble in water, which should be administered shortly after solution, but which will retain its activity for up to 14 days if stored in a domestic refrigerator. Although first investigated by Johnson, Wright and Svoboda [27] in 1959, its mode of action remains uncertain, but probably resembles that of the anti-metabolites.

Haemopoietic and other effects.- Moderate to severe depression of white cell count and haemoglobin level develop within 10 to 20 days of commencing treatment; depression persists for 5 to 15 days and then slowly reverts to normal. Gastro-intestinal symptoms are not marked but hallucinations, depression, occasional paranoid states and neuritis accompany its use. Vinblastine sulphate has a mild vesicant action and will produce indolent ulceration if injected extra-vascularly.

Indications.- The principal indications for its use are malignant disorders of the reticulo-endothelial system, particularly Hodgkin's Disease, but it is also valuable in treatment malignancies of /

of the breast and ovary.

Dosage and administration.- Two-15 mg. may be administered by single intravenous injections at intervals of 2 to 7 days. This dose may be continued for many weeks before significant toxic effects develop.

b) 2-Ethyl-Hydrazine (S.P.I.)

This agent is not commercially available and is presented in 2 mg. ampoules for intravenous or intra-arterial injection. Its mode of action is uncertain but again closely resembles that of the anti-metabolites.

Haemopoietic and other effects.- These are similar to vinblastine sulphate.

Indications.- The principal indication appears to be the treatment of malignant melanoma, but it is also of value in the management of Hodgkin's Disease.

Dosage and administration.- Single intravenous injections of 200 to 400 mg. may be given to a total dose of 1 G. in any 24 hours. It is best administered in courses lasting 2 to 3 days at intervals of 6 to 8 weeks.

4. OTHERS

Thiocolciran / 54

54
Thiocolciran

Nature and mode of action.- This agent, which is presented in the form of a yellow powder, readily soluble in water, combines an ethylene-imine with colchicine. In its mode of action it, therefore, resembles both the alkylating agents and antimetabolites.

Haemopoietic and other effects.- Effects on the bone marrow are minimal but gastro-intestinal disturbances particularly pain, vomiting and diarrhoea are marked. Mild alopecia may occur in a few patients.

Indications.- The principal indications for the use of this drug are gastro-intestinal and breast carcinomas.

Dosage and administration.- Single intravenous injections of 10 to 30 mg. at intervals of 1 to 2 weeks may be continued for many months. The total dose is determined by regular monitoring of the peripheral blood count and by the incidence and severity of gastro-intestinal disturbances.

a) METHODS OF APPLICATION OF ANTI-CANCER AGENTS

1. Prophylactic Use 55,56,57,58,59,60,61,62.

Manipulation of a tumour, however gently performed, results in the dissemination of malignant cells along any of the recognised avenues of spread. Only a very few of these cells survive to form /

form metastases, but it would seem logical to reduce the risk of spread by any means available. Cytotoxic agents have been shown experimentally and under certain clinical conditions to reduce the number of circulating malignant cells. How effective this is in reducing the number of metastases that develop is unknown. Nevertheless, it is considered that to use anti-cancer drugs as a means of reducing spread or implantation of malignant cells, particularly at the time of operation, is a justifiable technique.

The two principal ways in which cytotoxins have been used prophylactically in this study are:

1) by a series of single intravenous injections for a few days before, on the day of, and for a few days after operation;

2) by infusing the operative area during the course of the operation itself.

The first method has been used in such tumours as those of the testis, rectum and colon and to "cover" biopsy procedures. The second method has been employed in dealing with carcinomas of the kidney and during the course of radical mastectomy for carcinoma of the breast. In these cases, arterial cannulation has been carried out and mannitol mustard or cyclophosphamide slowly infused during and for a short period after the operation.

2. Used as Adjunct to Radiotherapy or Surgery [63, 64, 65, 66.]

Cytotoxic agents may be employed before, at the time of, or following /

following the application of standard surgical and radiotherapeutic procedures. Their use in this context is incompletely defined but there are four principal indications for adjuvant chemotherapy.

1. To potentiate the action of radiotherapy in certain tumours.- Actinomycin D in combination with radiotherapy, in the management of Wilms' tumour in childhood, is possibly the best-known example of adjuvant use. Certain alkaloids of the Periwinkle, e.g. vinblastine sulphate, are regarded as powerful potentiators of irradiation. It is believed that the same effect can be obtained from a smaller dose of irradiation when combined with vinblastine as can be obtained with a larger dose of irradiation alone.

2. To prevent or delay recurrence and implantation.- Cytotoxins may be used in combination with radiotherapy or surgery in an attempt to prevent or delay local recurrence, implantation, and the appearance of distant metastases. An example of such use is irrigation of the colon with a dilute solution of an alkylating agent at the time of resection for carcinoma.

3. To control existing metastases.- Cytotoxins may be used in an adjuvant sense to control metastases already present when these cannot be included in the initial surgical or radiotherapeutic fields. This constitutes the principal indication for adjuvant chemotherapy.

4. To reduce tumour bulk and activity.- By reducing the bulk and activity of tumour prior to surgery or radiotherapy, cytotoxins may /

may convert an unresectable tumour into a resectable one. The reduction in size of certain head and neck and of alimentary tract tumours are examples of such use.

The effect of such combined therapy is difficult to assess. Metastases may in some cases remain static for months or years. The control of associated infection and oedema may result in shrinkage in size of a tumour and thereby convert it into an operable form. The adjuvant role of cytotoxins is, nevertheless, important and each of the above indications has been employed in this study.

3. Used Alone in the Treatment of Advanced Disease

It is here that cytotoxins find their greatest use. This study is principally concerned with that group of patients in whom all conventional forms of therapy have already been used to their maximum effect and are no longer applicable and in those in whom the disease is already so far advanced at first diagnosis that conventional methods cannot be employed. It is in this context that conflicting views are expressed as to the value and justification of using potentially hazardous drugs when the outcome is inevitable.[2] For those patients who present with advanced malignant disease and who are distressed by pain, discharge, bleeding, anorexia and progressive inanition, any attempt to control these symptoms seems justifiable. The behaviour of two apparently similar tumours in /

in patients of similar age and sex may be entirely different. While certain tumours, such as those of breast and ovary, are much more likely to respond to chemotherapy, no tumour, whatever its site of origin, should be regarded as beyond the bounds of control until cytotoxins have been used in sufficient amount for an adequate length of time. Certain treatment patterns are beginning to emerge, but there are no hard and fast rules governing which drugs to use in which cases, in what doses, by which routes and for what length of time. It is the principal purpose of this study to examine the effectiveness of cytotoxins in treating patients with advanced malignant disease, to define, if possible, a group of effective agents, and to determine approximate dose schedules for a variety of tumours.

Use of Agents Singly or in Combination [67,68,69.]

Many agents are effective when used alone, but there are theoretical indications for using a combination of two or more anti-cancer drugs in the treatment of any particular tumour. By using a combination of agents, ideally from different groups, it should be possible to simultaneously attack more than one metabolic pathway and, at the same time, to employ a smaller dose of each agent. Effectiveness should be increased and toxicity reduced. The concept that a combination of anti-cancer drugs is preferable to using them singly appears valid in clinical practice and has been frequently adopted in this study.

Use in Intermittent Courses or as Continuous Maintenance Therapy

Whether chemotherapy should be used in intermittent courses over short periods of time, or as continuous maintenance, is still a matter for controversy. It is the experience of all, that however complete the initial remission, the tumour being treated will, with few exceptions, inevitably escape control within a matter of weeks or months. It is believed by some,[35,43] that if a good response is obtained, treatment should be stopped until relapse occurs when another course of therapy is given in an attempt to obtain further remission. Two, three or more courses of the same or of different cancericidal drugs may, therefore, be administered at intervals of a few weeks to a few months. Others[68,70] believe that, if remission is obtained, prolonged maintenance treatment at sub-toxic dose levels should be continued to prevent or delay relapse. Both methods have been employed in this study and are discussed in a later section.

e) ROUTES OF ADMINISTRATION

Anti-cancer agents may be administered in a number of ways, as follows:-

1. Topical application.
2. By mouth.
3. Intramuscular.
4. Intravenous
    (a) Intermittent injection
    (b) Continuous infusion.
5. /

5. Intra-arterial

   (a) Intermittent injection
   (b) Continuous infusion
   (c) Perfusion.

6. Intra-cavitary.
7. Direct injection into tumour.
8. Intra-lymphatic.

1. Topical application

The topical application of cytotoxins is limited to the management of a few small superficial tumours, such as squamous epitheliomas, and to the occasional control of ulcerating skin metastases in such conditions as carcinoma of the breast. In some measure, the use of cytotoxins in the control of pleural and peritoneal infusions and in the control of implantation at the time of surgery for colo-rectal and other tumours are examples of topical application. It is probable, however, that a certain amount of the agent is absorbed from the serosal surfaces thereby producing a systemic effect.

2. By Mouth

The administration of cytotoxic drugs by mouth is both convenient and effective. Only a few preparations are, however, available for administration by this route. The majority of these belong to the alkylating group of agents and the ones of most value in the treatment of solid tumours are cyclophosphamide, phenylalanine /

phenylalanine mustard (melphelan) and chlorambucil (leukeran). Methotrexate and 6-mercapto-purine are the only commonly used anti-metabolites which are suitable for oral administration. Approximately one-third to one-half of the orally administered dose is absorbed by the gastro-intestinal tract, but little is known of the sites of absorption and of the subsequent pathways to the tumour cell.

The principal advantage of oral administration is the ease with which patients can be maintained on out-patient treatment. It is also easier to disguise the exact nature of the treatment if this is felt desirable. Many of the patients in this study have been maintained for varying periods on oral maintenance therapy after an initial intravenous or intra-arterial course of cytotoxins. Among the disadvantages of oral administration, is the need to rely on patients taking their tablets at the stated times. It is sometimes difficult to persuade a patient to continue taking tablets which are known to cause nausea, vomiting and other unpleasant effects.

3. Intramuscular Administration

This route of administration is of little value. Apart from the occasional use of intramuscular thiotepa in the management of cancer of the breast there are few indications for the use of this route. When using androgenic or anabolic steroids, however, intramuscular administration is of considerable importance.

4. Intravenous Administration

Many of the agents at present in use for the chemotherapy of cancer /

cancer can be given in an intravenous form. Certain preparations can only be administered by this route and after suitable dilution. The majority of the patients in this study have commenced treatment on an intravenous regime and have either been maintained on intermittent intravenous injections, or on oral therapy, or on a combination of both.

When given intravenously, cytotoxic agents may be administered by continuous infusion over a short period of 24 to 36 hours or over a longer period of 5 to 10 days. The most frequently employed method, however, is a series of intermittent injections at intervals of hours, days or weeks. Both of these methods may be employed in the same patient and may be used concurrently. In-patient treatment may, therefore, commence with a 24-hour continuous infusion of a cytotoxic agent which is then continued at intervals on an out-patient basis.

The advantages of intravenous administration are the certainty of dose, the rapidly with which a large dose can be administered if this is required and the assurance that the drug is being administered at the desired time intervals. The disadvantages include the need for the patient to attend more frequently and the severe local tissue destruction that occurs when certain of the preparations, e.g. nitrogen mustard, are injected extravascularly.

5. Intra-arterial Administration [43, 71, 72, 73.]

Cytotoxic drugs may be administered intra-arterially by intermittent injection, by continuous infusion or by perfusion. The principal /

principal advantage of this route is the administration of a large dose of a cancericidal agent directly to the tumour area. When given by intermittent injection or continuous infusion, there is a considerable leakage of the drug into the systemic circulation, so that the total dosage which can be safely administered is the same as could be given intravenously. By the more elaborate method of arterial perfusion, whereby a limb or the pelvis may be isolated from the circulation and the venous and arterial supply routed through an oxygenator, leakage of drug is less marked and a much larger dose may be administered than would otherwise be safe. The systemic leakage[74] in this technique has, however, been variously estimated as 20% to 80% of the administered dose, so that severe side-effects may still develop. The principal indications for this method are recurrent melanoma of a limb and the rare haemangiosarcomas that are associated with chronic lymphoedema.

Which-ever of the intra-arterial methods of administration is employed, the technique requires additional time, skill and in-patient care and more elaborate equipment. Intermittent intra-arterial injections may be given under local anaesthesia, but usually require general anaesthesia. The injection may be given directly by syringe over a period of 10 to 15 minutes and the needle or cannula withdrawn. Alternatively, the cannula may be inserted into a main artery supplying the tumour area and the drug administered over a longer period of time (3-7 days) by means of a slow infusion pump or by suspending the infusion bottle from a height. Other complications /

complications of intra-arterial administration include infection, arterial thrombosis and occasionally massive haemorrhage. In this study, the arterial route has been employed for local infusion of an area at the time of operation, e.g. radical mastectomy and for intermittent injection, particularly where it has been possible to isolate the main artery of supply, as in renal carcinoma.

40

6. Intracavitary Administration

The principal indications for this route of administration are malignant, pleural or peritoneal effusions. Aspiration of an effusion should be carried out to relieve symptoms, but it is not necessary to aspirate to dryness before instillating cytotoxic drugs. It is uncertain whether agents administered by this route act in a cytotoxic manner or simply as sclerosing agents. It has, however, been shown that a varying amount of the drug is absorbed into the systemic circulation so that this may account for part of the effect obtained. Despite these uncertainties, this is one of the most satisfactory means of administering cytotoxic agents and their use in this manner is associated with few complications.

7. Direct Injection into a Tumour

The administration of cytotoxic drugs directly into a tumour is of limited value. Methods are now available for injecting solutions of cytotoxic drugs through intact skin to a depth of a few mm., but /

but this has found little favour in the management of superficial malignancies. In extensive chest wall recurrence of breast carcinoma, local injections of thiotepa may be of limited value, but usually cause considerable necrosis and haemorrhage before tumour regression is obtained. This technique has not been employed in any of the cases discussed.

f) ROUTINE INVESTIGATIONS

In addition to routine clinical examination, certain investigations must be carried out in every patient receiving cytotoxic drugs. The investigations carried out in this study may be grouped as follows.

1. Haematology

a) Haemoglobin
b) Packed-cell volume
c) Erythrocyte sedimentation rate
d) Total white cell count
e) Differential white cell count
f) Platelet count
g) Reticulocyte count
h) Bone marrow examination.

The haemoglobin, packed cell volume, erythrocyte sedimentation rate, white cell count and differential white cell count and platelet count were carried out in every case prior to commencement of cytotoxic therapy. In many cases the reticulocyte count was also estimated. These investigations were repeated at frequent and often daily intervals during the course of cytotoxic treatment and continued at weekly or two-weekly intervals while the patient remained /

remained under observation. Examination of the bone marrow was carried out in the majority of patients prior to treatment and again at intervals of 1 to 6 months after.

In the management of patients receiving anti-cancer drugs, accurate, reliable and readily available haematological investigations are essential.[75] Treatment schedules must be based on current blood counts and not on those obtained days or weeks previously. It is also important to obtain absolute values rather than percentages. A rapidly falling haemoglobin or white cell count may be the first indication of severe toxic effects on the bone marrow and serve as an indication that administration of the drug must temporarily cease. A falling platelet count is of less significance and treatment may be safely continued with smaller amounts of drug, despite low platelet counts.

Examination of the bone marrow is of diagnostic value in malignant disorders of the reticulo-endothelial system and blood-forming organs, but also allows accurate assessment of the toxic effects being produced by the use of anti-cancer drugs.

2. Biochemistry

a) Liver function tests

I. serum bilirubin
II. alkaline phosphatase
III. thymol turbidity
IV. zinc sulphate turbidity
V. serum glutamic oxaloacetic transaminase
VI. serum glutamic pyruvic transaminase
VII. bromsulphthalein excretion
VIII. plasma proteins.

b) /

b) Serum electrophoresis
c) Serum uric acid.

The toxicity of anti-cancer drugs is largely due to their effects on normal, rapidly dividing cells particularly those of the bone marrow, liver and intestinal tract. The possibility that these agents may produce sufficient damage to cause jaundice is an indication for the routine investigation of liver function by standard tests such as serum bilirubin, alkaline phosphatase, zinc sulphate turbidity, thymol turbidity, S.G.O.T. and S.G.P.T. These tests were carried out before the administration of cytotoxic drugs, within 7 to 14 days of commencing treatment and at intervals of 1 to 3 months thereafter.

Frequent determinations of the plasma proteins were made and the serum electrolytes estimated when they have otherwise been indicated. In addition, this study has included routine estimation of serum electrophoresis and uric acid before and at intervals after the commencement of cytotoxic therapy. The significance of these will be elaborated in the discussion.

These various tests must be carried out accurately and the results should be available before treatment is commenced, changed or continued.

3. Radiology

a) Routine diagnostic investigations
b) /

b) Chest
c) Pelvis and spine
d) Serial X-rays of metastatic sites
e) Follow-up X-rays of inoperable alimentary tract neoplasms.

In addition to the radiological investigations carried out to determine the nature of the primary disease, and the extent of known or suspected deposits, routine X-rays of the chest, pelvis and spine have been obtained to establish the existence of otherwise unsuspected metastases. Serial X-ray examination of known metastatic sites at intervals of one week to six weeks have also been obtained. In addition, follow-up X-rays of alimentary tract neoplasms, originally found inoperable, have been carried out in an attempt to assess response to treatment.

4. Bacteriology

a) Urine
b) Sputum
c) Blood
d) Wounds
e) Superficial tumours.

The possibility that cytotoxic drugs lower host resistance to infection has been considered throughout this study. Repeated bacteriological examination of urine, sputum and blood specimens for pathogenic organisms have been carried out before and at intervals after commencing cytotoxic therapy. Careful bacteriological control of all intercurrent infections, of infected wounds and of superficial tumour discharge has also been undertaken.

5. Photography /

5. Photography

The use of photography in clinical cancer chemotherapy finds its greatest value in assessing response to treatment which produces a change in the appearance of a superficial tumour or in visible skin and glandular deposits. Photography is also of value for recording the occurrence and course of toxic effects, such as skin rashes, buccal ulceration and cutaneous pigmentation.

6. Pathology

a) Histological.- The histological confirmation of malignancy was obtained in every case prior to commencing treatment. In the majority of cases the tissue for histological examination was obtained from the primary tumour. In others the tissue was obtained from deposits in lymph glands, liver, skin or omentum. In these cases the primary site was established at laparotomy, by X-ray examination, or at autopsy. In four cases the primary site could not be determined by appropriate investigation and in one was still not identified at post-mortem.

All tumours in this series were histologically graded in order that a final assessment might be made of the relationship between tumour grade and response to cytotoxic therapy. It was hoped to study in detail changes in morphology of a tumour following exposure to cytotoxic therapy.[76] Although it was possible in a few cases to obtain serial /

serial biopsies for this purpose, in the majority it was only possible to make this assessment on the basis of material initially obtained from the primary tumour or its metastases and that ultimately obtained at post-mortem. As a result of rapid tissue autolysis and necrosis, much of this post-mortem material proved valueless. The assessment of morphological change is further made difficult by the lack of information on the changes which occur with time during the natural history of untreated tumours and this aspect of the study was largely abandoned.

Histochemical techniques to determine such things as changes in cell enzyme content and activity with cytotoxic therapy, have not been employed in this study.

b) Macroscopic.- Post-mortem examination was obtained in only 42 (54%) of the 78 deaths in this series. It was hoped to obtain a much higher percentage, but many patients died at home and suitable arrangements for post-mortem examination could not be made. In those cases in which it was carried out particular note was made of the site and extent of the primary tumour, the sites and extent of metastases and the presence of such features as obvious necrosis or marked fibrosis. In those cases in which the primary tumour had either been removed or found inoperable at laparotomy, interest was concentrated on the extent of recurrence or extension at the primary site. Careful note was also made of the existence of such features as pericarditis, unsuspected pleural or peritoneal effusions and changes in the adrenal glands, bone marrow and liver where these were not /

not the site of overt metastases. An attempt was made in each case to assess the approximate bulk of primary and metastatic tumour present in each case. This was subsequently compared with the nature and duration of cytotoxic therapy, with the occurrence of toxic effects, intercurrent infection and other features, as a clinical assessment of the concept that cytotoxic drugs may occasionally act in a harmful manner by suppressing "immunity mechanisms". In a few cases post-mortem examination was of value in correcting a previously wrong clinical diagnosis of site and nature of primary tumour. In those cases not submitted to post-mortem examination, the nature of the primary tumour was established with confidence by clinical, X-ray and biochemical investigation, in all but the four cases previously discussed.

g) LABORATORY RESEARCH INVESTIGATIONS

I. Lymphocyte Transformation

The *in vitro* transformation of lymphocytes by phyto-haemagglutinin has proved of great importance in elucidating the role of the lymphocyte in antigen-antibody reactions and in the body immune defence mechanisms. Certain malignant conditions, particularly those involving the reticulo-endothelial system, react in some manner, as yet unknown, to alter the immune response of the host, usually in favour of the tumour.[3] By studying lymphocyte transformation in *in vitro* culture it was hoped to investigate /

investigate the immune response of patients before and after the administration of cytotoxic drugs.

The technique involved the separation of the buffy layer from a 20 ml. sample of venous blood, the isolation of lymphocytes and their culture in tissue culture media. Phytohaemagglutinin was then added to the cultures and the rates and stages of transformation following cytotoxic therapy compared with those observed before treatment. The results obtained in this investigation were limited by the sensitivity of the lymphocytes *in vitro* to even minute dilutions of cytotoxic agent so that the cultures were regularly arrested and cell disintegration produced. The technique was abandoned.

II. Chromosome Changes

As a byproduct of this work, however, chromosome smears were obtained by spreading cultures, arrested in metaphase by colchicine, on slides frozen on carbon dioxide snow. It was found that pleural effusions were most suitable for producing cells for this purpose, but the facilities available did not allow accurate description of the chromosome configurations encountered.

III. Red Cell Survival Studies [77]

The development of anaemia is a common event in the course of malignant disease. In some cases, however, the degree of anaemia is out of proportion to the stage of the disease and cannot be attributed to/

to blood loss or the effects of radiotherapy or chemotherapy.

The "anaemia of malignancy" may result from the action of a haemolytic process, from maturation defects or from a reduction in the life-span of the red cell. It was considered that a reduction in the normal 100 to 120 day life-span of red cells may occur more frequently in cancer than has previously been thought and that further reduction might follow the use of cytotoxic agents. Red cell survival studies were accordingly carried out in ten patients before and at some stage after the administration of cytotoxic drugs. The technique consisted of "tagging" the red cells of a 20 ml. sample of the patients blood with radio-active chromium ^{51}. The sample was then re-injected at a stated time and the dose of radioactivity given was noted - usually 100 µc. Eight samples of red cells (10 ml.) were taken over the following twenty-one days and assayed for chromium ^{51} activity. By this means it was possible to calculate red cell survival times.

In five cases the red cell survival time was abnormal before treatment commenced, e.g. 40 days in Case No. 104, and was further reduced by cytotoxic agents. In four cases, survival time was normal initially and only minimal impairment followed cytotoxic therapy. In the remainder, the results were normal throughout.

In the five cases showing abnormally low survival times, radio-active scanning was carried out over the spleen to detect evidence of abnormal breakdown of red cells in this site. Evidence of increased breakdown was obtained in only one of these, Case No.2, in /

in whom the spleen was grossly enlarged (Case No.2; Fig. 1). This demonstration that patients with malignant disease have, in some cases, a loweredred cell survival time which can be further reduced by cytotoxic agents, is of significance in the causation and management of the anaemia of malignancy. The use of routine haematinic preparations in these cases is unsatisfactory and repeated blood transfusions are required to maintain normal haemoglobin and red cell levels.

In the five cases demonstrating an initial reduction in red cell survival time, three had urobilinogen in the urine and one of these had a positive Coomb's test. In the remaining two patients there was no evidence of abnormal haemolysis. Bone marrow studies in these five cases showed varying degrees of hypoplasia of all cell elements, but there was no gross deficiency in the erythroid series. It would appear, therefore, that the survival time in these cases is reduced partly as a result of circulating haemolysins, but may be also due to an intrinsic defect in the structure or function of the red cells, resulting in increased fragility and premature disintegration. The influence of cytotoxic agents on these mechanisms requires further study.

ASPECTS OF CANCER CHEMOTHERAPY

SECTION V

RESULTS

a) Tabulated Results

TABLES 1 - 19	Case Abstracts: Diagnosis, History, Treatment, Progress and Result
TABLE 20	Duration of Survival
TABLE 21	Agents Used
TABLE 22	Use of Hormones
TABLE 23	Methods of Application
TABLE 24	Routes of Administration
TABLE 25	Results of Liver Function Tests, Serum Proteins, Electrophoresis and Uric Acid
TABLE 26	Post-mortem Examinations
TABLE 27	Assessment of Response to Cytotoxic Therapy
TABLE 28	Patterns of α_2 Globulin and Uric Acid by Principal Tumour Groups
TABLE 29	Patterns of Liver Function Tests by Principal Tumour Groups
TABLE 30	Nature and Incidence of Toxic Effects
TABLE 31	Nature, Incidence and Severity of Toxic Effects
TABLE 32	Nature of Supportive Therapy
TABLE 33	Causes of Death

Section V (contd.)

RESULTS

b) Assessment of Response to Treatment in Principal Tumour Groups

Pages 52 - 59

RESULTS

The results obtained in this study have been detailed in Table form and are incorporated in Tables 1 to 33, inclusive. The assessment of these results, when the tables are not self-explanatory, is included in appropriate sections of the Discussion.

The difficulties of obtaining complete follow-up results in patients with advanced malignant disease are self-evident. It is considered, however, that sufficient data is presented to draw worthwhile conclusions, although no attempt has been made to give them statistical significance. It is to be noted that the detailed day to day results of the haematological investigations have not been included, because of their enormous bulk. Representative examples have been plotted in graph form and are found in relation to the case synopses, Tables 1 to 19, inclusive. Also included in relation to the Case synopses, are the relevant clinical photographs, arranged by Case number.

KEY TO TABLES 1 - 19

0 = No benefit or harmful

1 = Symptomatic relief only

2 = Good symptomatic and objective response

3 = Complete remission

CHEMOTHERAPY OF CANCER

KEY TO GRAPHS OF PERIPHERAL BLOOD COUNTS

GRAPH A	: TOTAL WHITE CELL COUNT	:	
	POLYMORPHS	:	
	LYMPHOCYTES	:	
GRAPH B	: HAEMOGLOBIN	:	
	PLATELET COUNT	:	

ABBREVIATIONS FOR CYTOTOXIC AGENTS : SEE APPENDIX I

BLOOD TRANSFUSION : ONE PINT :

GROUP A : HODGKIN'S DISEASE

Table 1a

Case: 1	J.G. 17/8/60	Age: 23	Sex: F
Diagnosis:	Hodgkin's disease. (Biopsy of axillary gland.)		
History:	First noted painless glands in (L) axilla - July 1960. No other symptoms, but found to have widespread lymphadenopathy. No relevant previous or family history.		
Previous or concurrent treatment:	(1) Radiotherapy:	3000r to (L) side neck) 3500r to (L) axilla)	1/9/60-21/9/60
		3000r to lumbar spine	13/6/61-6/7/61
		3000r to (R) side neck) 2600r to (R) axilla)	28/11/61-14/12/61
		3400r to mediastinum	16/1/64-7/2/64
	(2) Haematinics:	Intermittently	
	(3) Prednisone:	2.5-15 mg. daily	14/9/61-16/9/62
Cytotoxic treatment:	(1) Chlorambucil:	580 mg. orally (4 mg./day)	22/8/60-4/1/61
	(2) Vinblastine sulphate:	106 mg. by I.V.I. 32 mg. by I.V.I.	15/1/62-10/5/62 11/10/62-5/12/62
Clinical course and comments:	Clinically acute form of Hodgkin's disease when first diagnosed. Disease controlled by serial courses of radiotherapy to both sides of neck, axillae, spine and mediastinum between September 1960 and December 1961. Chlorambucil 4 mg. daily to 580 mg. was given with above courses of radiotherapy. Readmitted with generalised relapse January 1962 but marked regression of disease process obtained with vinblastine. Treatment suspended May 1962 when patient became pregnant - but aborted at 16 weeks. Further relapse in October 1962 again responding to treatment with vinblastine. Intermittently experienced mild backache, frequency of micturition, easy fatigue and wheeziness but no further recurrence of disease process until January 1964. Mediastinal recurrence treated with radiotherapy without undue incident. At last review 12/3/64 was well with continued remission of disease. Symptoms well controlled by combination of cytotoxic therapy and radiotherapy.		
Autopsy report:	-		
Result:	2-3 for 3 years 8 months		

Table 1b

Case: 2	P.O'S. 5/3/62 Age: 39 Sex: M	
Diagnosis:	Hodgkin's disease. (Biopsy of neck gland.)	
History:	Histologically proven Hodgkin's disease August 1957 treated by radiotherapy. Remained symptom-free until March 1962 when patient admitted with pain in back and (L) hypochondrium troublesome for two months. No other significant symptoms. No relevant family history.	
Previous or concurrent treatment:	(1) Radiotherapy: to neck and mediastinum - 1957. Details not known.	
	(2) Blood transfusions: total of 44 pints of whole blood.	18/4/62-1/7/63
	(3) Antibiotics: including tetracycline, erythromycin, ampicillin and chloramphenicol in interrupted courses	11/4/62-20/7/63
	(4) Prednisone: 25-40 mg./day orally	2/2/63-20/7/63
Cytotoxic treatment:	(1) Mannitol mustard: 1,000 mg. by I.V. drip	9/3/62-13/3/62
	1,000 mg. by I.V. drip	16/3/62-21/3/62
	1,000 mg. by I.V. drip	22/10/62-27/10/62
	1,000 mg. by I.V. drip	30/10/62-4/11/62
	(2) Vinblastine sulphate: 16 mg. by I.V.I.	16/3/63-27/3/63
	(3) Nitrogen mustard: 47 mg. by I.V.I.	2/4/63-20/4/63
	(4) Vinblastine sulphate: 49.5 mg. by I.V.I.	21/5/63-2/7/63
	(5) Cyclophosphamide: 2,400 mg. orally	1/6/63-2/7/63
	(6) Uracil mustard: 75 mg. orally	2/7/63-21/7/63
Clinical course and comments:	Admitted in March 1962 with hepato-splenomegaly and obvious relapse after five years' control of disease by radiotherapy. Good response to initial course of mannitol mustard (2 x 1,000 mg.) but further relapse in October 1962 - main feature being massive splenomegaly. Short-lived remission following second 2,000 mg. course of mannitol mustard but severe depression of bone marrow function and infective complications. Reasonably well for 4 months and then further relapse responding on this occasion to vinblastine. Degree of hyper-splenism demonstrated and repeated blood transfusions required. Never fit enough for elective splenectomy and prednisone exhibited. From May 1963 symptoms steadily progressive and only temporary response obtained to further therapy with cytotoxins singly and in combination. Severe chest involvement terminally and died suddenly 21/7/63. Initial response to chemotherapy good but thereafter disease process steadily advancing despite protracted cytotoxic and supportive therapy.	
Autopsy/		

Table 1b (continued)

Autopsy report:		Right-sided heart failure due to pulmonary Hodgkin's disease and chronic bronchitis. Haemolytic anaemia due to hypersplenism. Pigment gallstones. Generalised involvement of reticuloendothelial system by Hodgkin's disease. Considerable hypoplasia of marrow.
Result:		2-3 for 14 months

Case No. 2: Hodgkin's Disease

Fig. 1: Massive Splenomegaly : Hypersplenism

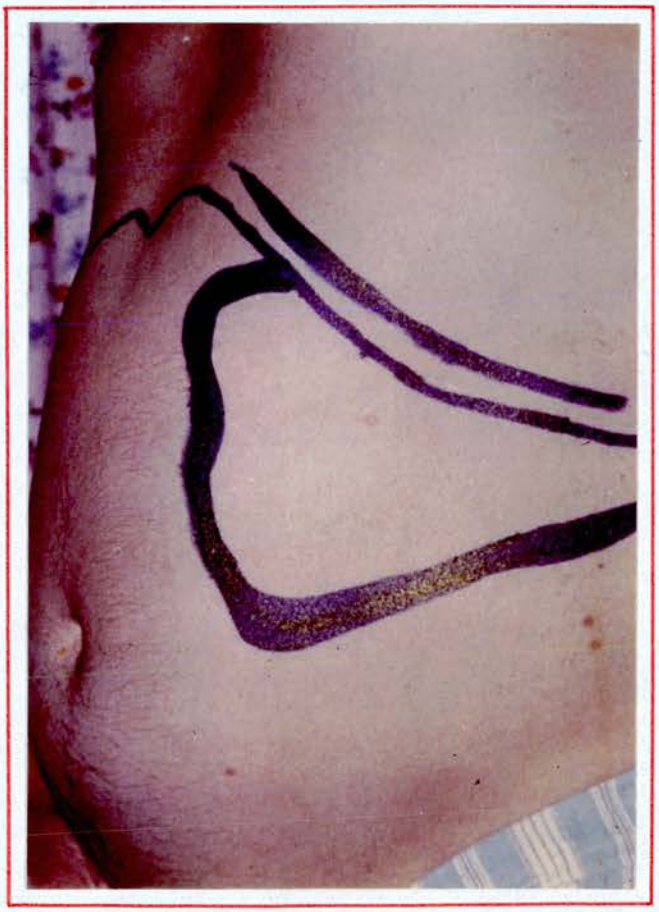


Table 1c

Case: 3	G.R. 9/7/62 Age: 26 Sex: M	
Diagnosis:	Hodgkin's disease	
History:	Accidentally noted swelling in (R) side of neck while shaving - June 1962. No other significant symptoms.	
Previous or concurrent treatment:	(1) Radiotherapy: 4,000r to (R) side neck) 3,500r to mediastinum)	8/10/62-9/11/62
	(2) Marrow extraction:	12/3/63
	(3) Marrow replacement:	14/3/63
	(4) Blood transfusions: total of 6 pints	13/3/63-14/6/63
	(5) Antibiotics:	
	(6) Haematinics:	
Cytotoxic treatment:	(1) Nitrogen mustard: 30 mg. by I.V.I.	18/7/62-22/7/62
	(2) Mannitol mustard: 1,000 mg. by I.V. drip	25/7/62-29/7/62
	1,500 mg. by I.V. drip in 24 hours	12/3/63
	400 mg. orally	8/4/63-8/5/63
	(3) Vinblastine sulphate: 71 mg. by I.V.I.	21/5/63-1/8/63
	(4) Nitrogen mustard: 18 mg. by I.V.I.	7/8/63-12/8/63
	(5) Cyclophosphamide: 2,100 mg. by I.V. drip	4/9/63-5/9/63
	500 mg. by I.V.I.	13/9/63
Clinical course and comments:	Acute Hodgkin's disease with extensive involvement of mediastinum. Moderate response to initial course of nitrogen mustard and mannitol mustard (July, 1962) but mediastinum little improved. 3 month remission following radiotherapy (October, 1962) and then progressive relapse. 4 month remission following second course of mannitol mustard and a course of vinblastine sulphate (March-May 1963). Thereafter progressive mediastinal and pulmonary involvement not responding to continued treatment. Died in respiratory failure 25/9/63.	
Autopsy report:	Acute corpulmonale and respiratory failure due to mediastinal obstruction secondary to Hodgkin's disease. Deposits of Hodgkin's tissue in liver, spleen and lymph nodes. Hypoplasia of bone marrow.	
Result:	2-3 for 12 months	

Table 1d

Case: 4	J.B. 17/8/62 Age: 19 Sex: M
Diagnosis:	Acute Hodgkin's disease. (Gland biopsy (R) pectoral region.)
History:	First admitted to another hospital on 14/7/62 with a history of a five-day febrile illness two months previously with spontaneous recovery. Vague general malaise, easy fatigue and lassitude persisted. Anorexia marked and progressive weight loss ($1\frac{1}{2}$ stones). Upper abdominal pain and diarrhoea for 1 week. Investigated as a case of P.U.O. and diagnosis established by gland biopsy.
Previous or concurrent treatment:	(1) Antibiotics: (2) Blood transfusion: total of 31 pints of whole blood 18/8/62-11/6/63 (3) Prednisone: 20-100 mg./day orally 21/8/62-28/6/63
Cytotoxic treatment:	(1) Vinblastine sulphate: 110 mg. by I.V.I. 4/10/62-8/12/62 (2) Nitrogen mustard: 76 mg. by I.V.I. 4/1/63-25/1/63 (3) Mannitol mustard: 1,500 mg. orally 11/4/63-26/4/63 (4) Imuran: 26 G. orally 19/3/63-30/5/63
Clinical course and comments:	Running high grade pyrexia on admission and not responding to prednisone. Within two weeks of commencing vinblastine marked subjective and objective improvement was evident. Continued improvement with gain in weight and control of fever; marked effects of prednisone, however, apparent. Moderate control until January 1963 when readmitted with recurrent lymphadenopathy, anorexia and high pyrexia. Marked, but short-lived remission of symptoms following a course of nitrogen mustard. Thereafter course rapidly progressive with widespread adenopathy, high swinging pyrexia, profuse sweating and weight loss. Symptoms only temporarily relieved by further courses of mannitol mustard and imuran. Deteriorated to death in coma on 29/6/63. Fulminating disease running rapid course. Gross striae formation trunk and chest. Disease process only temporarily relieved by cytotoxic treatment.
Autopsy report:	Marked striae on trunk and chest - cortisone effect. Widespread involvement of lymph nodes of neck, mediastinum and abdomen - particularly marked in para-aortic nodes. Many glands demonstrated necrosis.
Result:	1-2 for 10 months

Case No. 4

Fig. 1: Chest X-ray 21/7/62.

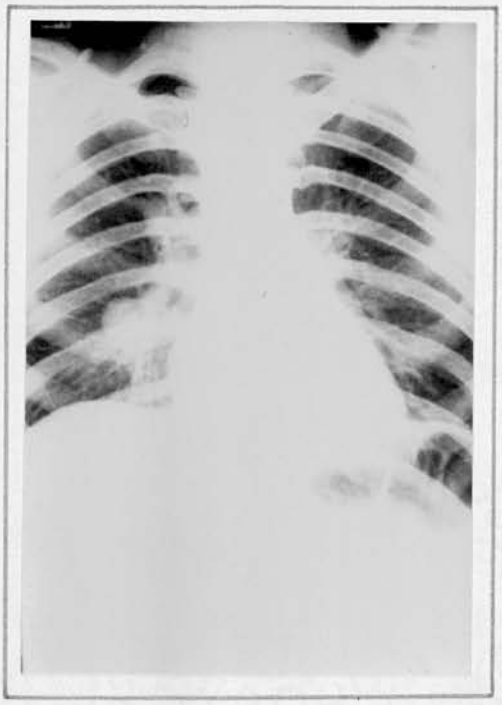


Fig. 2: Chest X-ray 25/9/62.

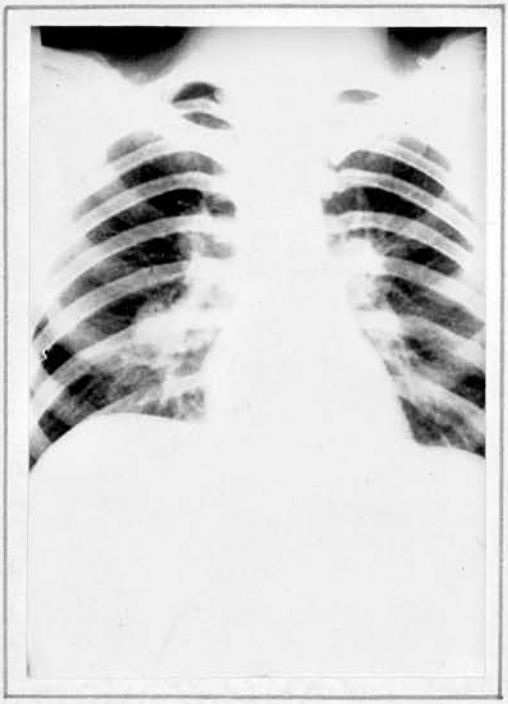


Fig. 3: Chest X-ray 27/11/62.

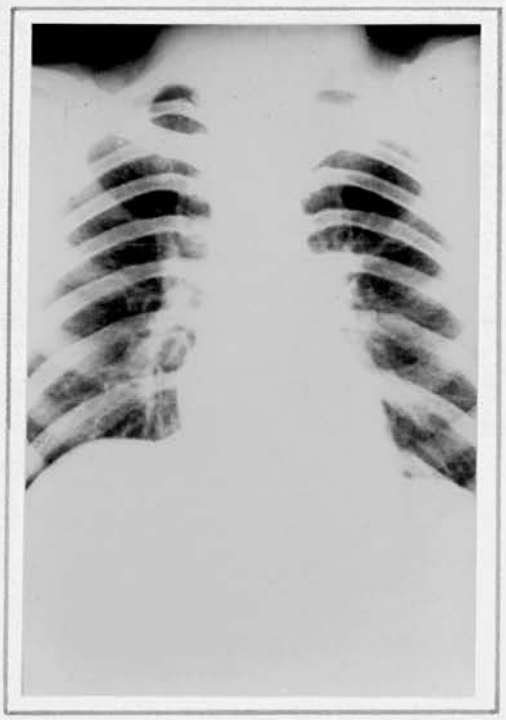
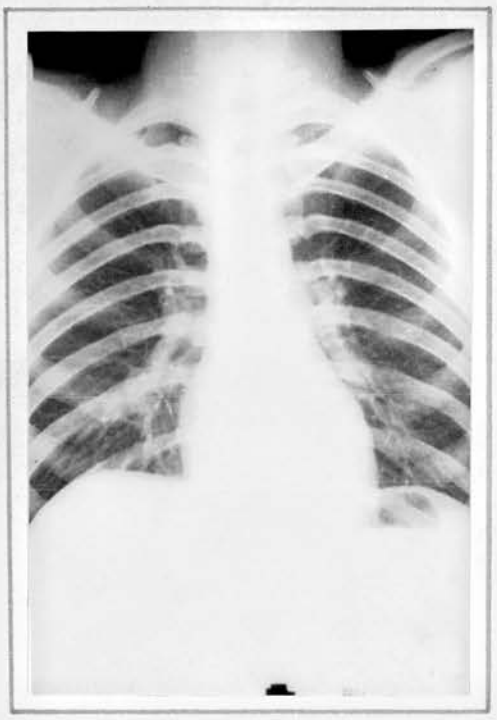


Fig. 4: Chest X-ray 22/1/63.



Case No. 4.

Fig. 5: Chest X-ray 25/3/63.

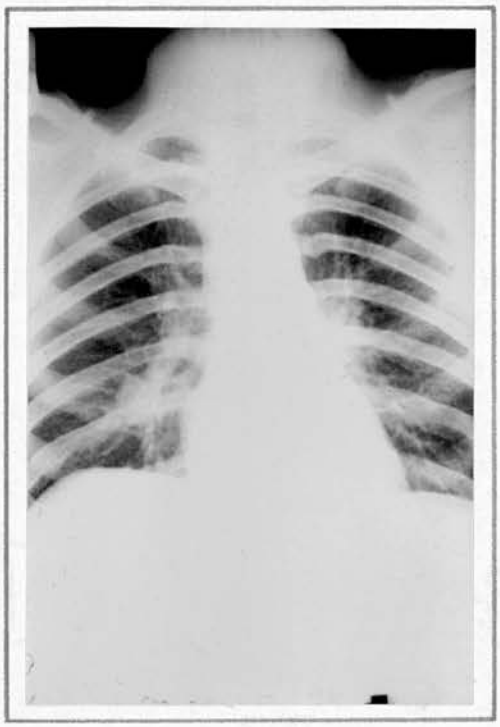


Fig. 6: Chest X-ray 7/6/63.

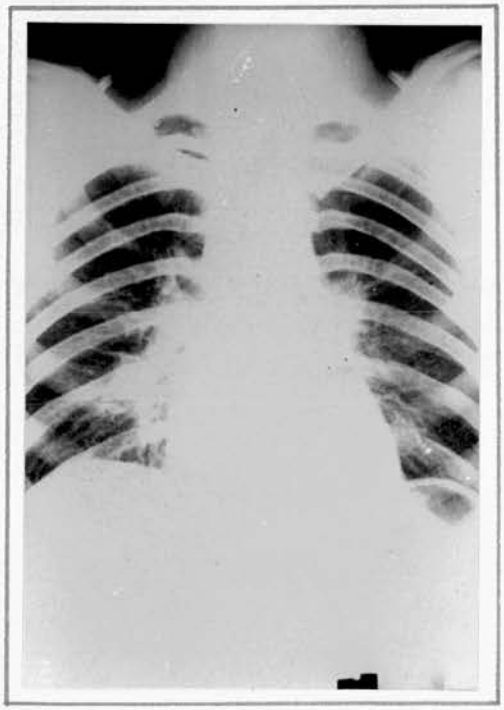


Table 1e

Case: 5	W.McG. 15/10/62 Age: 50 Sex: M
Diagnosis:	Hodgkin's disease and carcinoma of lung. Histology: Biopsy of gland (R) axilla on two occasions and tumour removed at pneumonectomy.
History:	Increasing malaise, weight loss and productive cough for 3 months. No relevant family or previous history. Non-smoker.
Previous or concurrent treatment:	(1) (R) pneumonectomy: 20/9/62 (2) Excision of glands (R) axilla: 25/10/62 (3) Radiotherapy: 4,000r to abdominal gland mass 20/2/62-19/3/62 (4) Antibiotics:
Cytotoxic treatment:	(1) Nitrogen mustard: 20 mg. by I.V.I. (operation cover) 22/10/62-24/10/62 (2) Mannitol mustard: 1,000 mg. by I.V. drip 31/10/62-4/11/62 1,000 mg. by I.V. drip 7/11/62-11/11/62
Clinical course and comments:	First admitted 4 weeks after pneumonectomy - ill, pyrexial with axillary and abdominal gland masses - Hodgkin's disease. Initial good response to mannitol mustard, but recovery delayed by chronic (R)-sided empyema requiring repeated aspiration and antibiotic treatment. Short periods only out of hospital. Development of severe epigastric pain prompted treatment with radiotherapy - temporary remission only. Progressive symptoms and signs of Addison's disease. Terminal stage short and died 24/1/63. Case of interest from apparent presence of dual pathology but post-mortem examination failed to confirm presence of Hodgkin's disease.
Autopsy report:	Widespread deposits of adenocarcinoma from carcinoma (R) lower lobe bronchus. Carcinomatous replacement of both adrenals. Involvement of glands in chest, neck and abdomen by poorly differentiated adeno-carcinoma. No evidence of Hodgkin's disease in any tissue examined. (R) hemi-thorax partly filled by solid tumour with small blood-stained effusion above it. Addison's disease.
Result:	2-3 for 6 months.

Table 1f

Case: 6	G.C. 9/4/62 Age: 22 Sex: M
Diagnosis:	Hodgkin's disease. (Biopsy of neck gland.)
History:	Swellings in both sides of neck; first noted on (R) side four weeks previously and on the (L) one week previously. Dry, non-productive cough for 2 months. Occasional night sweats - 2 months. Loss of 6 lb. in 3 months. No relevant family or previous history.
Previous or concurrent treatment:	(1) Radiotherapy: 200r to mediastinum 25/4/62 (course interrupted because of severe reaction) 3,000r to both sides of neck and axillae 21/3/63-16/5/63 (2) Antibiotics:
Cytotoxic treatment:	(1) Nitrogen mustard: 30 mg. by I.V.I. 7/5/62-11/5/62 (2) Mannitol mustard: 1,000 mg. by I.V. drip 14/5/62-19/5/62 2,000 mg. by I.V. drip over 24 hours 18/10/62 (3) Chlorambucil: 250 mg. orally 14/12/62-14/3/63 184 mg. orally 10/10/63-19/12/63 (4) Mannitol mustard: 600 mg. orally 19/12/63-11/1/64 (5) Vinblastine sulphate: 86 mg. by I.V.I. 19/12/63-6/3/64 (6) Cyclophosphamide: 1,800 mg. by I.V.I. 11/1/64-21/1/64 900 mg. orally 1/2/64-7/2/64
Clinical course and comments:	Presenting with acute Hodgkin's disease affecting glands of neck and mediastinum. Rapidly became seriously ill. Initial dose of radiotherapy (200r) produced rapid and severe oedema of neck and chest wall with gross swelling of neck glands - treatment stopped and cytotoxins used alone. Marked improvement following mannitol mustard and discharged 5/6/62. Remained well until October 1962 when readmitted with severe relapse - bull-neck, sweating, large gland masses in axillae and mediastinum. Further marked remission with mannitol mustard but haemopoeisis severely depressed for 3 weeks. Remained in remission for 5 months. Then widespread recurrence of disease on this occasion responding without incident to radiotherapy. Further recrudescence of disease in October 1963 but good control maintained to last review 17/2/64 with various cytotoxins either singly or in combination.
Autopsy report:	-
Result:	2-3 for 10 months

Table 1g

Case: 7	R.P. 8/1/64 Age: 17 Sex: M
Diagnosis:	Acute Hodgkin's disease. (Biopsy of axillary gland)
History:	Three week history of general malaise, pyrexia, sweating, anorexia, pain in the back and abdomen and loss of 2 st. in weight. No relevant previous or family history.
Previous or concurrent treatment:	(1) Blood transfusion: 2 pints whole blood 11/1/64 (2) Antibiotics: (3) Aspiration of (L) pleural effusion: 300 ml. 22/1/64 (4) Prednisone: 40-60 mg./day orally 18/1/64-14/2/64
Cytotoxic treatment:	(1) Nitrogen mustard: 20 mg. by I.V.I. 9/1/64-12/1/64 (2) Cyclophosphamide: 3,000 mg. by I.V.I. 16/1/64-7/2/64
Clinical course and comments:	Gravely ill on admission with gross abdominal tenderness and generalised tender lymphadenopathy. Initial rapid response to nitrogen mustard so that by 13/1/64 he was apyrexial, his abdominal tenderness was much less marked and all nodes were smaller. Rapid return of pyrexia, tachycardia, pleural effusion and adenopathy. By 18/1/64 was demonstrating gross respiratory distress and his condition was critical. Prednisone and cyclophosphamide produced marked improvement which was maintained for 3 weeks. Thereafter he again developed increasing, tender lymphadenopathy, gross abdomen distension and tenderness, hepatosplenomegaly, pyrexia, and pleural effusion. Peripheral circulatory failure ensued and he died in coma on 15/2/64, 6 weeks from onset of symptoms.
Autopsy report:	Widespread deposits of Hodgkin's tissue in liver, spleen, kidneys, pancreas, and bone marrow. Gross involvement of lymph glands in all areas. Bilateral blood-stained pleural effusions.
Result:	1 for 4 weeks.

Case No. 7

Fig. 1: Chest X-ray 6/1/64.

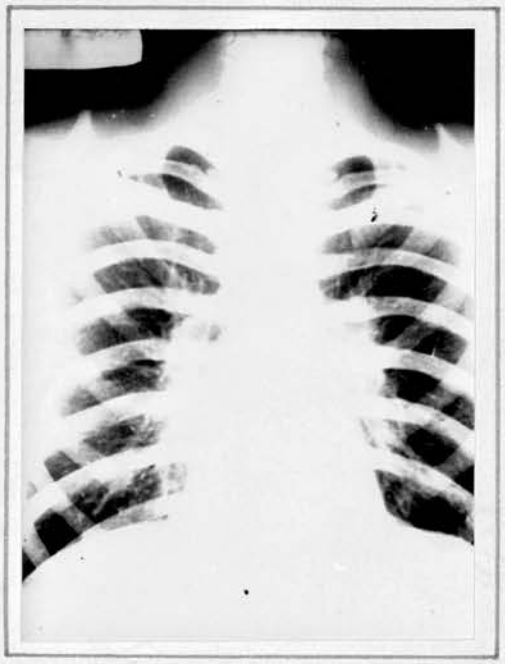


Fig. 2: Chest X-ray 17/1/64.

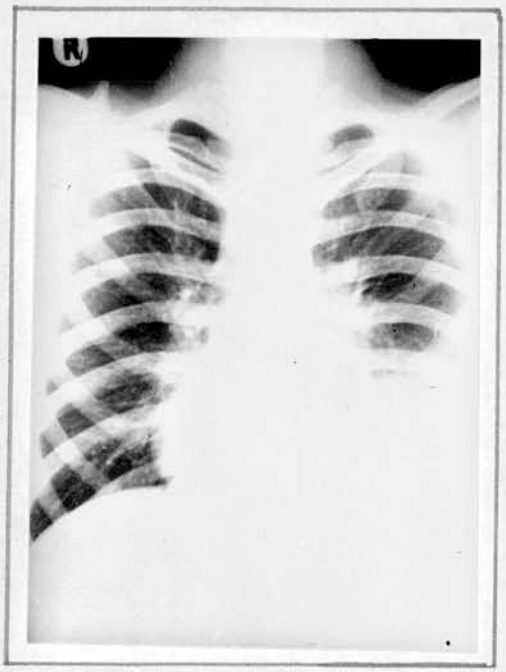


Fig. 3: Chest X-ray 29/1/64.

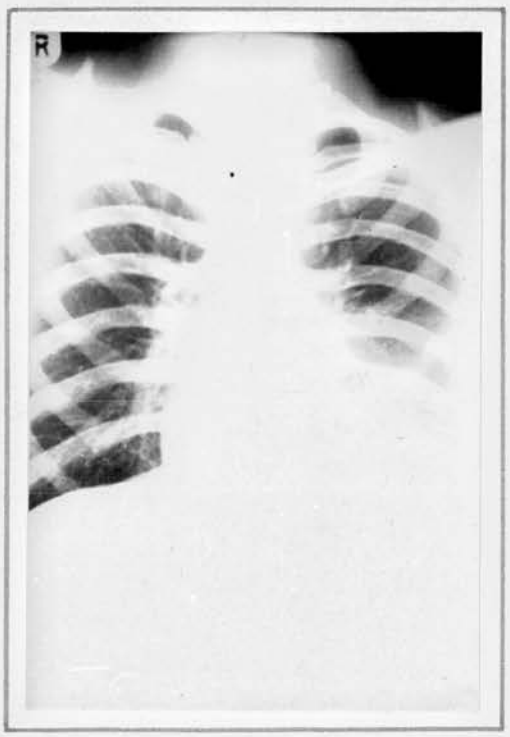
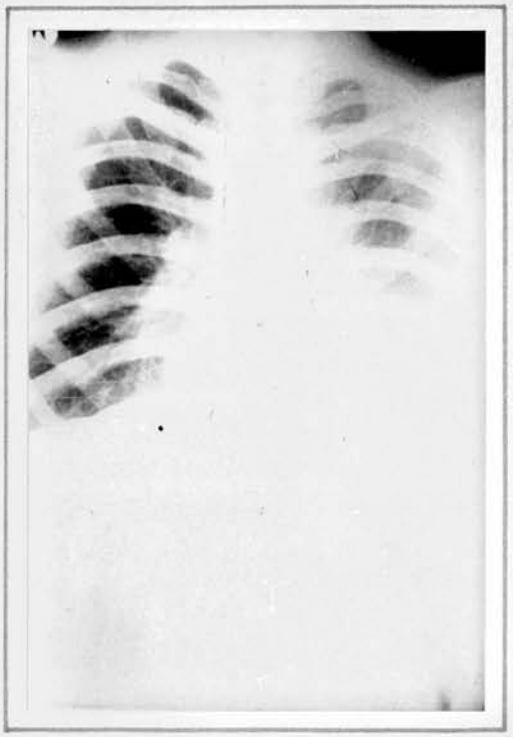


Fig. 4: Chest X-ray 11/2/64.



GROUP B : CARCINOMA OF LUNG

Table 2a

Case: 8	A.A.W. 24/11/61 Age: 53 Sex: M
Diagnosis:	Carcinoma of (R) lower lobe bronchus. (Biopsy of fungating mass in (R) lower lobe bronchus at bronchoscopy 22/11/61)
History:	One week's pyrexial illness with (R) sided chest pain and productive cough five months prior to admission. Chest X-ray at that time (July, 1961) suggested an inflammatory lesion (R) base and patient treated with antibiotics. Symptoms resolved, but two subsequent chest X-rays revealed little change in (R) lower zone. Reported again in November 1961 with increasing anorexia, lassitude and productive cough. Bronchoscopy now confirmed bronchogenic neoplasm.
Previous or concurrent treatment:	(1) Antibiotics: July 1961 and intermittently between 26/2/62 and 21/5/63 (2) Radiotherapy: 6,505r to primary 28/11/61-22/1/62 (3) Chlorpromazine: 25 mg. B.I.D. orally 11/1/63-25/6/63
Cytotoxic treatment:	(1) Cyclophosphamide: 1,000 mg. by I.V.I. 11/1/63-15/1/63 21,100 mg. orally 16/1/63-25/6/63 (2) Vinblastine sulphate: 24 mg. by I.V.I. 30/5/63-18/6/63
Clinical course and comments:	Patient remained well for one year following radiotherapy with gain in weight and only mild to moderate breathlessness on exertion. Required intermittent courses of antibiotics to control episodes of productive cough. Readmitted 10/1/63 with hepatic metastases and slow, general deterioration. Started cyclophosphamide 11/1/63. Remained out of hospital and reasonably well for 4 months before being readmitted following a brief haemoptysis. Thereafter became listless, apathetic and deteriorated to death at home on 26/6/63.
Autopsy report:	Not obtained - died at home.
Result:	3 for 1 year and 2-3 for 5 months.

Case No. 8: Carcinoma of Lung

Fig. 1: Chest X-ray 27/2/60.

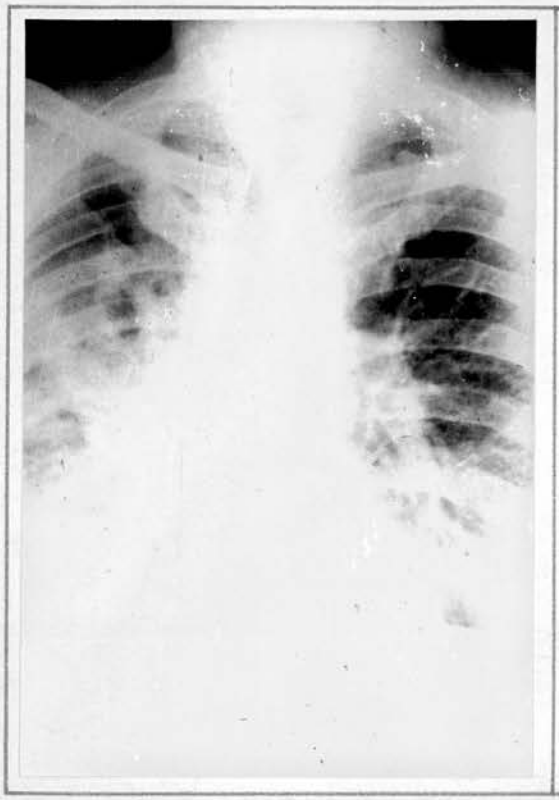


Fig. 2: Chest X-ray 6/12/61.

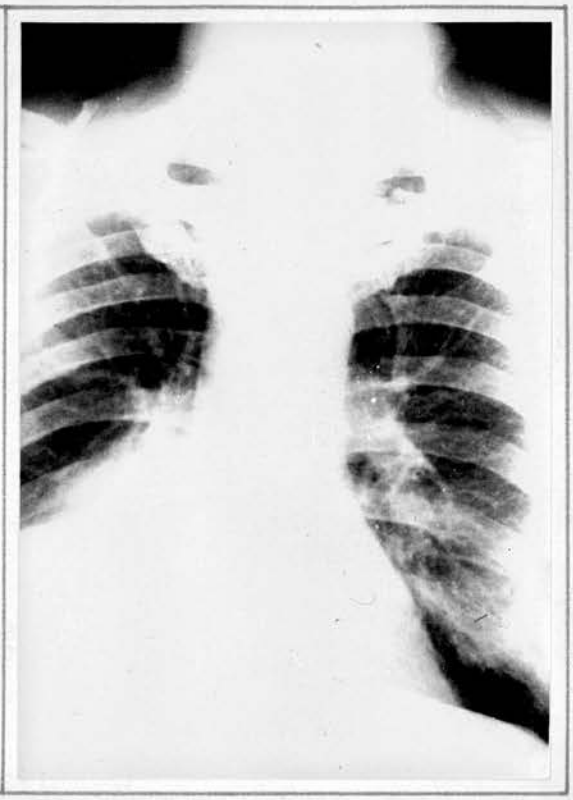


Fig. 3: Chest X-ray 16/8/62.

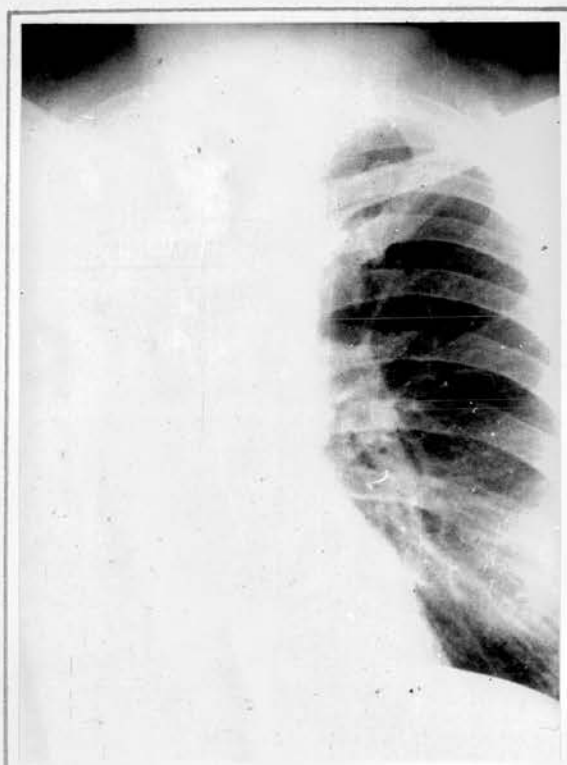


Fig. 4: Chest X-ray 18/6/63.

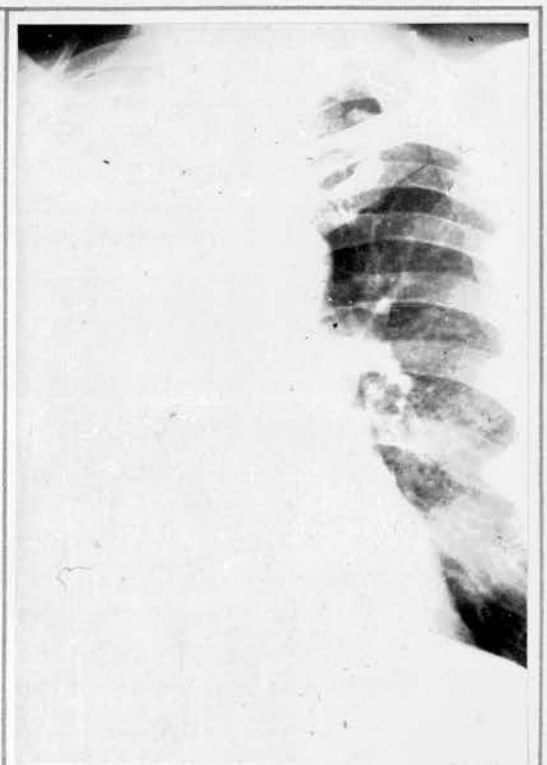


Table 2b

Case: 9	J.C.G. 22/9/62	Age: 39	Sex: M
Diagnosis:	Carcinoma of the larynx. (Biopsy of (L) vocal cord)		
History:	Increasing hoarseness for 9 months; no pain cough or dysphagia. Had smoked 40 cigarettes a day for 15 years. Intrinsic carcinoma of larynx revealed by laryngoscopy and biopsy.		
Previous or concurrent treatment:	(1) Radiotherapy:	6,440r to primary lesion	2/10/62-9/11/62
	(2) Laryngectomy:	2/8/63	
	(3) Radiotherapy:	1,000r to neck glands	12/10/63-18/10/63
Cytotoxic treatment:	(1) Cyclophosphamide:	4,225 mg. by I.V. drip	28/10/63-5/11/63
	(2) Vinblastine sulphate:	6 mg. by I.V.I.	30/10/63-4/11/63
Clinical course and comments:	Well for 7 months following radiotherapy and then developed pain beneath (L) ear and increasing hoarseness. Direct laryngoscopy 11/7/63 revealed ulceration of posterior third of (L) vocal cord and biopsy confirmed active tumour. Complete laryngectomy carried out on 2/8/63 with rapid recovery; discharged 31/8/63 already acquiring pharyngeal speech. Readmitted 7/10/63 with a mass of enlarged confluent glands in the (R) side of the neck and obvious recurrence around the tracheostomy stoma. 1,000r to the neck glands produced no improvement. Following cyclophosphamide there was an initial rapid shrinkage in size of neck glands, but effect short-lived. Frequent episodes of respiratory distress occurred and the patient died with severe pulmonary oedema on 11/11/63 - one year and 2 months from initial diagnosis.		
Autopsy report:	Confluent mass of tumour tissue in neck, surrounding vessels and tracheostomy stoma. Involved mediastinal lymph glands. Bilateral pulmonary collapse and oedema. Death due to acute respiratory failure secondary to collapse of lung and pulmonary oedema, secondary to metastases in neck and thorax, secondary to carcinoma of larynx.		
Result:	3 for 7 months following initial radiotherapy. 0-2 for 3 months following chemotherapy.		

Case No. 9: Carcinoma of Larynx

Fig. 1: Chest X-ray 9/12/62.

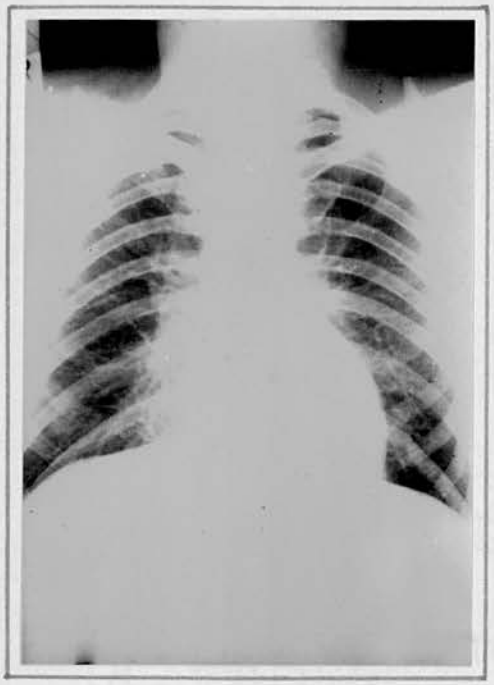


Fig. 2: Chest X-ray 12/9/63.

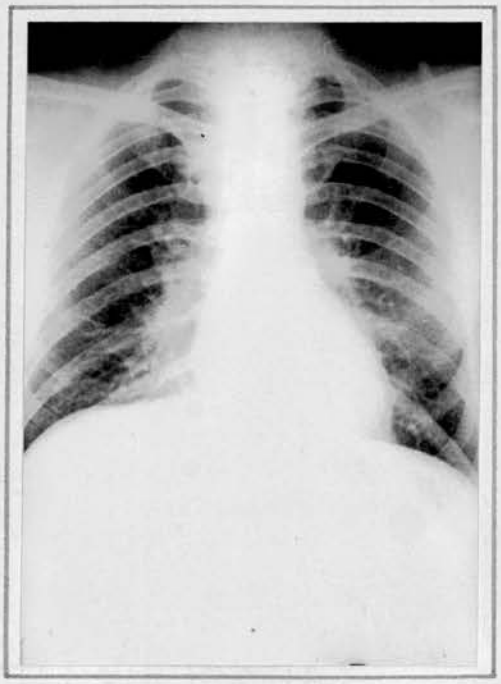


Fig. 3: Chest X-ray 10/7/63.

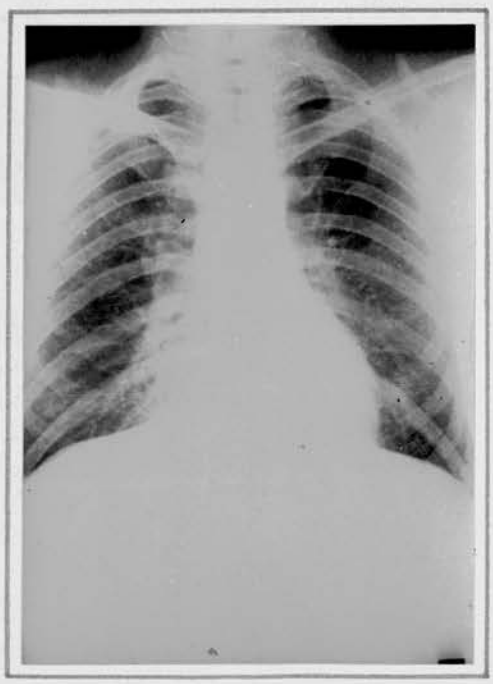


Fig. 4: Chest X-ray 8/11/63.

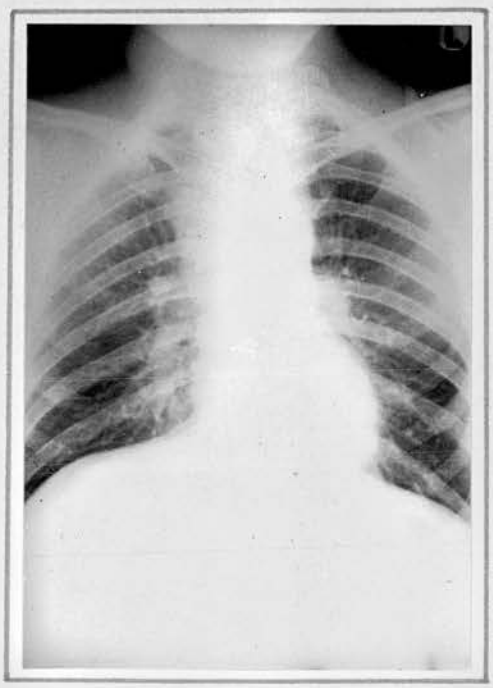


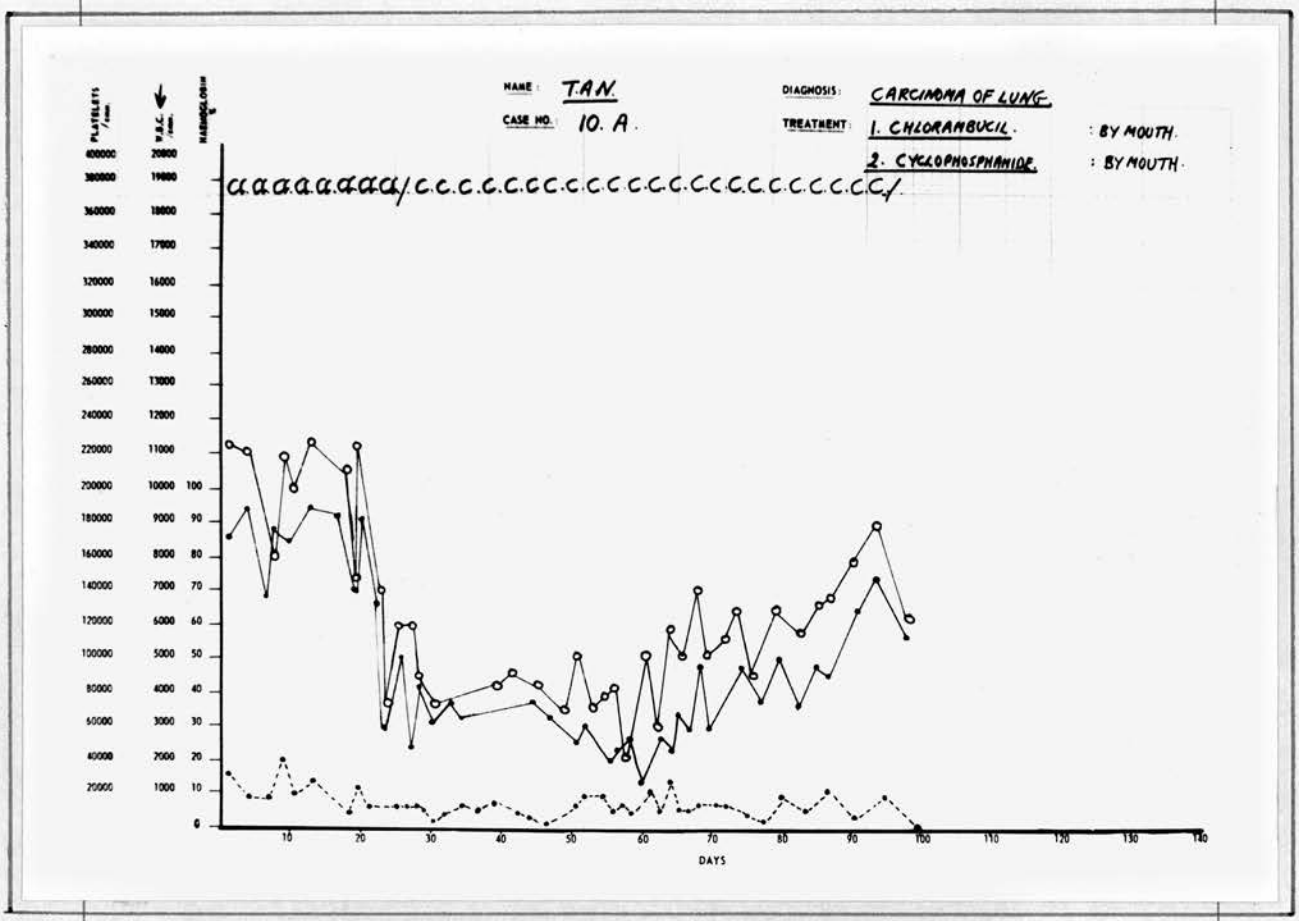
Table 2c

Case: 10	T.A.N. 22/11/62 Age: 43 Sex: M
Diagnosis:	Carcinoma of the (L) lung with spinal metastases. (Biopsy of spinal deposits at laminectomy 1/11/62.)
History:	First reported in July 1962 with pain in (L) lumbo-sacral area. Recent loss of 1 stone in weight, but no other symptoms. Symptoms considered orthopaedic in origin but little response to treatment. By mid-October was virtually crippled by pain in back and in (L) leg. Admitted to hospital where he developed bilateral foot drop and disturbance of bladder function. X-ray of chest and lumbar spine now suggested a diagnosis of carcinoma of lung with spinal metastases.
Previous or concurrent treatment:	(1) Physiotherapy: July-August 1962 (2) Bed rest and pelvic traction: October 1962 (3) Laminectomy and spinal decompression: 1/11/62 (4) Radiotherapy: 5,000r to lumbar spine 28/11/62-21/12/62 (5) Urinary antibiotics and antiseptics: In repeated courses between 22/11/62 and 25/1/63
Cytotoxic treatment:	(1) Chlorambucil: 210 mg. orally 29/11/62-12/12/62 (2) Cyclophosphamide: 7,500 mg. orally 20/12/62-16/2/63
Clinical course and comments:	Following decompression and radiotherapy, power improved considerably and pain virtually cleared. Remained subject to occasional severe muscle cramps and required an indwelling catheter. Between 19/12/62 and 21/1/63 he was able to walk short distances and spent a short period at home. Thereafter his condition began to deteriorate; he required catheterisation and regular enemata. On 15/2/63 he developed an influenzal illness, became much weaker and bedridden. Glands appeared in neck and (L) axilla but lung primary remained static. On 21/2/63 he began vomiting blood and this recurred intermittently until death on 26/2/63. Case of interest because of long delay in reaching a diagnosis and lack of response to cytotoxins.
Autopsy report:	Not obtained
Result:	1 for 4 months

CASE NO. 10

PERIPHERAL BLOOD COUNTS

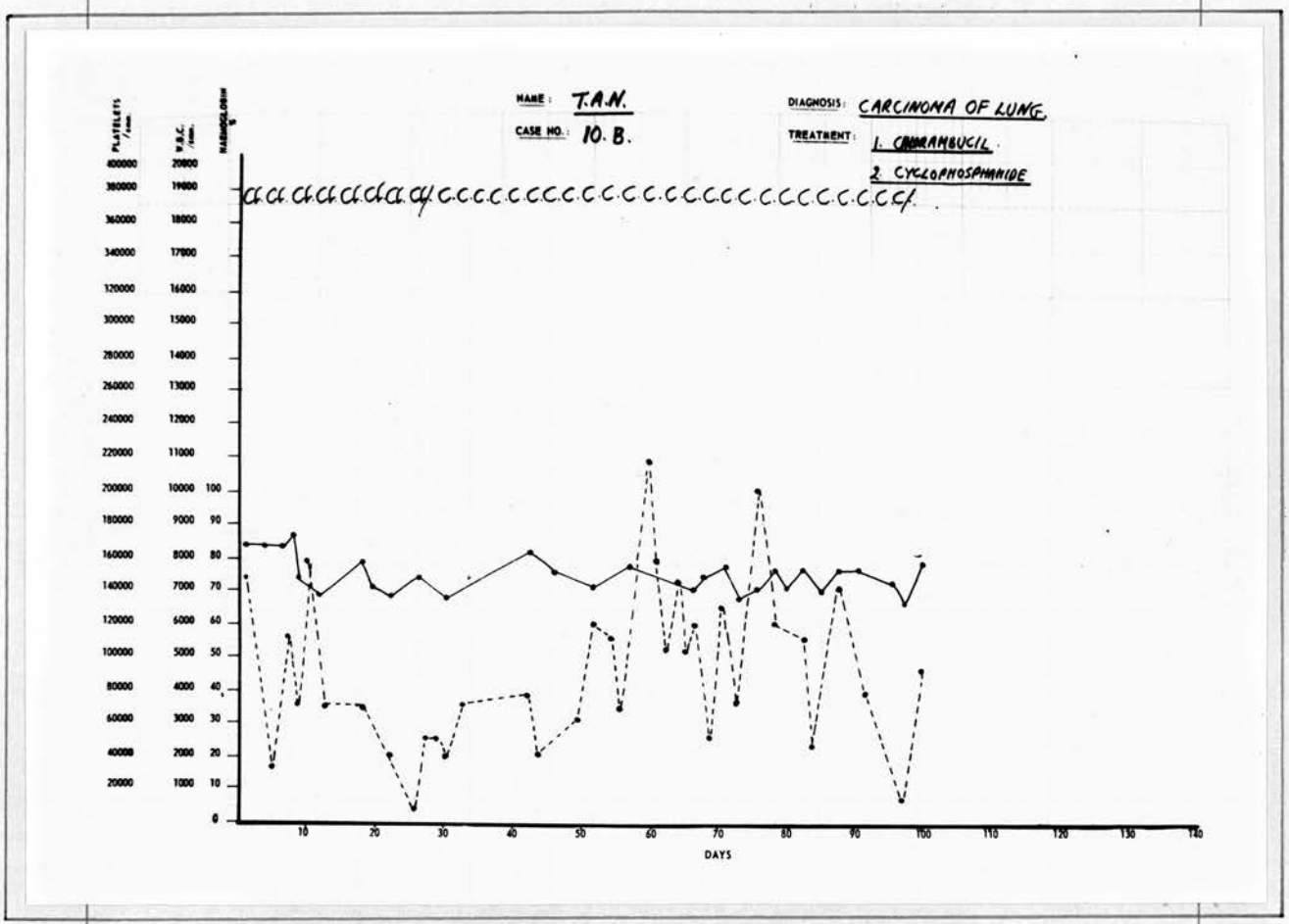
GRAPH A



CASE NO. 10

PERIPHERAL BLOOD COUNTS

GRAPH B



Case No. 10: Carcinoma of Lung

Fig. 1: Chest X-ray 19/7/61.

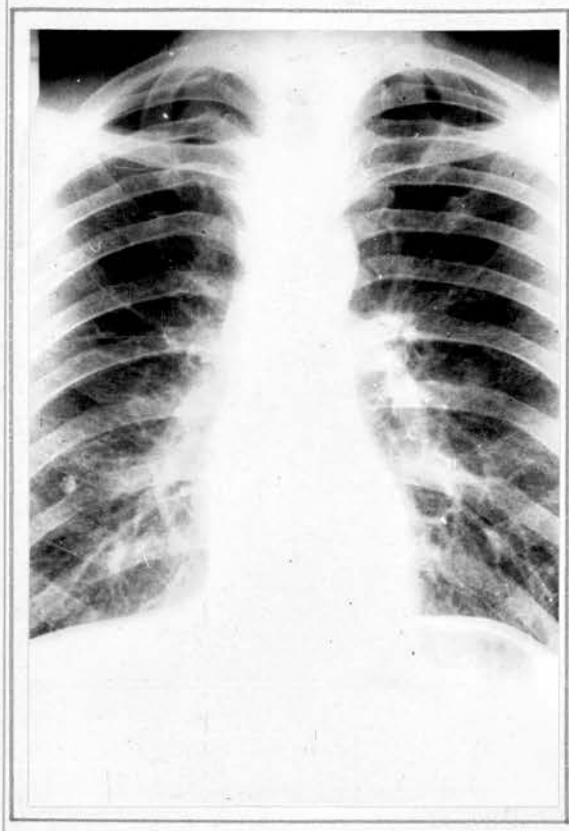


Fig. 2: Chest X-ray 29/10/62.

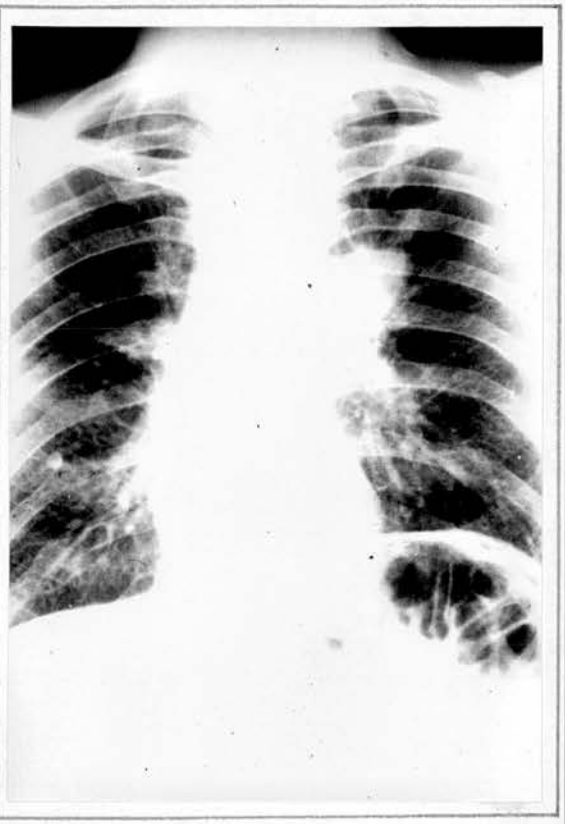


Fig. 3: Chest X-ray 21/1/63.

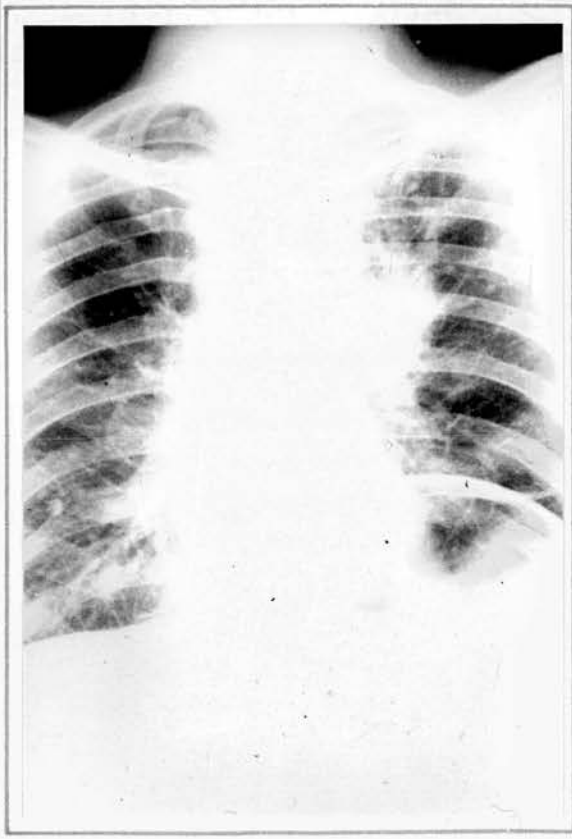


Fig. 4: Chest X-ray 5/2/63.

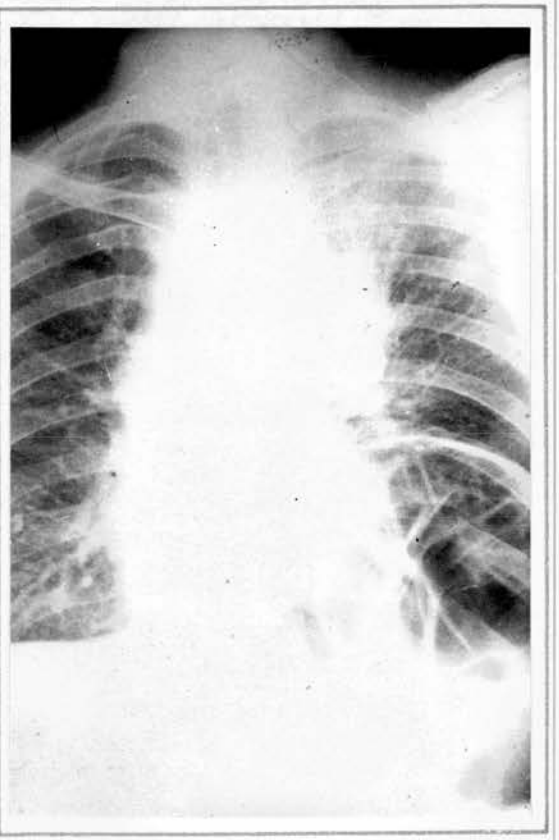


Table 2d

Case: 11	L.W.T. 1/12/63 Age: 50 Sex: M
Diagnosis:	Carcinoma of (L) lung with gangrene of (R) leg and pulmonary osteo-arthropathy.
History:	First admitted to another hospital 22/10/63 with a 6 weeks' history of pain in (L) chest, dyspnoea, listlessness, constant cough, sweating and anorexia. Two weeks prior to admission he had developed aching pains in wrists and ankles with swelling of both lower limbs. Chest X-ray revealed mottled opacities (L) lower lobe and a pleural effusion. Antibiotics produced no improvement and on 21/11/63 (R) foot became pulseless and blue. Bronchogenic neoplasm now suspected although bronchoscopy and pleural biopsy had been negative.
Previous or concurrent treatment:	(1) Antibiotics: Penicillin, erythromycin and tetracycline in separate courses 23/9/63-25/11/63 (2) Blood transfusion: 4 pints packed cells 17/12/63 (3) (R) mid-thigh amputation: 3/12/63 (4) Nystatin: 9/12/63-15/12/63
Cytotoxic treatment:	(1) Cyclophosphamide: 3,300 mg. by I.V.I. 2/12/63-17/12/63
Clinical course and comments:	Patient presenting with rapidly advancing carcinoma of lung initially regarded and treated as an infection. Demonstrated pulmonary osteo-arthropathy and developed gangrene of (R) foot ? due to femoral artery thrombosis, which required mid-thigh amputation. No response to cyclophosphamide and died in respiratory failure on 20/12/63 - 3 months from onset of symptoms.
Autopsy report:	Acute respiratory failure secondary to pulmonary oedema and bronchopneumonia, secondary to carcinoma of (L) lung. Recent infarct (L) ventricle. Large bilateral pleural effusion. (L) lung collapsed and densely infiltrated with anaplastic squamous cell carcinoma. One $2\frac{1}{2}$ cm. metastasis in (R) lobe of liver. Malignant cells in marrow.
Result:	0 for 3 months

Table 2e

Case: 12	H.S. 22/2/63 Age: 36 Sex: M
Diagnosis:	Carcinoma of (R) lung. (Pleural biopsy - 13/2/63)
History:	Admitted to another hospital on 9/1/63 with a history of general malaise, anorexia, listlessness and weight loss over the previous 9 months. Developed superficial venous thrombosis of (R) arm three days prior to admission. Chest X-ray revealed a large mass in (R) side of chest. ? bronchogenic neoplasm. ? tuberculosis. Rapidly developed a massive (R) pleural effusion requiring aspiration. Bronchoscopy was negative but pleural biopsy revealed adeno-carcinoma. All investigations for T.B. were negative.
Previous or concurrent treatment:	(1) Aspiration of pleural effusion: On repeated occasions between 29/1/63 and 23/3/63. Amounts ranging from 50-3,000 ml. aspirated.
Cytotoxic treatment:	(1) Thiotepa: 45 mg. by intrapleural instillation 1/3/63-23/3/63 (2) Cyclophosphamide: 3,000 mg. by I.V.I. 1/3/63-21/3/63 2,700 mg. by mouth 25/3/63-18/4/63 26,400 mg. by mouth 19/4/63-17/3/64
Clinical course and comments:	Patient of Western extraction presenting with history simulating pulmonary tuberculosis. Diagnosis of malignant disease established by pleural biopsy and treatment with cytotoxins commenced earlier. Intrapleural thiotepa resulted in gradual clearing of (R) pleural effusion so that aspiration has not been required for 12 months to date. With the addition of systemic cyclophosphamide patient's general condition improved rapidly, he gained weight, appetite returned to normal and remained continuously at work from 30/4/63. At review 17/3/64 remained reasonably well but had an irritant cough, had had three episodes of migratory thrombophlebitis and chest X-ray revealed gradual extension of disease process.
Autopsy report:	-
Result:	3 for 12 months

Case No. 12

Fig. 1: Chest X-ray 9/1/63.

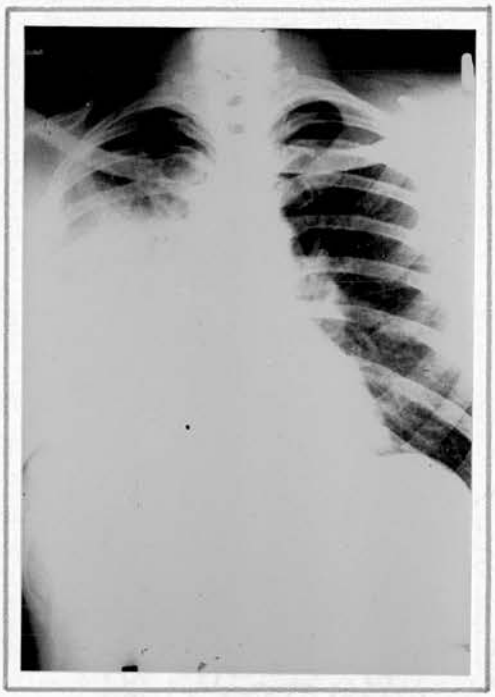


Fig. 2: Chest X-ray 1/2/63.

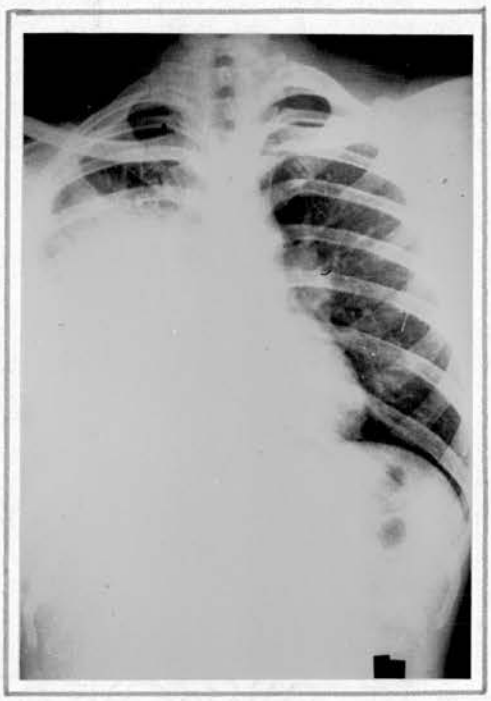


Fig. 3: Chest X-ray 26/2/63.

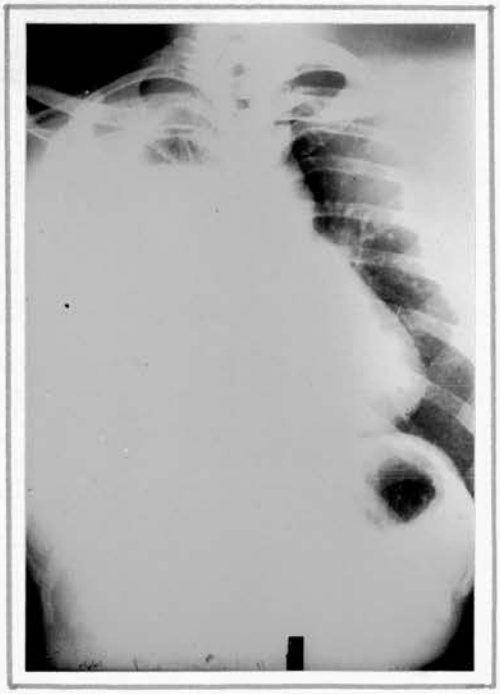
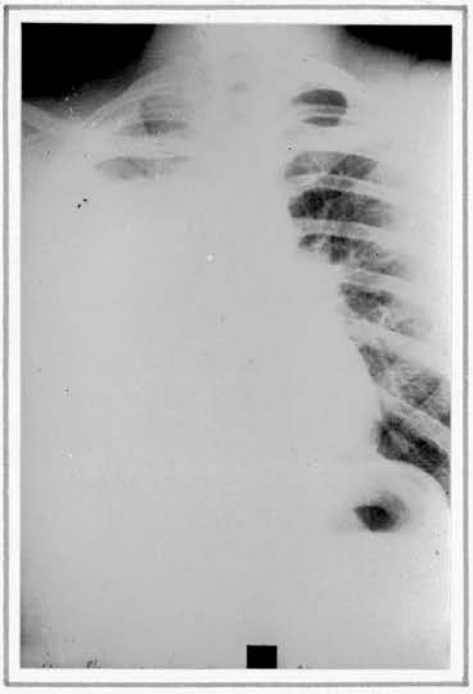


Fig. 4: Chest X-ray 2/4/63.



Case No. 12.

Fig. 5: Chest X-ray 16/1/64.

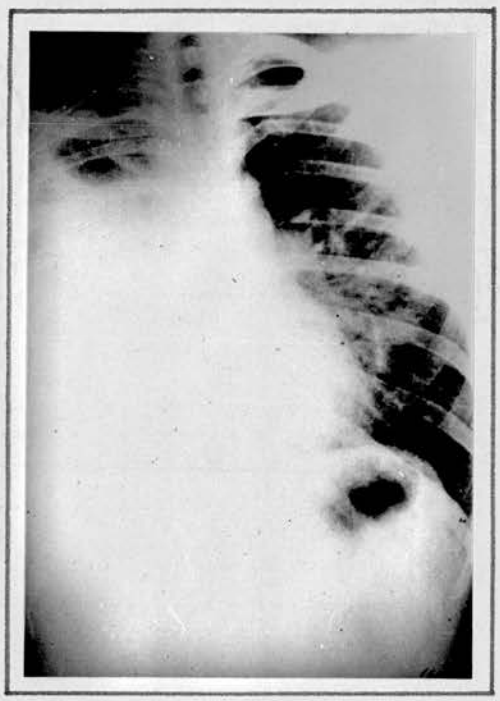


Table 2f

Case: 13	J.P. 27/2/63 Age: 65 Sex: M	
Diagnosis:	Carcinoma of (L) lung. (Biopsy of gland (L) side of neck)	
History:	Emergency admission in severe respiratory distress. History of chronic chest trouble commencing in 1951 when had a (R) lower lobectomy for proven carcinoma of the lung. Acute exacerbation of respiratory symptoms two weeks prior to admission. Loss of 2 stones in weight over previous three months with anorexia and listlessness. Chest X-ray revealed a (R) middle lobe pneumonia and (L) upper lobe bronchogenic neoplasm.	
Previous or concurrent treatment:	(1) Antibiotics: Chloramphenicol, penbritin	27/2/63-14/3/63 31/5/63-19/7/63
	(2) Bronchodilators: Aminophylline and cholinetheophyllinate	
	(3) Physiotherapy: throughout	
	(4) Radiotherapy: 4,000r to primary (L) upper lobe 4,000r to (L) side of neck	27/3/63-3/5/63
Cytotoxic treatment:	(1) Nitrogen mustard: 46 mg. by I.V.I. 35 mg. by I.V.I.	4/3/63-9/3/63 19/7/63-29/7/63
	(2) Cyclophosphamide: 1,500 mg. by I.V.I. 700 mg. orally	20/8/63-26/8/63 2/9/63-8/9/63
Clinical course and comments:	Patient in marked respiratory distress on admission. Only slight improvement after one week's treatment with antibiotics, antispasmodics and physiotherapy. In view of desperate condition a course of nitrogen mustard was given by I.V.I. This resulted in considerable improvement so that the patient was able to complete a course of radiotherapy to primary lesion and neck glands. On completion of this course improvement in condition marked. Previous stridor and distress relieved and radiologically lesion had regressed. Re-admitted 2 months later again in severe respiratory distress. A further course of nitrogen mustard produced only minimal improvement and there was no significant response to cyclophosphamide. Progressive respiratory distress to death on 9/9/63, seven months after initial emergency admission.	
Autopsy report:	Not obtained	
Result:	1-2 for 6 months	

Case No. 13: Carcinoma of Lung

Fig. 1: Chest X-ray 27/2/63.

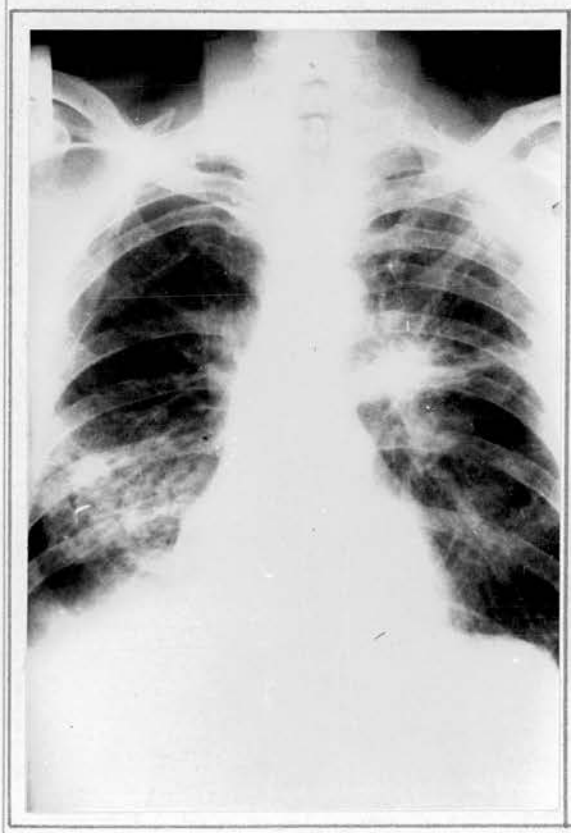


Fig. 2: Chest X-ray 4/4/63.

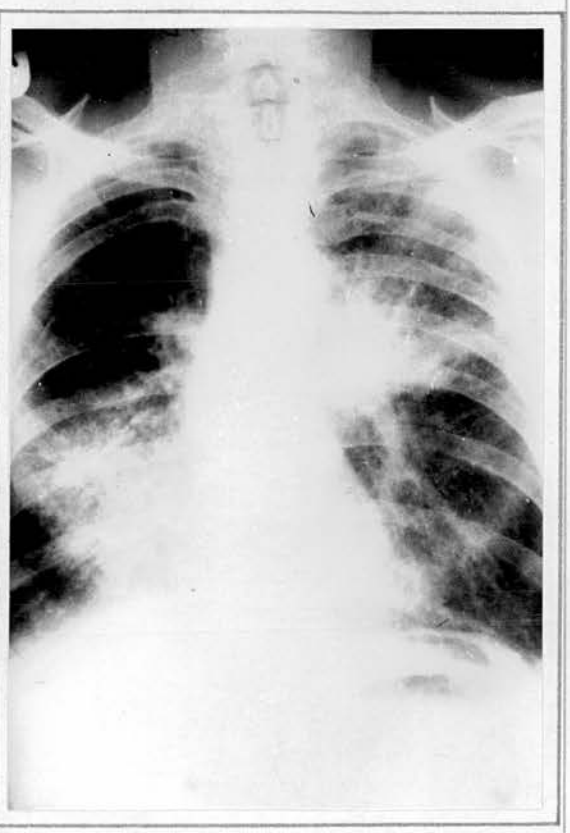


Fig. 3: Chest X-ray 30/4/63.

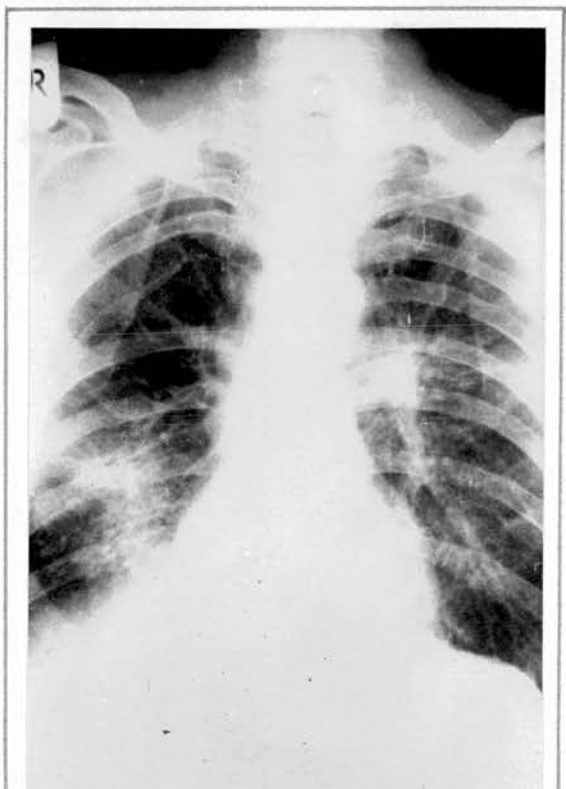


Fig. 4: Chest X-ray 20/8/63.

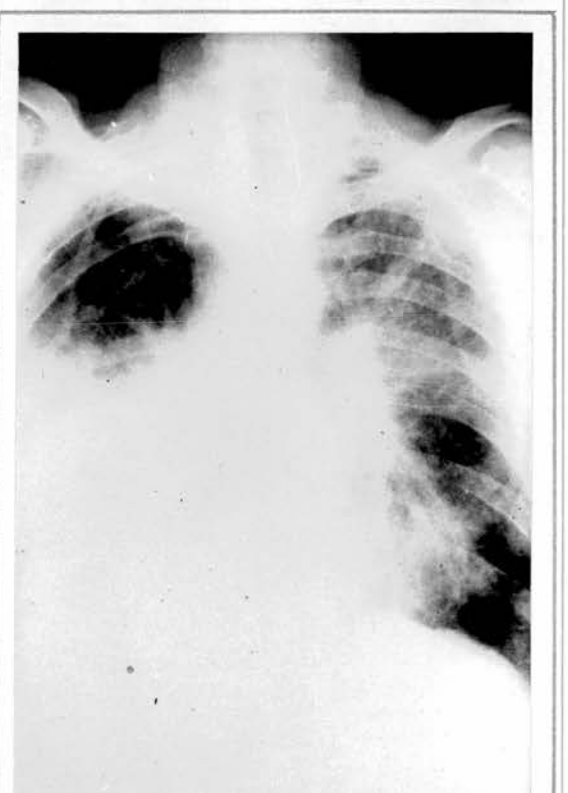


Table 2g

Case: 14	A.M. 25/3/63	Age: 46 Sex: M
Diagnosis:	Metastasising bronchial adenoma (L) lung. (Biopsy of tissue obtained at thoracotomy)	
History:	First reported January 1963 with persistent, chronic non-productive cough troublesome for about 3 months, loss of one stone in weight over the past six months and anorexia, easy fatigue and transient (L) shoulder pains for 1 month. Clinical examination and chest X-ray suggested a diagnosis of carcinoma of (L) lung; confirmed by bronchoscopy. Hopelessly inoperable neoplasm found at thoracotomy on 31/1/63.	
Previous or concurrent treatment:	(1) (R) thoracotomy: Inoperable neoplasm (2) Blood transfusion: Total of 13 pints whole blood between 30/3/63 and 31/6/63 (3) Physiotherapy: (4) Radiotherapy: 4,000r to primary lesion (L) chest	31/1/63 1/5/63-14/6/63
Cytotoxic treatment:	(1) Cyclophosphamide: 3,000 mg. by I.V.I. 7,800 mg. by mouth	1/4/63-18/4/63 18/4/63-30/6/63
Clinical course and comments:	Slow recovery from thoracotomy and general condition improved by blood transfusion. Repeated attempts to aspirate (R) chest failed to produce fluid. Very little response to initial course of cyclophosphamide and patient remained weak, nauseated and anorexic. Moderate improvement following radiotherapy; requiring repeated transfusions. Home for two weeks 14/6/63-30/6/63 but following re-admission became dyspnoeic, cachectic, and unaffected by continued treatment with oral cyclophosphamide. Collapsed and died suddenly on 4/7/63, 6 months from diagnosis.	
Autopsy report:	Extensive, invading tumour obliterating entire (L) pleural cavity. Tumour necrotic with areas of calcification. Tumour arising from (L) main stem bronchus. Marked mediastinal deviation. There were no metastases in any site. Histologically the tumour proved to be a metastasising bronchial adenoma.	
Result:	0-1 for 4 months	

Case No. 14: Carcinoma of Lung : Metastasising Adenoma

Fig. 1: Chest X-ray 2/7/62.
(6 months before patient referred to hospital)

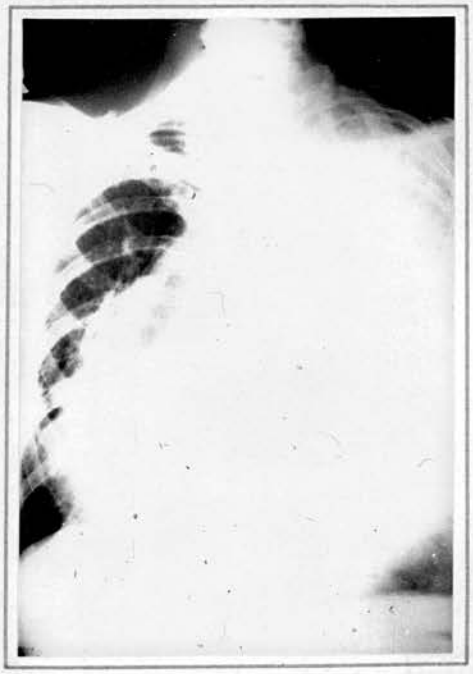


Fig. 2: Chest X-ray 25/1/63.

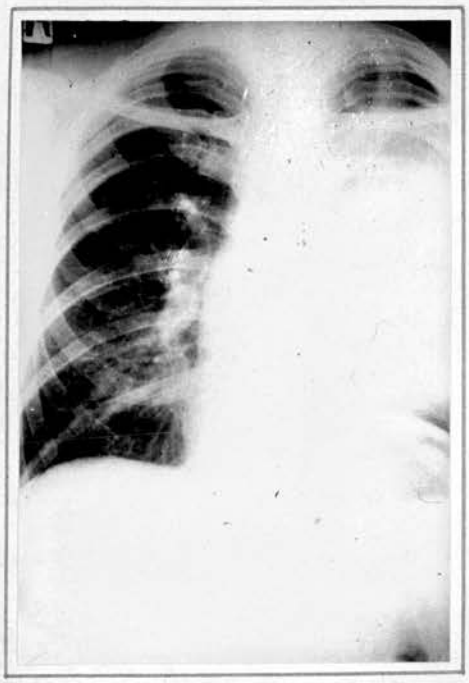
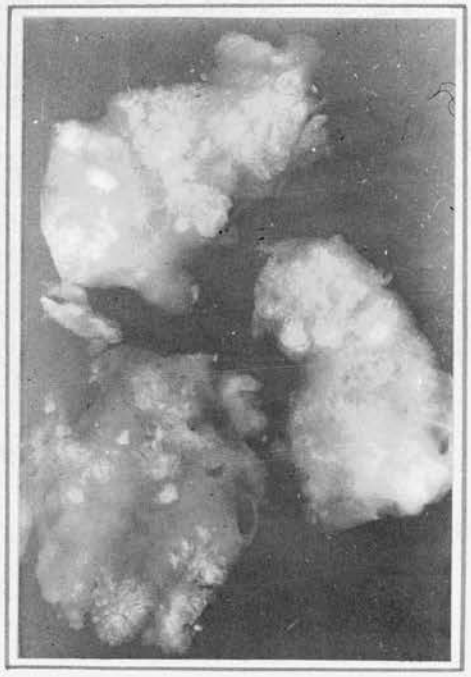


Fig. 3: P.M. X-ray of Lung to show tumour calcification.



Case No. 14.

Fig. 4: Cut section of lung.

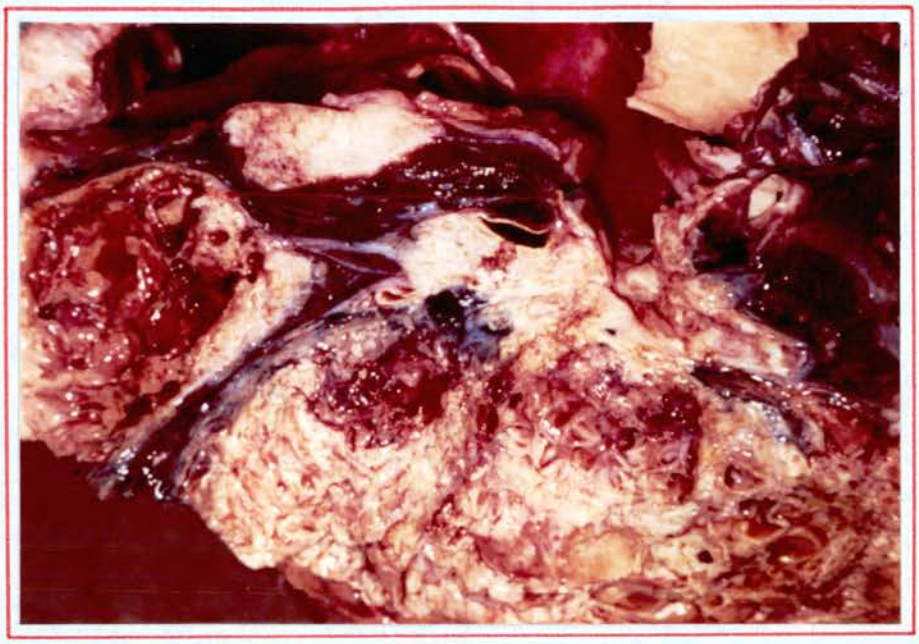


Fig. 5: Heart : Myocarditis and Pericarditis.

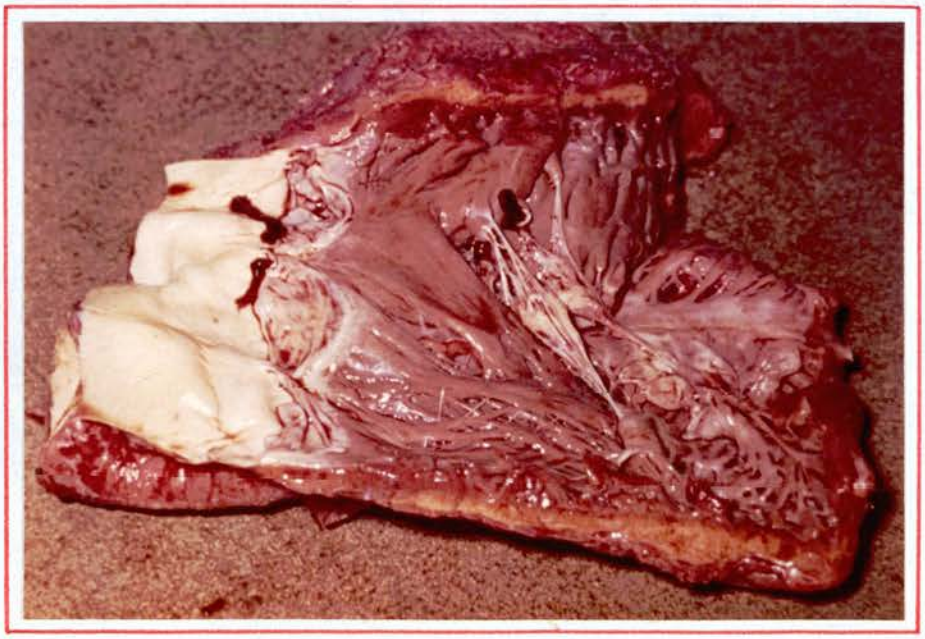


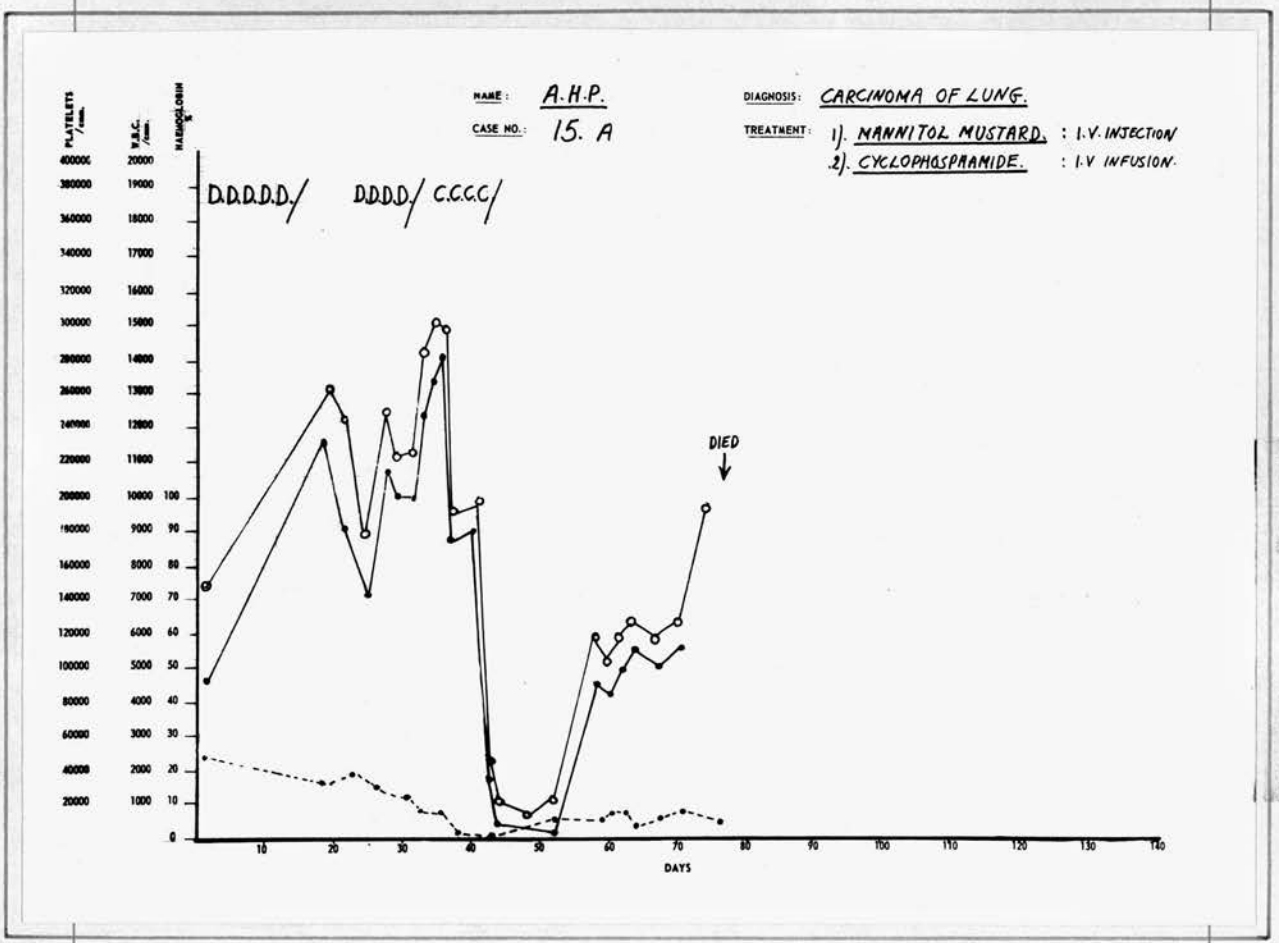
Table 2h

Case: 15	A.H.P. 8/4/63	Age: 32	Sex: M
Diagnosis:	Carcinoma of (L) lung with metastases in (L) 4th rib, adrenals and brain. (Biopsy of rib deposit)		
History:	Gnawing pain and swelling in (L) pectoral region for 5 months. Headaches, dizziness, diplopia, anorexia, nausea and occasional vomiting for 3 weeks.		
Previous or concurrent treatment:	(1) Local heat to (L) pectoral region and Physiotherapy:		17/12/62-21/12/63 3/1/63-15/1/63
	(2) Analgesics: throughout		
Cytotoxic treatment:	(1) Mannitol mustard:	500 mg. by I.V.I. 400 mg. by I.V.I.	11/4/63-15/4/63 24/4/63-29/4/63
	(2) Cyclophosphamide:	3,000 mg. by I.V. drip	2/5/63-5/5/63
Clinical course and comments:	Symptoms initially regarded as musculo-skeletal in origin and diagnosis delayed for $4\frac{1}{2}$ months. During this period symptomatic treatment produced no benefit. Although chest pain temporarily decreased by cytotoxic therapy the patient pursued a rapid downhill course with vomiting, anorexia, and progressive cachexia. He became ataxic, double vision persisted and developed nystagmus. Epilated. Short periods of improvement in general condition between 26/4/63 and 5/5/63 but thereafter condition deteriorated to death in coma on 4/6/63.		
Autopsy report:	Large tumour mass in (L) 4th rib anteriorly. Small area of tumour in (R) main bronchus confluent with a mass of tumour replacing the para-bronchial and tracheal nodes. Histology of tumour showed muco-epidermoid carcinoma. Multiple metastases in liver, cerebral cortex, cerebellum and adrenals.		
Result:	0-1 for 2 months		

CASE NO. 15

PERIPHERAL BLOOD COUNTS

GRAPH A



CASE NO. 15 PERIPHERAL BLOOD COUNTS

GRAPH B

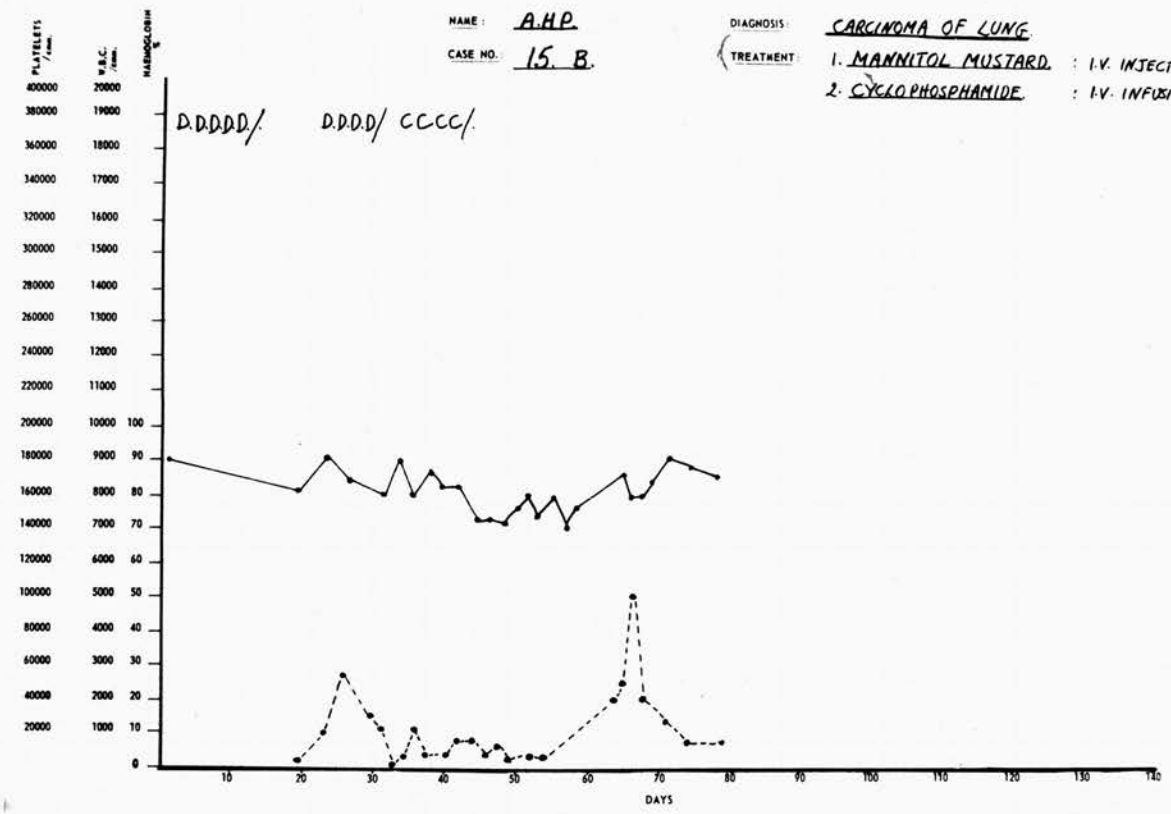
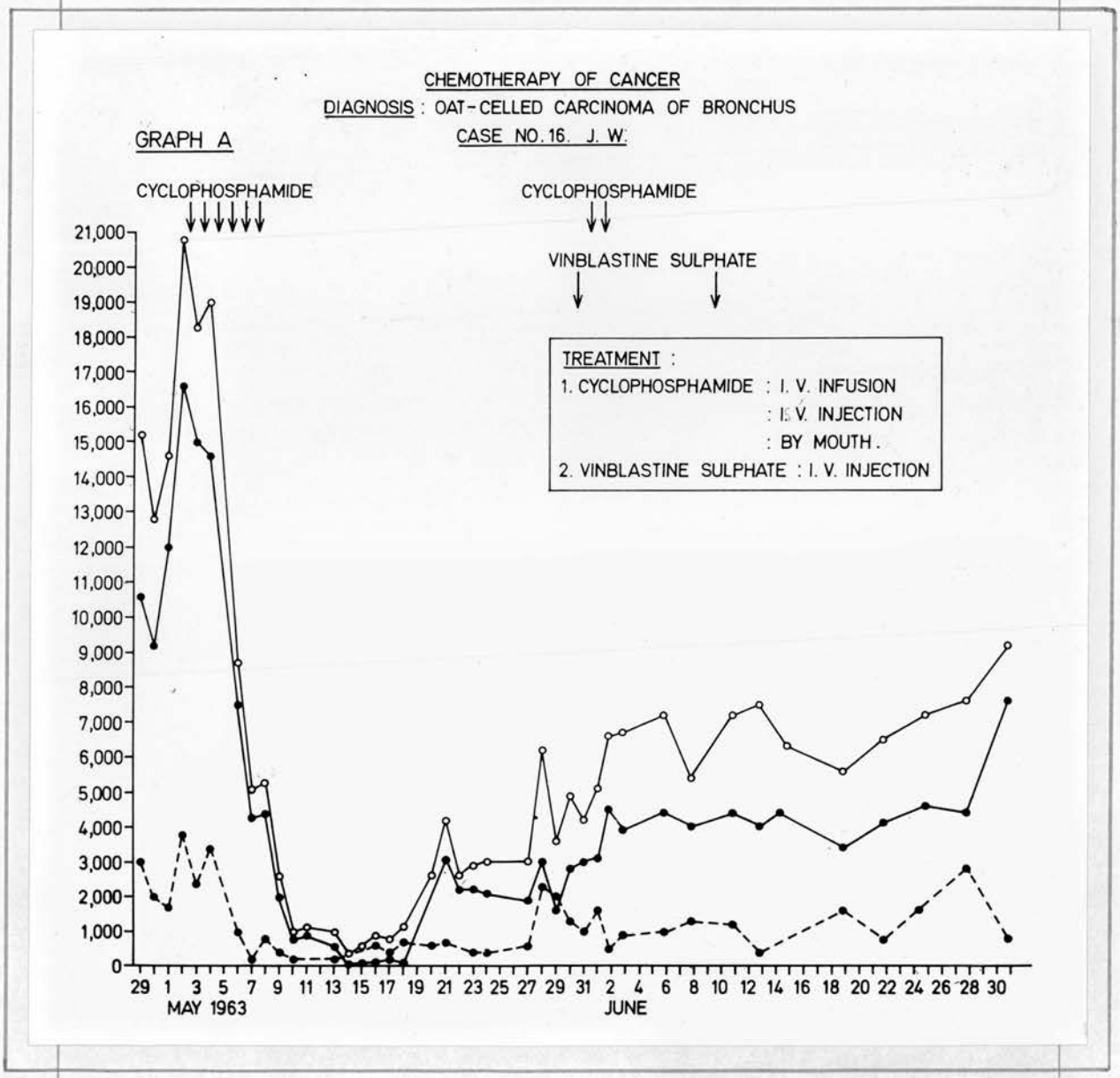


Table 2i

Case: 16	E.J.W. 26/4/63 Age: 49 Sex: M
Diagnosis:	Carcinoma of (L) lung with skeletal and hepatic metastases. Gross biochemical disturbances, i.e. "functioning" tumour.
History:	Six weeks' history of increasing cough, dyspnoea, wheeziness, generalised muscle pains particularly in chest and back, anorexia, lethargy, sweating attacks and weight loss. Had smoked 20-30 cigarettes a day for many years. No relevant past or family history.
Previous or concurrent treatment:	(1) Massive I.V. therapy with electrolyte solutions: 30/4/63-16/5/63 (2) Antibiotics: Penicillin, 14 G. 25/5/63 (3) Blood transfusion: 4 pints whole blood 20/7/63
Cytotoxic treatment:	(1) Cyclophosphamide: 6,050 mg. by I.V. drip 2/5/63-6/5/63 2,600 mg. by I.V.I. 30/5/63-9/7/63 3,600 mg. orally 20/7/63-17/8/63 1,200 mg. by I.V.I. 17/8/63-19/8/63 2,500 mg. intrapleurally 20/8/63-30/8/63 Total = 15,300 mg. (2) Vinblastine sulphate: 28 mg. by I.V.I. 30/5/63-17/7/63
Clinical course and comments:	Patient extremely ill on admission with gross biochemical and electrolyte disturbances secondary to carcinoma of the lung. Symptoms and gross biochemical derangements were reversed for 6 weeks by cyclophosphamide, although marked depression of haemopoiesis and alopoecia induced initially. At home for this period. Readmitted 15/8/63 with massive hepatic and skeletal metastases, pleural effusion, peripheral oedema and return of symptoms. Transient response only to further cytotoxic therapy and died in coma on 10/9/63 - 3 months from diagnosis. Case of especial interest because of polyglandular syndrome associated with carcinoma of bronchus.
Autopsy report:	Primary carcinoma of (L) main bronchus. Widespread metastases in liver, pleural cavities, lymph nodes and skeleton. Histologically an oat-cell carcinoma of lung.
Result:	1-2 for $3\frac{1}{2}$ months

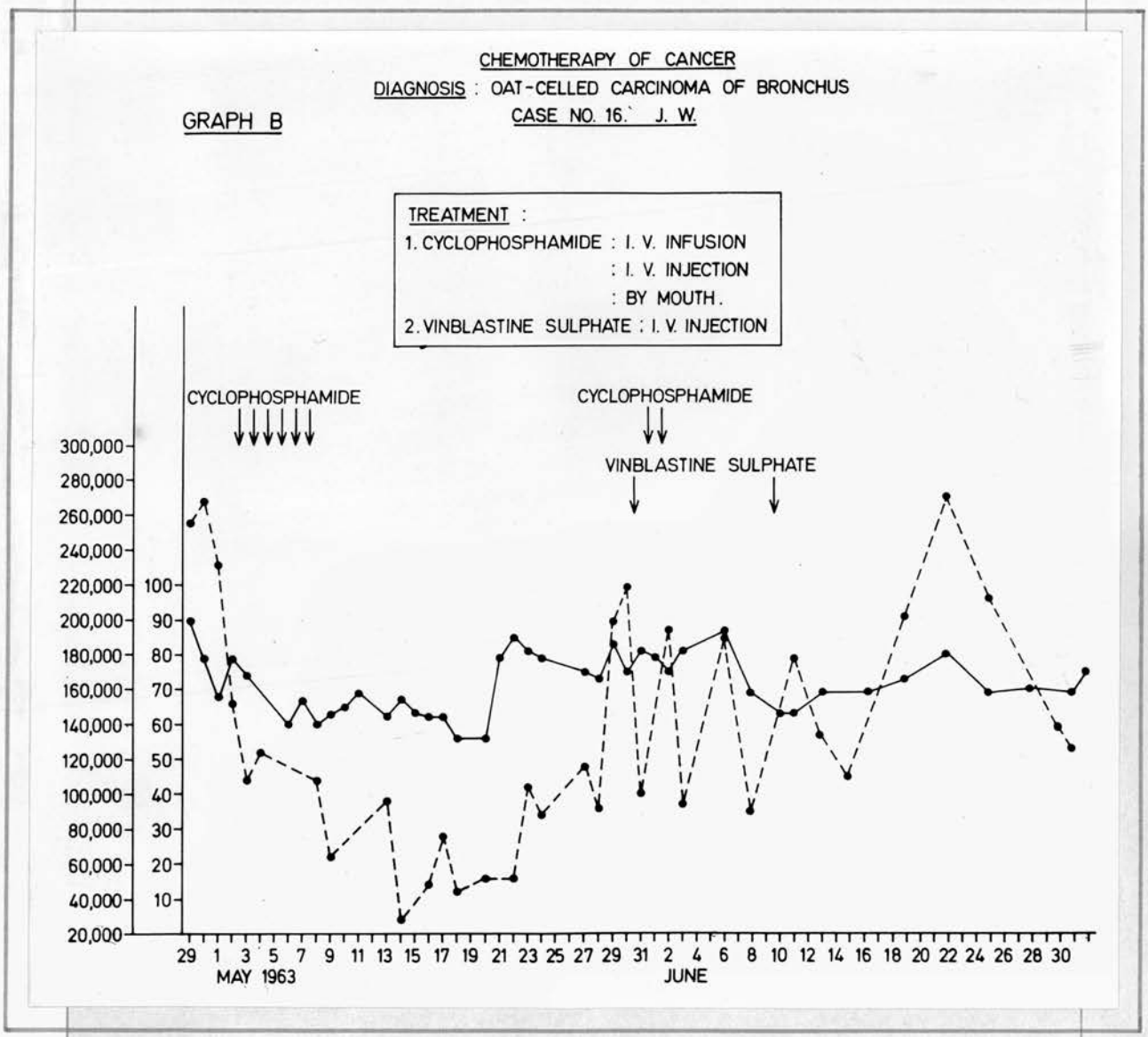
CASE NO. 16 PERIPHERAL BLOOD COUNTS

GRAPH A



CASE NO. 16 PERIPHERAL BLOOD COUNTS

GRAPH B



Case No. 16: Carcinoma of Lung

Fig. 1: Chest X-ray 6/5/63.

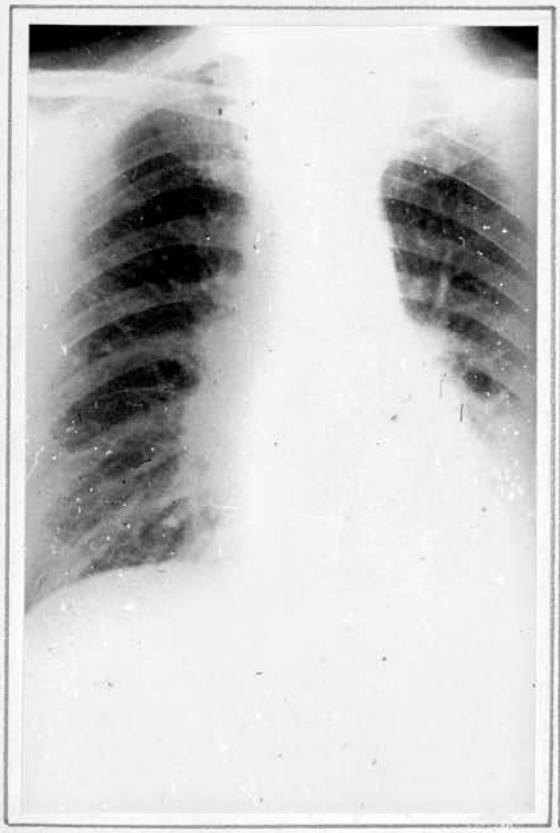


Fig. 2: Chest X-ray 4/6/63.

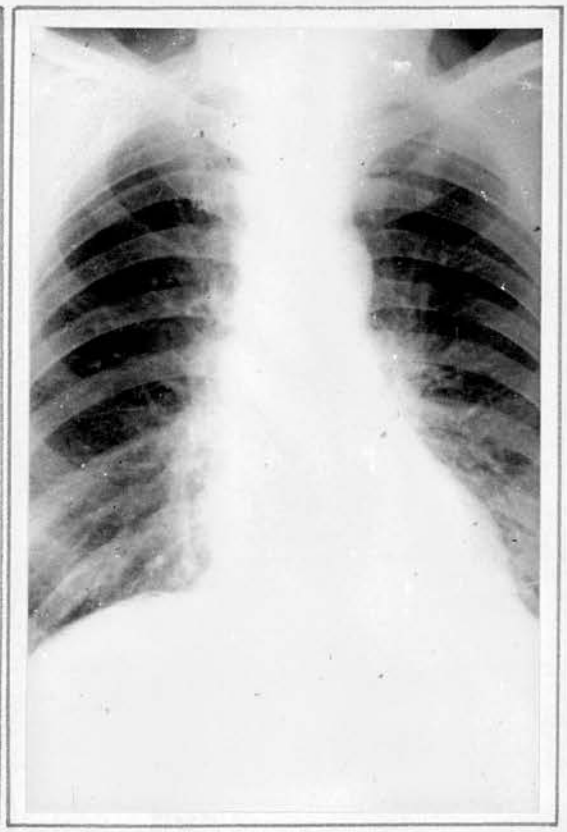


Fig. 3: Chest X-ray 31/8/63.

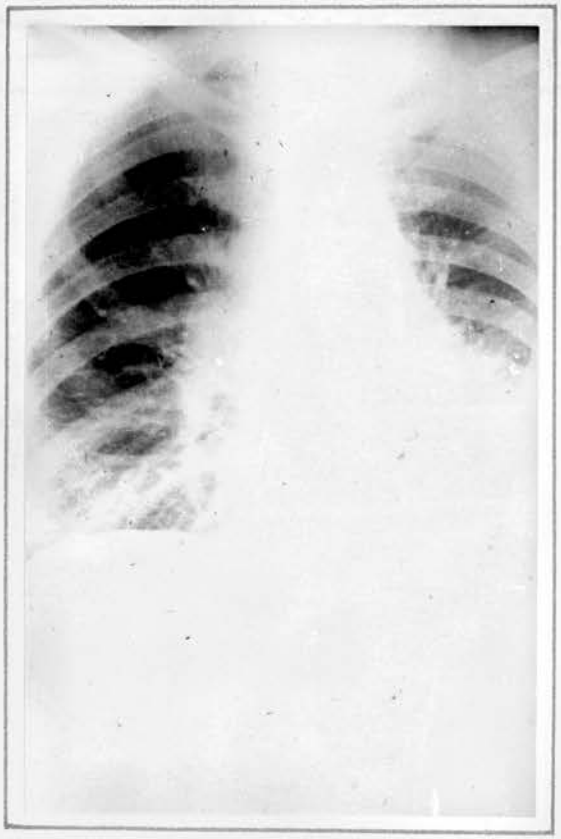


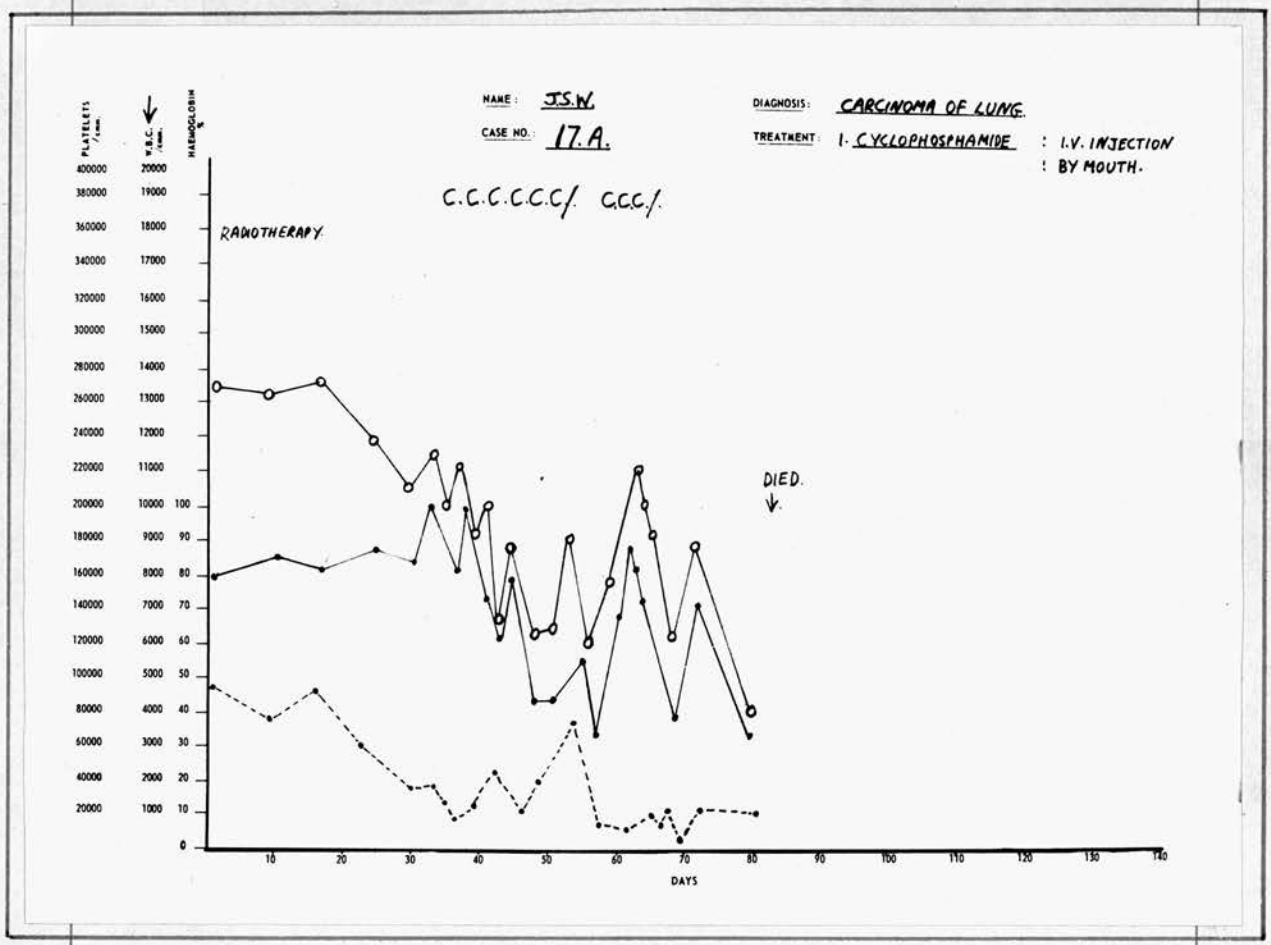
Table 2j

Case: 17	J.S.W. 2/6/63 Age: 50 Sex: M	
Diagnosis:	Carcinoma of (L) lung with cerebellar metastases. (Biopsy of deposit in cerebellum)	
History:	Found to have a (L) lower lobe bronchogenic neoplasm on a routine "three-year" chest X-ray in January 1963. Had previously reported in October 1962 and again in November 1962 with a persistent, non-productive cough. Symptomatic treatment only and no chest X-ray. (L) pneumonectomy was carried out in another hospital on 14/2/63. Remained well until mid-March when he developed symptoms and signs of a cerebellar lesion confirmed by posterior fossa craniotomy carried out in London on 16/5/63.	
Previous or concurrent treatment:	(1) Antibiotics: Penicillin by I.M.I.	19/10/62-25/10/62
	(2) (L) pneumonectomy:	14/2/63
	(3) Posterior fossa craniotomy:	16/5/63
	(4) Radiotherapy: 4,068r to posterior fossa	11/6/63-19/7/63
Cytotoxic treatment:	(1) Cyclophosphamide: 3,000 mg. by I.V.I.	14/8/63-20/8/63
	4,500 mg. orally	2/9/63-16/10/63
Clinical course and comments:	Patient admitted two weeks after posterior fossa craniotomy. General condition fair; he was free of headache and had no significant respiratory symptoms. Completed a course of radiotherapy to posterior cranial fossa but complained of parietal headaches and became progressively more ataxic, confused and drowsy. By 29/7/63 was sleeping most of the time, demonstrated gross memory defects and cerebration was grossly impaired. Improved a little and allowed home for 10 days. Cyclophosphamide was commenced on 14/8/63 and thereafter condition gradually improved. By 2/9/63 general and cerebral conditions markedly improved and allowed home on 18/9/63. Readmitted 1 month later following an epileptic fit. Thereafter condition rapidly deteriorated, further epileptiform episodes occurred and he died on 30/10/63.	
Autopsy report:	Not obtained	
Result:	0-2 for $3\frac{1}{2}$ months	

CASE NO. 17

PERIPHERAL BLOOD COUNTS

GRAPH A



CASE NO. 17 PERIPHERAL BLOOD COUNTS

GRAPH B

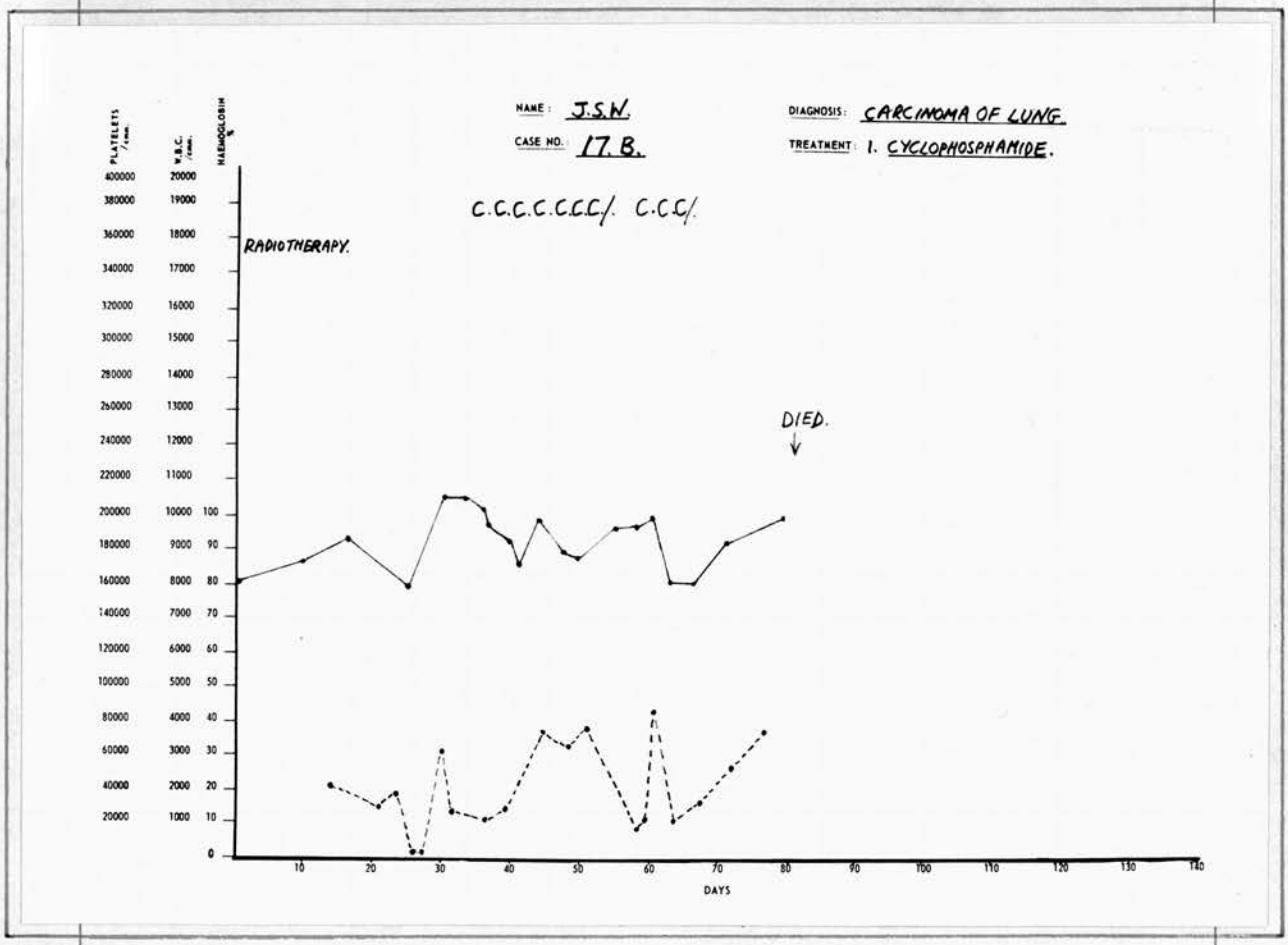


Table 2k

Case: 18	A.McL. 13/6/63	Age: 43	Sex: F
Diagnosis:	Carcinoma of (R) lung with cervical gland and hepatic metastases. (Bronchoscopy and biopsy of neck gland)		
History:	Five months history of persistent productive cough and aching discomfort in (R) side of chest. Chest X-ray in March 1963 revealed (R) lower lobe collapse but bronchoscopy reported negative and treated symptomatically. Reported again in June 1963 with glands in (L) side of neck and diagnosis of carcinoma of lung now established.		
Previous or concurrent treatment:	(1) Physiotherapy:		March 1963
	(2) Gland biopsy neck:		13/6/63
Cytotoxic treatment:	(1) Mannitol mustard:	300 mg. by I.V.I. (operation cover)	13/6/63-15/6/63
	(2) Cyclophosphamide:	2,000 mg. by I.V. drip 2,700 mg. orally	23/6/63-24/6/63 1/7/63-25/7/63
Clinical course and comments:	General condition fair on admission; large mass of hard fixed glands in (L) side of neck and palpable mass in epigastrium. Commenced cyclophosphamide on 23/6/63 and by 28/6/63 there was definite decrease in size of neck glands. Patient claimed to feel well. Thereafter steady improvement in general condition with further shrinkage of glands and epigastric mass. Home 12/7/63. Readmitted 27/7/63 with increasing jaundice for 6 days. Anorexia, listlessness and weight loss now marked; increasing size of metastases; jaundice increasing with marked pruritus. Epileptiform episode on 6/8/63; recovered but by 19/8/63 was moribund, incontinent and vomiting. Died 22/8/63 following further seizures.		
Autopsy report:	Not obtained. (Refused)		
Result:	2 for 3 weeks only		

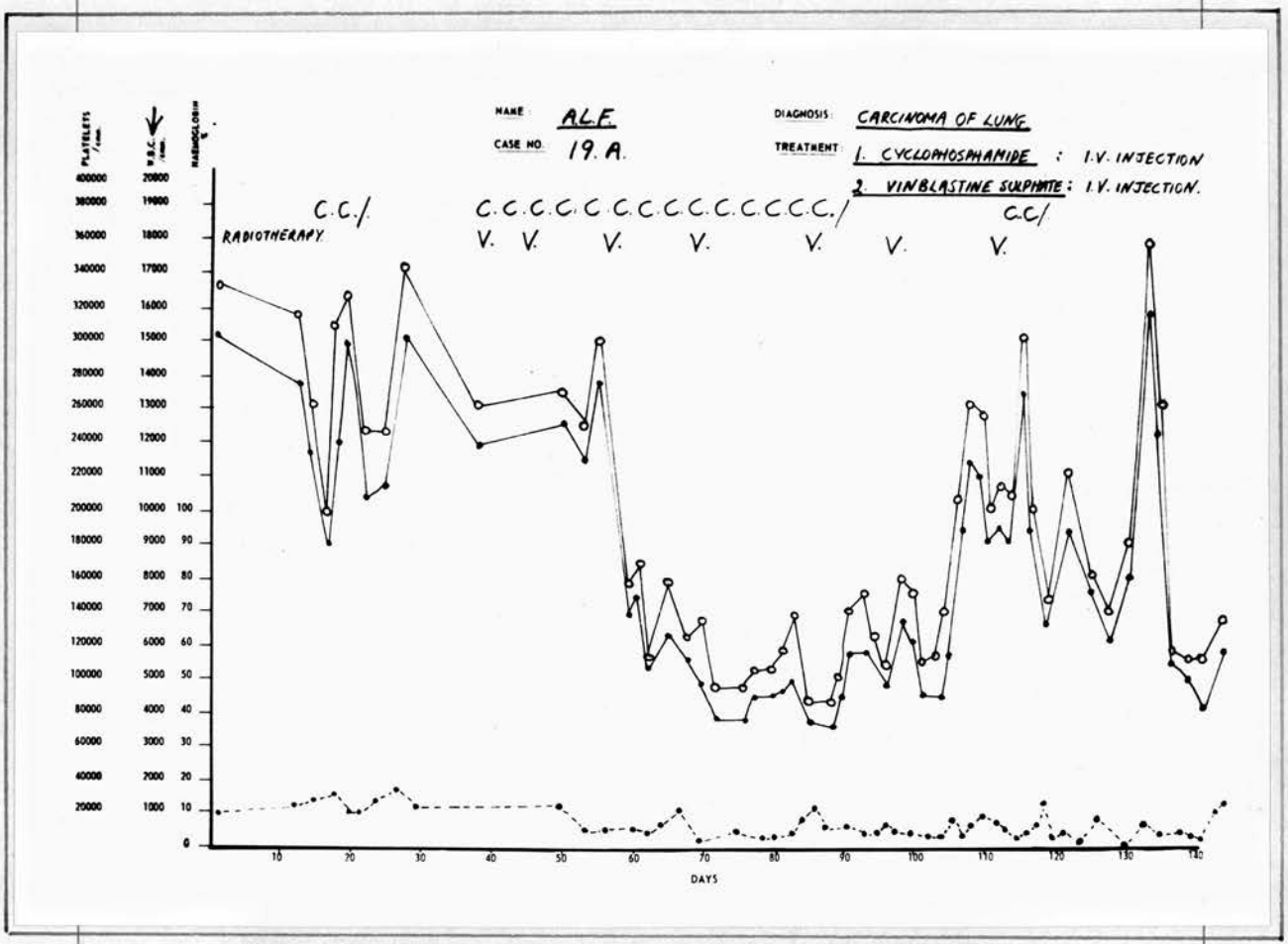
Table 21

Case: 19	A.L.F. 27/6/63 Age: 37 Sex: M
Diagnosis:	Carcinoma of (R) lung. Anaplastic, giant-cell carcinoma of lung. (Biopsy of mass (R) posterior chest wall and autopsy histology)
History:	First reported on 25/4/63 with a 6 weeks' history of continuous gnawing pain in (R) side of chest posteriorly. Chest X-rays in December 1962 and on this occasion reported negative. Treated as arthritis of spine but symptoms persisted; psychiatric opinion sought. Finally mass in (R) posterior chest revealed by tomography 26/5/63. (R) thoracotomy in London 13/6/63 revealed inoperable, apparently chest wall tumour. Biopsy. In past history patient had had recurrent episodes of bronchitis 1953-1962 with one episode of haemoptysis in 1962. Smoked 15-20 cigarettes daily.
Previous or concurrent treatment:	(1) Physiotherapy: April-May 1963 (2) Bed rest and pelvic traction: 27/4/63-1/5/63 (3) Cervical suspension: 1/5/63-7/5/63 (4) Analgesics: throughout (5) Blood transfusion: 2 pints whole blood 14/8/63 (6) (R) thoracotomy: 13/6/63 (7) Radiotherapy: 6063r to primary tumour (R) posterior thoracic area) 3,375r to lumbar spine) 1/7/63-7/8/63 (8) Prednisone: 20-30 mg. daily 22/7/63-20/8/63
Cytotoxic treatment:	(1) Cyclophosphamide: 7,100 mg. by I.V.I. 29/6/63-22/9/63 (2) Vinblastine sulphate: 52 mg. by I.V.I. 20/7/63-18/9/63
Clinical course and comments:	Patient admitted two weeks after (R) thoracotomy. He was ill-looking, had obviously lost weight and his chest wall pain remained constant and severe. Thoracotomy wound well healed but palpable mass medial to (R) scapula. Cyclophosphamide commenced 29/1/63 and considerable relief of pain (previously resistant to powerful analgesics) obtained in 24 hours; general condition also improved. Following radiotherapy to primary area, combined with cyclophosphamide, chest wall pain further eased, but developed increasingly severe pain in dorso-lumbar area and also skin deposits. Back pain unrelieved by analgesics or cyclophosphamide, only partly relieved by radiotherapy. Patient by now addicted to pethidine and constantly demanding drugs. Developed further skin and axillary gland metastases and gradually deteriorated to death on 1/10/63 - 3 months from first diagnosis.
Autopsy report:	Large tumour in upper lobe of (R) lung adherent to ribs posteriorly and invading upper thoracic vertebrae. Smaller metastases in both lungs, glands of neck, axillae, mediastinum, and inguinal areas invaded; skin deposits. Two small hepatic metastases. Histologically tumour highly anaplastic carcinoma containing numerous giant cells.
Result:	0-1 for 3 months

CASE NO. 19

PERIPHERAL BLOOD COUNTS

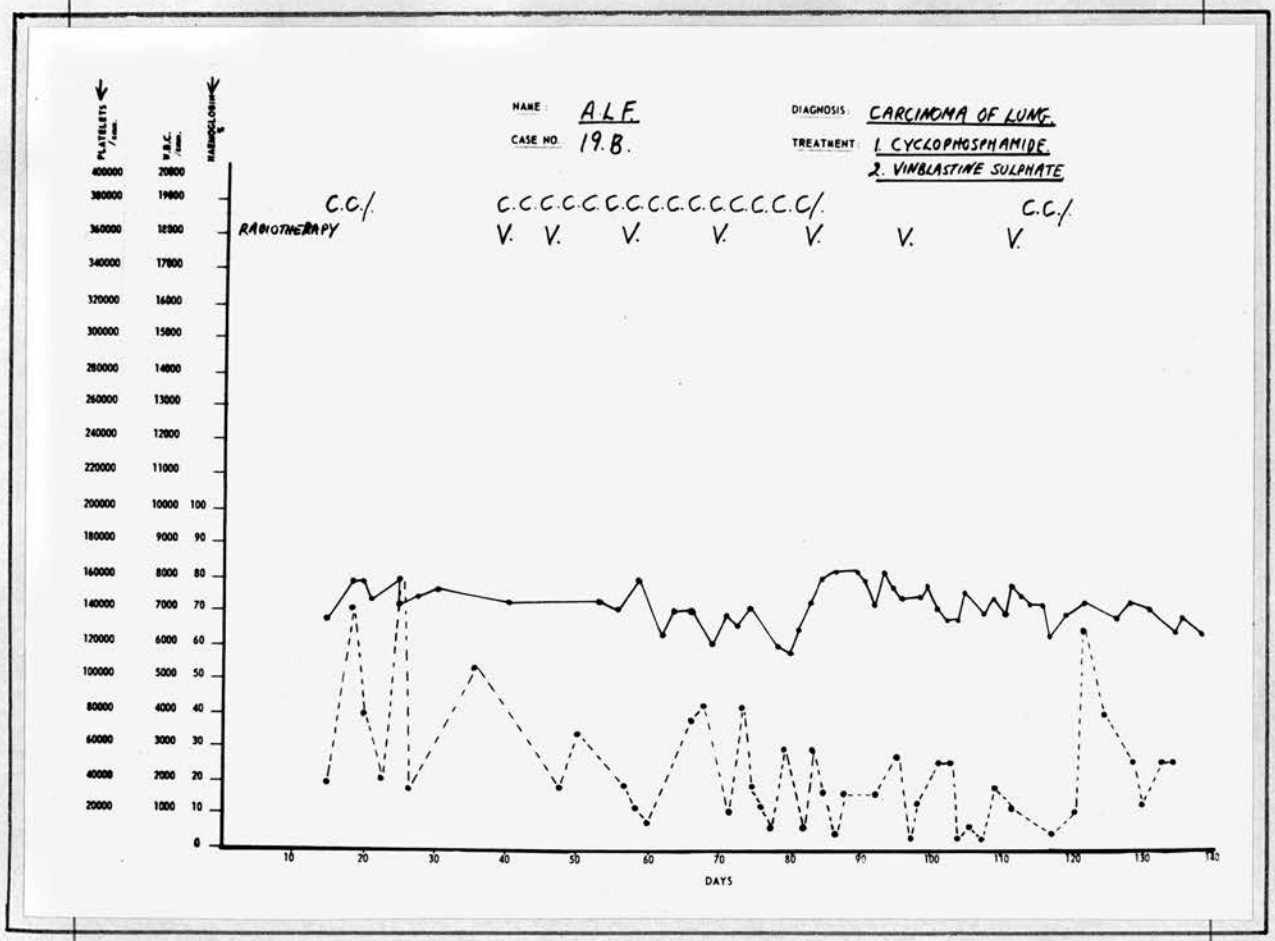
GRAPH A



CASE NO. 19

PERIPHERAL BLOOD COUNTS

GRAPH B



Case No. 19: Carcinoma of Lung

Fig. 1: Chest X-ray 10/1/63.

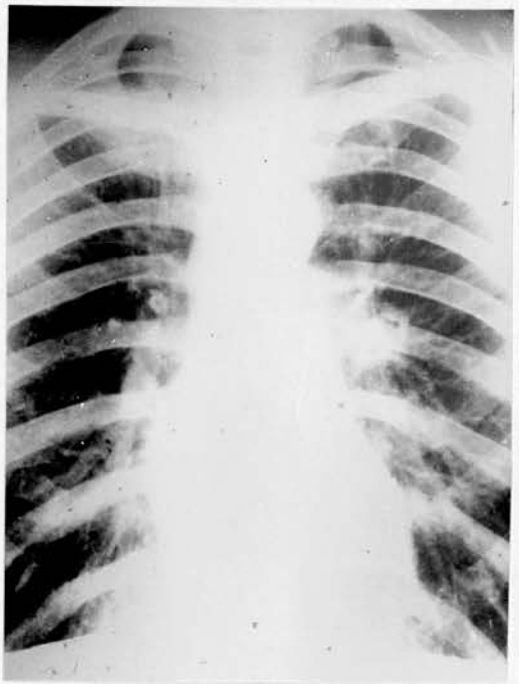


Fig. 2: Chest X-ray 2/4/63.

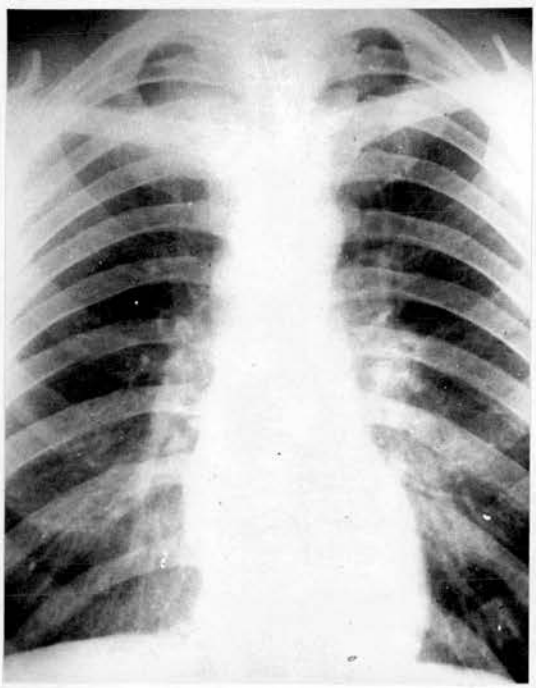


Fig. 3: Chest X-ray 16/9/63.

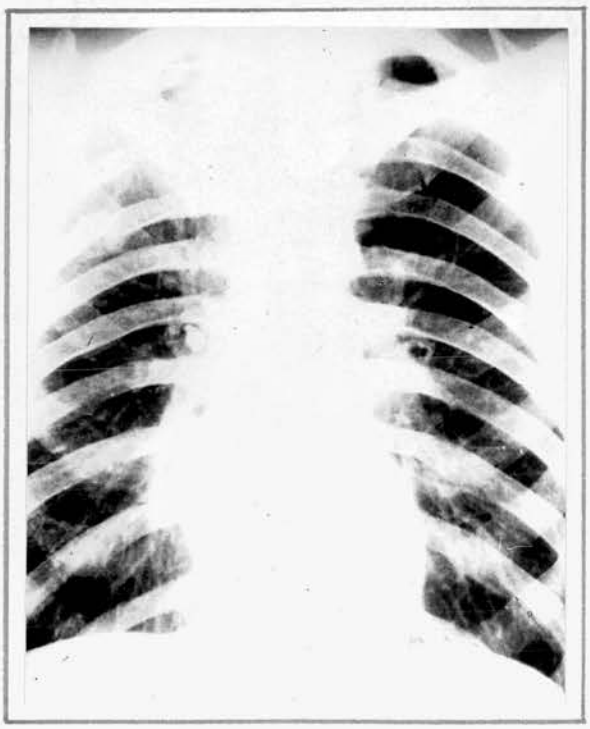


Table 2m

Case: 20	R.J.C. 7/10/63 Age: 51 Sex: M	
Diagnosis:	Carcinoma of (L) lung with adrenal metastases. (Biopsy of mass (L) main bronchus.)	
History:	Persistent productive cough for 8 months, increasing anorexia, weight loss and exertional dyspnoea for 4 months. Admitted to another hospital 16/7/63 where diagnosis of (L) bronchogenic neoplasm established by chest X-ray and bronchoscopy. (L) thoracotomy 8/8/63 revealed an extensive operable neoplasm of (L) lung.	
Previous or concurrent treatment:	(1) (L) thoracotomy:	8/8/63
	(2) Digoxin: 0.25 mg. - 1 mg. daily by mouth	7/10/63-2/1/64
	(3) Cortisone acetate: 50 - 100 mg. daily by mouth	7/10/63-2/1/64
	9∝fludrocortisone: 0.1 mg. daily by mouth	7/10/63-2/1/64
	(4) Antibiotics: Tetracycline, ampicillin	7/10/63-30/12/63
Cytotoxic treatment:	(1) Cyclophosphamide: 3,000 mg. by I.V.I.	16/10/63-5/11/63
	7,300 mg. orally	14/11/63-30/12/63
Clinical course and comments:	On admission patient was deeply pigmented and was thought to have Addison's disease secondary to adrenal metastases. He was fibrillating and in congestive cardiac failure. This responded to intensive medical treatment and cyclophosphamide was commenced 10 days after admission. Thereafter general condition slowly improved but an episode of acute left ventricular failure on 31/10/63 required urgent treatment. Rapid recovery. Chest infection 21/11/63 with Staph. aureus in sputum cleared with tetracycline and home for 1 month from 3/12/63. Readmitted 31/12/63 again in congestive cardiac failure with clinical and E.C.G. evidence of pericarditis. Condition rapidly deteriorated and patient died in coma on 3/1/64.	
Autopsy report:	Large carcinoma of hilum (L) lung with infiltration of mediastinal nodes. Collapse and infection distal to neoplasm. Extensive fibrinous pericarditis and haemorrhagic pericardial effusion. No liver metastases and no glands involved other than those in mediastinum. Adrenals were normal. Death due to cardio-respiratory failure secondary to pericarditis secondary to carcinoma of lung.	
Result:	1-2 for 2 months	

Case No. 20: Carcinoma of Lung

Fig. 1: Chest X-ray 22/7/63

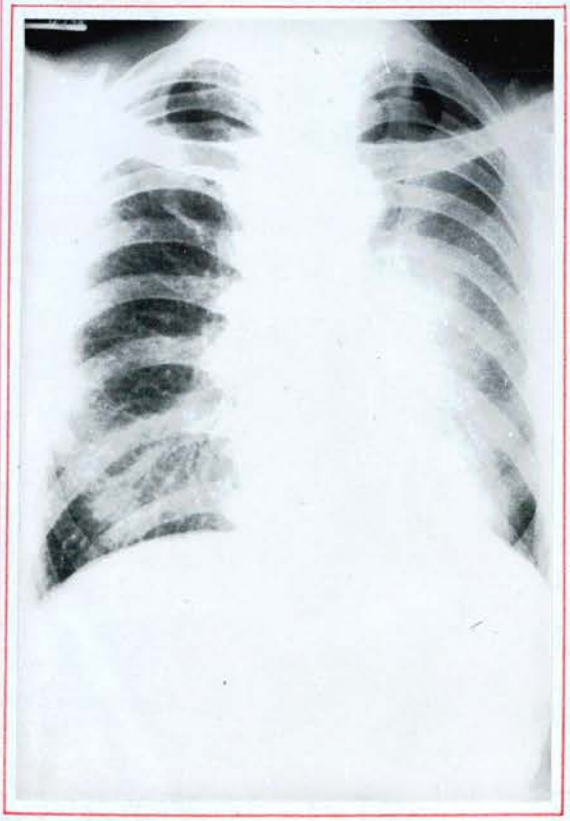


Fig. 2: Chest X-ray 31/12/63

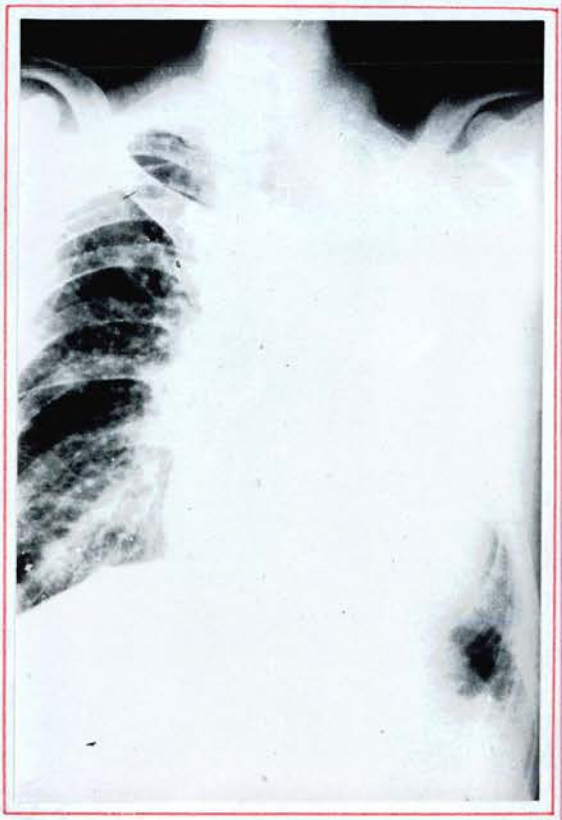


Fig. 3: Carcinoma of Lung : Addison's Disease

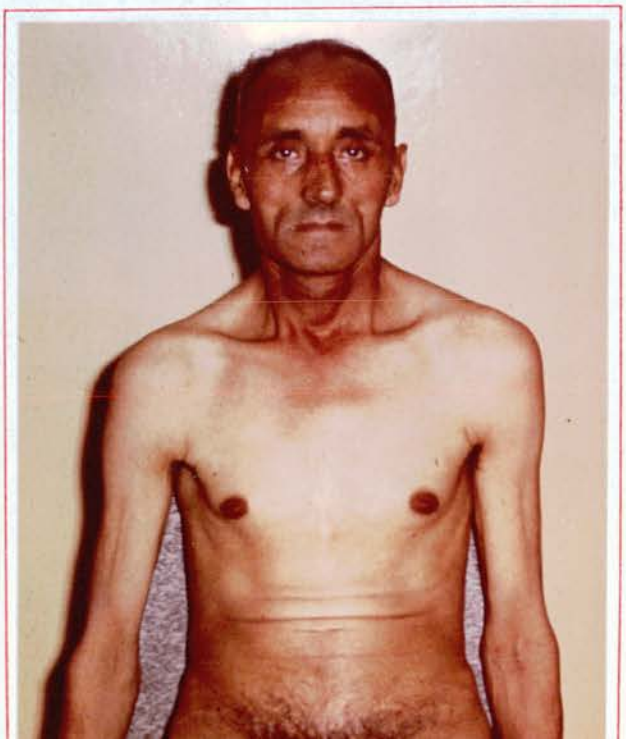


Table 2n

Case: 21	M.W. 2/8/65 Age: 56 Sex: F
Diagnosis:	Carcinoma of (L) upper lobe bronchus with widespread metastases in skin, bone and peritoneum. Anaplastic small-cell carcinoma.
History:	First admitted to another hospital 2/8/65 with a 1 month history of central chest pain and "lumps" in the skin. Also complained of breathlessness, weakness and pain in (R) leg and inability to weight-bear for 2 weeks. Haemoptysis three days prior to admission. Cough for 1 month. Poor appetite and loss of 3 lb. in weight over 3 weeks. N.B. 1 year previously had been treated in medical ward for (L)-sided pleurisy - followed up for 3 months. Smoked 20/day for many years. No family history of note.
Previous or concurrent treatment:	(1) Stilboestrol: 15 mg. by mouth daily 12/8/65-26/8/65 (2) Blood transfusion: 1 litre of whole blood 4/1/66 (3) Analgesics: Ponstan throughout Omnopon/morphine in increasing dosage from 3/1/66 (4) Excision biopsy of skin nodules August 1965 - in another hospital - and 29/10/65
Cytotoxic treatment:	(1) Cyclophosphamide: 3,400 mg. by I.V.I. 26/8/65-30/9/65 1,200 mg. orally 9/9/65-23/9/65 (2) Thiocolciran: 170 mg. by I.V.I. 21/10/65-8/1/66 (3) Methotrexate: 50 mg. orally 21/10/65-10/1/66 (4) 2-ethyl-hydrazine: 2 G. by I.V. infusion 19/1/66
Clinical course and comments:	Diagnosed as metastatic carcinoma but primary site was initially uncertain and thought most likely to be breast. No response to short course of stilboestrol and diagnosis revised to bronchogenic. Rapid and dramatic response to cyclophosphamide, but short-lived and required a single dose of radiotherapy to relieve pain from metastasis in (R) fibula. Subsequently a further good but short-lived response to thiocolciran and methotrexate. Treatment interrupted by oral ulceration. Reasonably well for 3 months and then required in-patient treatment for rapidly increasing pain in chest and skin metastases. Only transient benefit from further chemotherapy and terminally required increasing analgesia. Died 6 months from initial diagnosis, 19/2/66.
Autopsy report:	Multiple subcutaneous nodules over trunk and limbs - some ulcerated. Large tumour mass in (L) upper lobe invading mediastinum. Lymph gland and peritoneal metastases. Liver not involved. Histologically an anaplastic small-cell tumour of lung.
Result:	Remarkable but short-lived response to cyclophosphamide during which metastases melted away. Subsequent similar response to thiocolciran and methotrexate but also short-lived. Subsequently treatment of little benefit and pain required use of increasing doses of analgesic. Oral ulceration after 2 weeks of thiocolciran and methotrexate but treatment subsequently resumed without further trouble. 0-2 for 6 mth.

Table 2o

Case: 22	J.M. 29/3/65 Age: 61 Sex: M
Diagnosis:	Carcinoma of lung with widespread metastases - thought initially to be a hypernephroma. Diffusely infiltrating undifferentiated bronchogenic carcinoma.
History:	Three month history of intermittent, frank haematuria. Since onset of haematuria had steadily lost weight with progressive listlessness, dyspnoea, ankle swelling and anorexia, chronic productive cough for 3 months. Carcinoma of (R) maxillary antrum treated by radiotherapy in June, 1963. Out-patient investigation had shown a large tumour of (L) kidney, thought to be a hypernephroma with multiple pulmonary metastases. Referred for chemotherapy with this clinical ciagnosis.
Previous or concurrent treatment:	(1) Radiotherapy: for carcinoma of maxillary antrum June 1963 - details no known. (2) Chlorpromazine: 25 mg. 6-hourly I.M.I. from 2/4/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1000 mg. by intra-arterial infusion (L) renal artery 2/4/65. 400 mg. by I.V.I. 5/4/65 - 8/4/65 Total = 1400 mg.
Clinical course and comments:	Clinically this patient was thought to have an advanced (L) hypernephroma with widespread metastases. By selective arterial catheterisation 1 G. of cyclophosphamide was infused directly into (L) kidney and tumour on 2/4/65. A further 400 mg. of cyclophosphamide was given by intravenous injection. Patients' general condition was critically poor; following treatment deterioration continued, he developed a severe chest infection and progressed to death in the ward, on 18/4/65.
Autopsy report:	Bronchogenic carcinoma of (R) lower lobe bronchus with metastases to both lungs, liver, lymph-nodes, both kidneys and (L) adrenal. Pulmonary abscess formation and widespread bronchopneumonia.
Result:	No benefit from cytotoxins, but small amount only given and condition already far advanced when treatment commenced. 0 for 3 weeks.

GROUP C : LYMPHOSARCOMA

Table 3a

Case: 23	T.W. 18/4/63 Age: 27 Sex: M	
Diagnosis:	Generalised lymphosarcoma.	
History:	Perfectly well until October 1962 when he began to feel vaguely unwell, began to lose weight and noted that he was breathless on exertion. Admitted to another hospital on 11/12/62 and noted to have a (R) sided pleural effusion. The diagnosis was considered to be tuberculosis and although this could not be substantiated a 4 month course of anti-tuberculous chemotherapy was completed (including prednisolone). Initially there was some improvement but continual reformation of fluid in both pleural cavities required repeated aspiration. A full course of prednisolone was carried out between 13/3/63 and 21/4/63. No response to this treatment; condition progressively deteriorating and provisional diagnosis of lymphosarcoma was made.	
Previous or concurrent treatment:	(1) Antituberculous chemotherapy:	
	(a) Streptomycin - 90 G by I.M.I.	24/12/62-12/4/63
	(b) Pasinah 25 - 8 cachets daily	24/12/62-21/4/63
	(c) Prednisolone - 5 mg. T.I.D. orally 5 mg. Q.I.D. orally	24/12/62-12/4/63 from 21/4/63
	(2) Antibiotics: Penbritin 250 mg. 6-hourly	11/5/63-17/5/63
	(3) Analgesics: increasing doses	
	(4) Diuretics: orally	from 11/6/63
	(5) Radiotherapy: 1,000r to mediastinum	19/6/63-19/7/63
	(6) Repeated chest aspirations between 15/12/62 and 18/6/63 - 20 litres	
Cytotoxic treatment:	(1) Thiotepa: 80 mg. intrapleurally divided between two sides of chest	20/4/63-29/4/63
	(2) Nitrogen mustard: 50 mg. by I.V.I.	23/4/63-1/5/63
	(3) Vinblastine sulphate: 34 mg. by I.V.I.	21/5/63-13/6/63
	(4) Cyclophosphamide: 1,000 mg. by I.V.I. 900 mg. by mouth	30/5/63-8/6/63 12/6/63-19/6/63
Clinical/		

Table 3a (continued)

Clinical course and comments:	Patient anxious, distressed, ill and dyspnoeic on admission. Had already been in hospital for 4 months, had been extensively investigated and, despite treatment, was progressively deteriorating. Diagnosis still in doubt at this stage but general opinion was for lymphosarcoma. Decided to treat by aspiration of both sides of chest, to give cytotoxins intrapleurally and systemically and ultimately to present patient for radiotherapy. Small glands first noted in (L) side of neck on 22/4/63 and by 24/5/63 it was possible to obtain histological proof of lymphosarcoma by gland biopsy. With initial high doses of chemotherapy, dyspnoea decreased and required less frequent chest aspiration. General condition remained poor. Developed hallucinations, massive swelling of (R) leg, distressed and dyspnoeic. Further course of cytotoxins using velbe and cyclophosphamide produced some improvement and patient referred for radiotherapy on 19/6/63. Was able to tolerate only a few doses and progressively deteriorated to death on 19/7/63 - 9 months from onset of illness.
Autopsy report:	Confirmed presence of lymphosarcoma particularly involving glands of neck and mediastinum. Massive pleural effusions.
Result:	Only minimal and short-lived symptomatic relief obtained from cytotoxins - and patient never left hospital. 0-1 for 5 months only.

Table 3b

Case: 24	T.H.W. 10/6/63 Age: 47 Sex: M
Diagnosis:	Generalised lymphosarcoma. Neck gland biopsy.
History:	First noted a swelling in (L) side of neck in May 1963. Admitted to another hospital on 7/5/63 for investigation. No other symptoms at that time and no other significant findings. Neck gland biopsy revealed lymphosarcoma. No previous or family history of note.
Previous or concurrent treatment:	(1) Gland biopsy (R) side of neck: in another hospital 29/5/63 (2) Radiotherapy: 4,200r to both sides of neck 3,600r to mediastinum 12/6/63-16/7/63 (3) Radiotherapy: 3,950r to both groins 28/11/63-24/12/63
Cytotoxic treatment:	(1) Chlorambucil: 168 mg. orally (4 mg. daily) 12/9/63-24/10/63 420 mg. orally (4 mg. daily) 29/11/63-18/3/63
Clinical course and comments:	Lymphosarcoma appearing as painless swelling of neck. Treated initially by radiotherapy to neck and mediastinum. Completed course without incident, but experienced considerable soreness of throat and lost 10 lb. in weight. Discharged home 16/7/63 with marked regression of neck glands. No other findings. Remained in reasonable health but easily fatigued for 1 month. Then found to have gland masses in groins and iliac fossae. Commenced cytotoxins. Two months later general health was improved with gain in weight; no sweating or pruritis. Glands in groin remained enlarged and further radiotherapy to these sites in November 1963. Mild tinglings in hands and feet at this time. At latest review, 18/3/63, was remaining in good general health but persisting symptoms of neuritis in lower limbs. No palpable glands; liver, spleen not palpable.
Autopsy report:	-
Result:	Cytotoxins commenced when disease becoming more widespread. Held in check for 2 months and probably acting as good adjuvant to radiotherapy. Ultimate prognosis poor. 2-3 for 8 months to date.

Table 3c

Case: 25	D.T.W. 25/3/63 Age: 47 Sex: M
Diagnosis:	Generalised lymphosarcoma. Neck gland biopsy.
History:	First reported to another hospital at beginning of March 1963 with a painful swelling in (R) groin present for 2 weeks. Biopsy of the swelling was attempted at that time under local anaesthesia but was unsuccessful. Transferred to another hospital on 13/3/63. Now had numerous soft glands in both axillae in (R) side of neck and (R) groin. No other symptoms. Gland biopsy of neck established a diagnosis of lymphosarcoma and patient was transferred for further management. No previous or family history of note.
Previous or concurrent treatment:	(1) Gland biopsy (R) side of neck: at another hospital 15/3/63 (2) Radiotherapy: 5,000r to (R) groin 4,000r to both axillae 17/4/63-20/5/63 (3) Radiotherapy: 500r to abdomen 7/8/63-13/8/63 (4) Renal dialysis: one 6-hour dialysis on Kolff twin-coil artificial kidney 16/8/63 (5) Radiotherapy: 3,000r to base of skull 1,500r to lumbar spine 2/10/63-30/10/63 (6) Abdominal paracentesis: 600 ml. 4/8/63 (7) Prednisone: 20 mg./day orally 10 mg. daily 10/4/63 continuing 30/3/63-9/4/63
Cytotoxic treatment:	(1) Cyclophosphamide: 4,600 mg. orally 2/10/63-14/12/63 (2) Vinblastine sulphate: 26 mg. by I.V.I. 2/12/63-23/12/63
Clinical course and comments:	Diagnosis of lymphosarcoma established after initial difficulty in obtaining biopsy. Marked regression of gland masses following first course of radiotherapy in April 1963 and remained well for $2\frac{1}{2}$ months. Then began to develop increasing listlessness, anorexia, weight loss and abdominal distension. Readmitted 2/8/63 when abdomen was found to be enormously distended with large intra-abdominal gland masses, ascites and hepatomegaly. No significant peripheral lymphadenopathy. Radiotherapy was given to the abdomen for three days resulting in profound collapse and acute renal failure due to hyperuricaemia. Dialysis was successfully carried out and by 13/9/63 he was fit for discharge. Two weeks later he developed signs and symptoms of an intra-cranial lesion and also severe pain in sacro-iliac region and both legs. These responded to radiotherapy combined with chemotherapy. By 4/11/63 was well and out of hospital. Temporal epilation. Readmitted 1/12/63 ill with generalised severe neuralgic pains, weakness and paraesthesia. Slight improvement with treatment but vomited blood and died 26/12/63.
Autopsy/	

Table 3c (continued)

Autopsy report:	Confirmed widespread lymphosarcoma. In particular the kidneys showed widespread replacement by lympho cells leaving little recognisable renal tissue. Probable cause of death was terminal bleeding from gastrointestinal tract.
Result:	1-2 for 8 months. Cytotoxins used initially in conjunction with radiotherapy. Response to the combined treatment was dramatic in degree but of short duration. Although a further course of chemotherapy was given in the last few weeks of the illness, the result was minimal only and patient died of gastrointestinal tract haemorrhage.

GROUP D : LEUKAEMIA

Table 4a

Case: 26	B.H.W. 20/6/62 Age: 38 Sex: M
Diagnosis:	Chronic myeloid leukaemia.
History:	First reported on 18/6/62 with a history of increasing anorexia, general malaise, and loss of 3 stones in weight over a period of 6 months. "Spots" on upper lip for 1 week, feverishness, nausea, vomiting, epistaxis and paraesthesiae in hands for 2 days. No symptoms referable to other systems. Malaria in 1943-44. Gonorrhoea in 1952-53. No other previous or family history. Diagnosed as chronic myeloid leukaemia on basis of 370,000 TWBC (71% myeloid series).
Previous or concurrent treatment:	(1) Blood transfusion: Total of 16 pints of whole blood transfused at intervals between 21/6/62 and 25/6/63 (2) Antibiotics: (a) Penicillin (oral) 250 mg. 4-hourly 18/6/62-21/6/62 (b) Tetracycline, 250 mg. 6-hourly 22/6/62-29/6/62 (c) Erythromycin, 250 mg. 6-hourly 21/6/63-3/7/63 (3) Prednisone: 75-15 mg. daily in divided doses 24/6/62-1/6/63
Cytotoxic treatment:	(1) Cyclophosphamide: 600 mg. by I.V.I. (3 x 200 mg.) 13/6/63-16/6/63
Clinical course and comments:	Disease already advanced when diagnosis made on clinical and haematological examination. Marked hepato-splenomegaly and acute chest infection when first admitted. Treatment commenced with antibiotics and prednisone with rapid response. Discharge from hospital after 5 weeks treatment and at this stage was well with marked reduction in size of liver and spleen. Remained well and at work for 10 months. Was then readmitted with pyrexia, splenomegaly and general malaise. Treatment with blood transfusion, increased steroids and cyclophosphamide on temporarily checked downhill course and died with virtual marrow failure on 8/7/63 - 1 year after first diagnosis.
Autopsy/	

Table 4a (continued)

Autopsy report:	Widespread petechial haemorrhages and ecchymoses in axillae and groins. Pericardial effusion (150 ml.). Spleen enormously enlarged (3,150 gm.). Liver greatly enlarged (3,000 gm.). Evidence of agranulocytosis and marrow failure. Final diagnosis: chronic myeloid leukaemia with terminal acute phase with infiltrates in marrow, spleen, liver and lymph nodes.
Result:	Cytotoxins only employed in terminal phases of illness and were of no benefit. It is to be noted, however, that prednisone produced a 10 month remission of symptoms.

Case No. 26: Chronic Myeloid Leukaemia

Fig. 1: Massive Splenomegaly

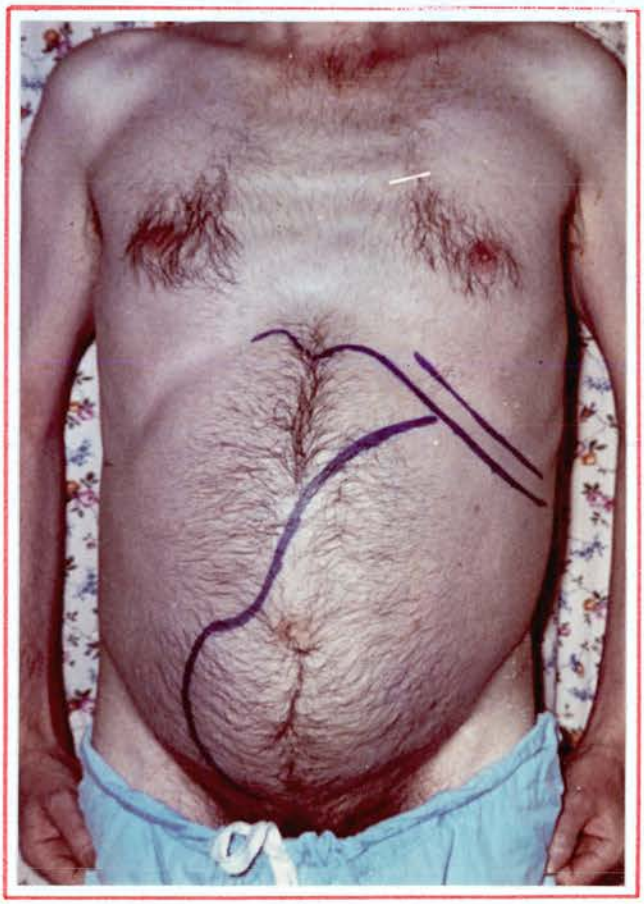


Table 14b

Case: 27	T.M.P. 27/5/63 Age: 18 Sex: M
Diagnosis:	Acute monocytic leukaemia.
History:	Admitted to another hospital on 15/5/63 with a 6 day history of fever, headache, anorexia and generalised aches and pains. While in hospital continued to run a high-grade fever, developed generalised lymphadenopathy and splenomegaly. Became lethargic, apathetic and confused. Progressive increase in size of glands. Transferred for further management on 22/5/63 and diagnosis of acute monocytic leukaemia established. Infective hepatitis 1 year previously. No other previous or family history.
Previous or concurrent treatment:	(1) Antibiotics: (a) Penicillin by I.M.I. 17/5/63-22/5/63 (b) Penbritin, 250 mg. 6-hourly 18/5/63-21/5/63 (c) Streptomycin, 1G daily 19/5/63-27/5/63 (d) Tetracycline, 500 mg. 6-hourly 19/5/63-23/5/63 (2) Blood transfusion: 1½ litres of whole blood 13/6/63 (3) Gland biopsy (R) side of neck: 28/5/63 (4) Prednisone: 75 mg.-30 mg. daily 31/5/63-10/7/63
Cytotoxic treatment:	(1) Cyclophosphamide: 1,200 mg. by intravenous infusion 4/6/63-13/6/63 300 mg. orally 22/6/63-27/6/63 2,000 mg. by intravenous infusion 28/6/63-1/7/63 400 mg. by I.V.I. 9/7/63 Total - 3,900 mg. (2) Vinblastine sulphate: 10 mg. by I.V.I. 21/6/63-24/6/63
Clinical course and comments:	Initially thought to have a severe infection ?septicaemia, and received massive antibiotic therapy. Rapid deterioration. Extremely ill on admission. Typical swelling of gums, widespread, discrete non-tender enlargement of all lymph gland groups. Commenced treatment with prednisone on 31/5/63; only minimal and short-lived response and accordingly cyclophosphamide therapy commenced on 4/6/63. General condition improved after 5 days treatment but then developed an episode of nausea, vomiting and abdominal pain - gradually subsided. After further period of deterioration condition improved dramatically by 2/7/63 and improvement maintained for 3 weeks. Then sudden deterioration with enlargement of all gland masses and died 22/7/63.
Autopsy report:	Widespread lymphatic involvement by leukaemic process. Evidence of terminal septicaemia in liver, spleen and bone marrow.
Result:	Transient benefit only from cyclophosphamide therapy. Total illness was only 2 months and patient in hospital throughout. 0-1 for 2 months. Mild loss of hair.

Table 4c

Case: 28	M.C.C. 7/6/63 Age: 6 Sex: M
Diagnosis:	Acute myeloid leukaemia.
History:	First diagnosed as acute myeloid leukaemia in another hospital in November 1962 when he presented with a 6 week history of bruising of arms and legs, progressive listlessness and apathy. He was treated at that time by blood transfusion, prednisone and 6-mercaptopurine. Remained reasonably well and at school until April 1963 when an acute relapse occurred. This again responded to treatment but transferred here on 7/6/63 because of rapidly weakening state. At this stage he was anaemic, listless and there was extensive bruising of limbs. Few soft glands in neck.
Previous or concurrent treatment:	(1) Prednisolone: 30 mg.-15 mg. daily by mouth 7/11/62-28/7/62 (2) Blood transfusion: 500 ml. 7/11/62 500 ml. 8/6/63 500 ml. 26/6/63 (3) Antibiotics: (a) Penicillin, 125 mg. 6-hourly by mouth from 11/6/63
Cytotoxic treatment:	(1) 6-mercaptopurine: 500 mg. by mouth (25 mg. daily) 24/11/62-14/12/62 1,425 mg. by mouth (ranging from 50 mg. daily down to 12.5 mg. on alternate days 27/4/63-27/7/63
Clinical course and comments:	Initial progress as under "History". Within a few days of admission on 7/6/63 he became generally unwell with anaemia and rising white blood count. Condition improved with blood transfusion and antibiotics but no further response to steroids. Accordingly 6-mercaptopurine was recommenced (50 mg. daily). Condition rapidly improved and discharged home 27/6/63. Thereafter remained reasonably well and fully active until 28/7/63 when he was readmitted as an emergency with severe (R) sided abdominal pain, grunting respirations, silent rigid abdomen and general appearances of terminal state. Diagnosis of perforated viscus made clinically (steroid therapy induced) but collapsed and died before any investigation or treatment could be carried out.
Autopsy report:	Large (R) axillary abscess - 80 ml. pus. Slight enlargement of all lymph nodes, of liver and spleen. No perforation of viscus. Lymph nodes, liver, kidneys, and spleen showed widespread infiltration with leukaemic cells. Death essentially unexplained but thought to be either acute septicaemia or gross biochemical derangement.
Result:	Good objective response to 6-mercaptopurine combined with prednisolone but no response to latter alone. Initial remission maintained for 6 months and thereafter only short periods of remission obtained. 1-2 for 10 months.

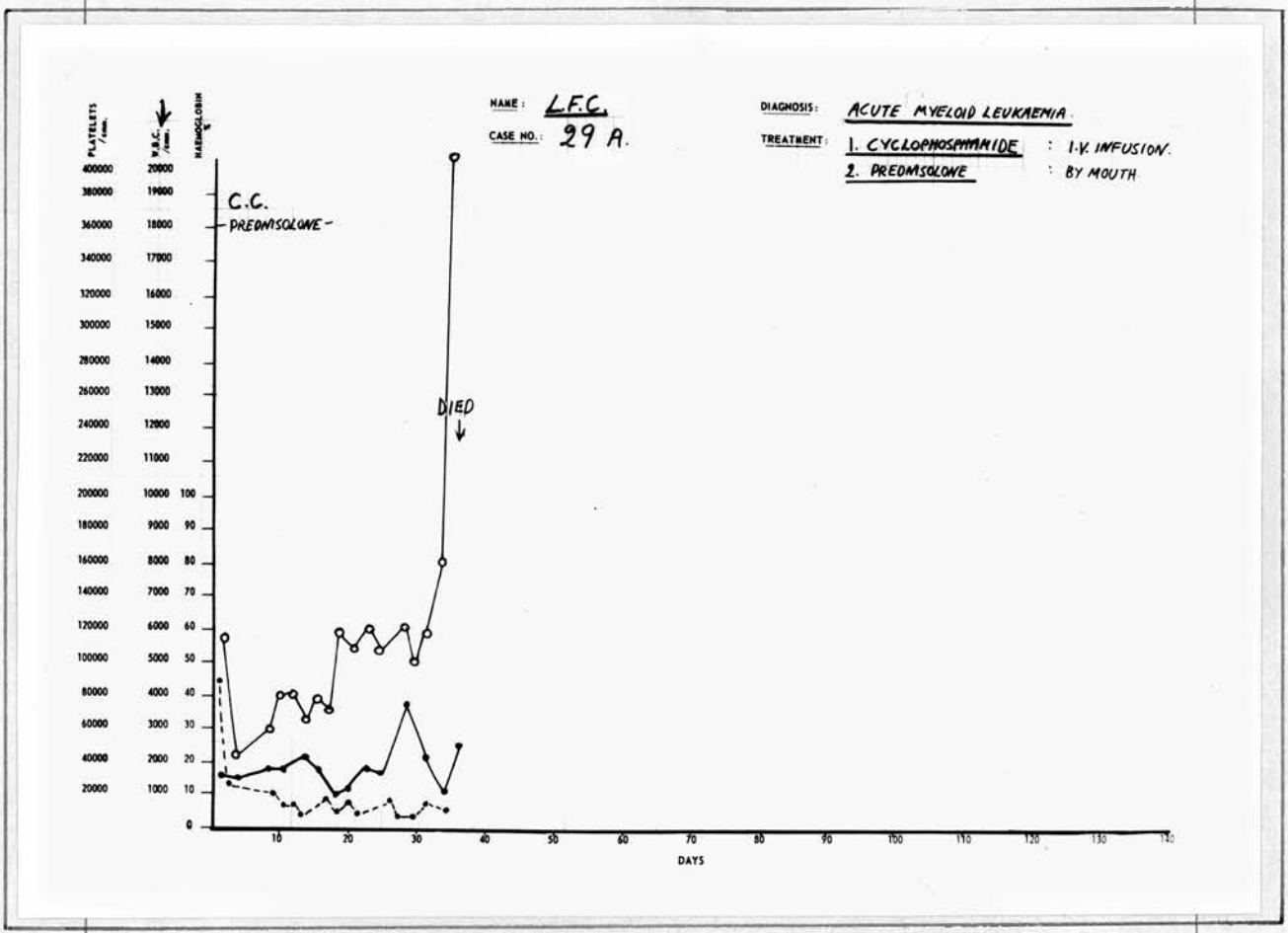
Table 14d

Case: 29	L.F.C. 14/8/63 Age: 21 Sex: M
Diagnosis:	Acute myeloid leukaemia.
History:	First reported on 8/8/63 having noticed bleeding from his gums while brushing his teeth the previous day. Has also noticed a fine "rash" around both ankles and present for 3 days. Over the previous month patient had noted occasional red blotches on arms and legs and a tendency to bruise more easily. No symptoms related to any system. No previous or family history of note.
Previous or concurrent treatment:	(1) Prednisolone: 100 mg.-60 mg. daily by mouth 9/8/63-31/8/63 (2) Antibiotics: (a) Penicillin, 250 mg. by mouth 6-hourly from 9/8/63 (3) Blood transfusion: 2 litres of whole fresh blood 29/8/63
Cytotoxic treatment:	(1) Cyclophosphamide: 500 mg. by intravenous infusion, 30/8/63
Clinical course and comments:	On admission his symptoms and good general condition belied the seriousness of his blood disorder. Despite prednisolone in high dosage there was a progressive fall in Hb and platelets. Remained well, however, until 29/8/63 when he became extremely ill with severe back and loin pain, bleeding from gums and mucous membranes. Clinically retroperitoneal haemorrhage. Despite blood transfusion and intravenous cyclophosphamide his condition deteriorated, became restless, dyspnoeic and died with terminal generalised bleeding 31/8/63 - $3\frac{1}{2}$ weeks from diagnosis.
Autopsy report:	Permission not obtained.
Result:	No benefit from prednisolone. Cyclophosphamide exhibited too late to have any effect whatsoever on course of disease. 0 for $3\frac{1}{2}$ weeks.

CASE NO. 29

PERIPHERAL BLOOD COUNTS

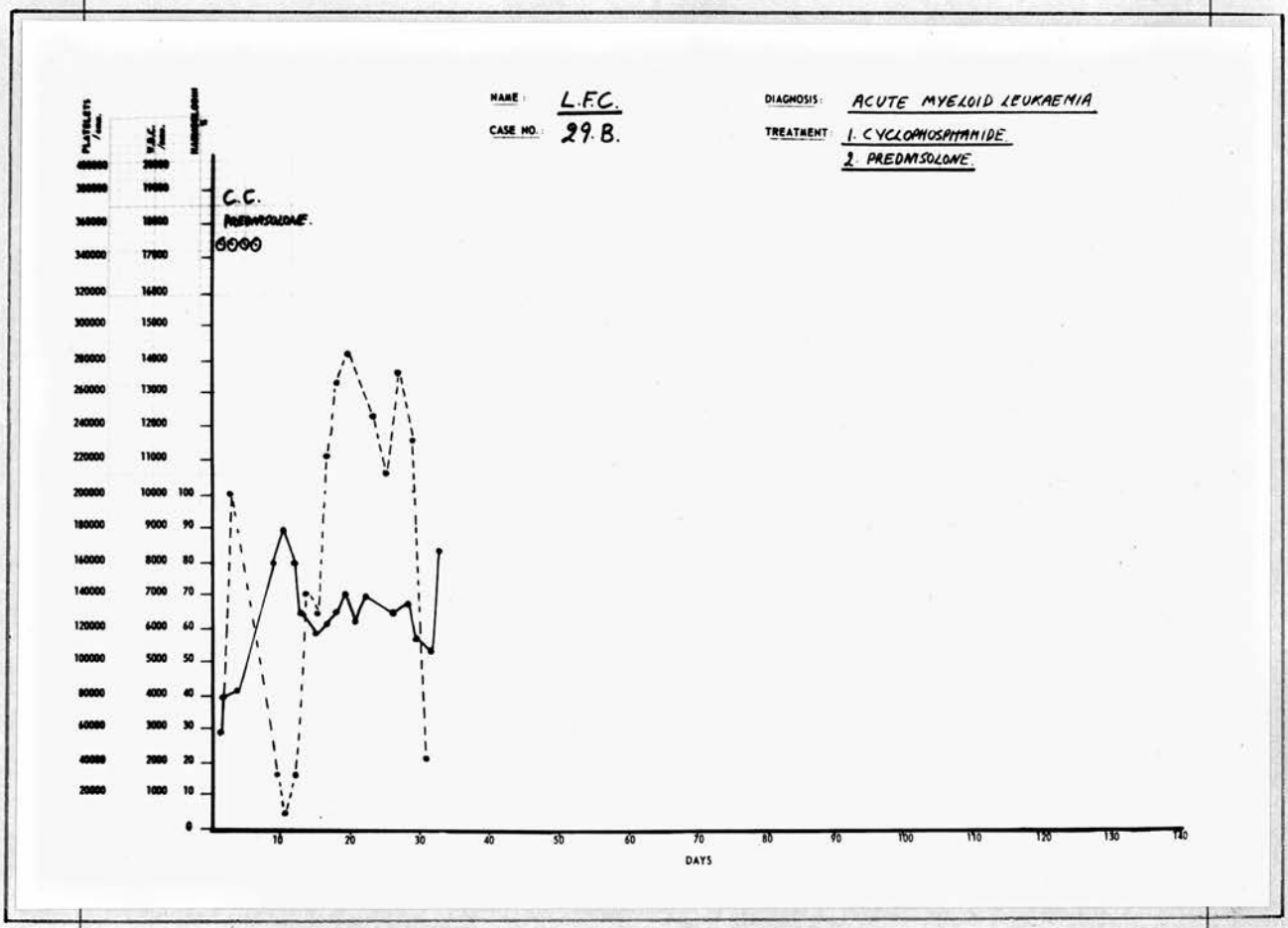
GRAPH A



CASE NO. 29

PERIPHERAL BLOOD COUNTS

GRAPH B



GROUP E : MULTIPLE MYELOMATOSIS

Table 5a

Case: 30	H.E.V. 22/2/63 Age: 50 Sex: M
Diagnosis:	Multiple myelomatosis
History:	First admitted to another hospital 23/1/63 with signs and symptoms of a (R) basal pneumonia which had failed to respond to usual measures. At this time was complaining of cough and haemoptysis, anorexia, marked exertional dyspnoea and loss of 1½ stones in weight over previous 9 months. In previous history patient had had recurrent bouts of pneumonia since December 1961 requiring in-patient treatment. On present occasion was thought to have a carcinoma of lung but investigation established a diagnosis of multiple myeloma and patient transferred for further management. One brother died of Hodgkin's disease; no other family history.
Previous or concurrent treatment:	(1) Antibiotics: in repeated courses between December 1961 and March 1963 - usually tetracycline or penicillin (2) Blood transfusion: 5½ litres of whole blood between 10/2/63 and 27/3/63 (3) Prednisone: 40 mg.-10 mg. daily by mouth 25/3/63-9/7/63
Cytotoxic treatment:	(1) Cyclophosphamide: 6,100 mg. by I.V.I. 24/2/63-24/4/63 8,100 mg. by mouth 24/2/63-9/7/63
Clinical course and comments:	Multiple myelomatosis presenting in typical way with recurrent episodes of pulmonary infection usually clearing with antibiotics and physiotherapy. On admission 22/2/63 was extremely ill with dyspnoea and cyanosis from extensive consolidation of (R) lower lobe. Thought to have (R) pleural effusion, but two attempts at aspiration were unsuccessful. 3 weeks after admission, however, chest was beginning to clear as the result of treatment with antibiotics; cyclophosphamide and physiotherapy. 2 months after admission appetite had returned to normal with gain of a few pounds in weight. Chest was now clear and blood picture satisfactory following transfusion and prednisone. Discharged home 24/4/63. Readmitted 16/5/63 with recurrent chest symptoms and involvement now of (L) upper lobe. Symptoms and signs resolved rapidly on this occasion and discharged on cyclophosphamide and prednisone 29/5/63. Dramatic improvement by 20/6/63 with chest entirely clear on X-ray. Remained well until 10/7/63 when readmitted as an emergency to a local hospital in extremis with diarrhoea and vomiting. Died in peripheral circulatory failure on same day.
Autopsy report:	Death considered due to pneumonia and acute (R)-sided heart failure. Confirmed myelomatosis but no extra-osseous myeloma deposits. Severe coronary artheroma. (R) lower lobe consolidation and pleural adhesions.
Result:	Short period of control with prednisone and cyclophosphamide, but sudden unexpected death suggests the possibility of septicaemia. 1-2 for 5 months.

Case No. 30: Multiple Myelomatosis

Fig. 1: Chest X-ray 13/12/61.

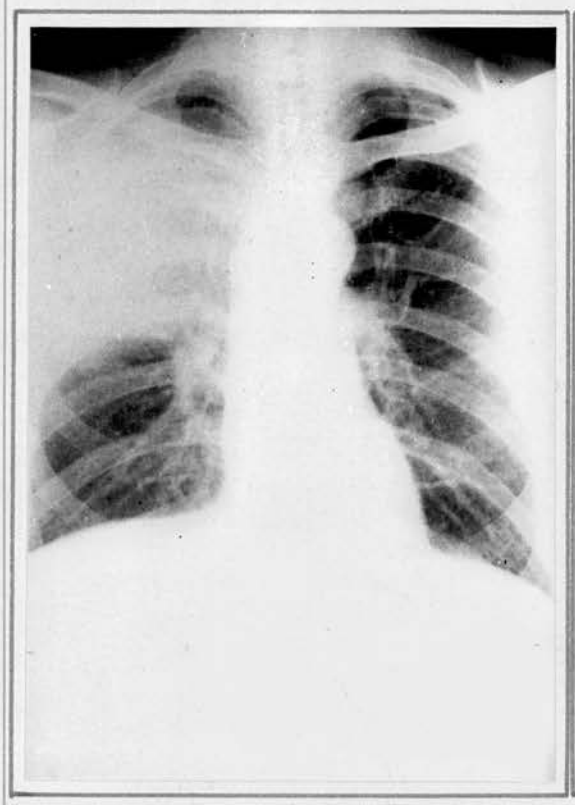


Fig. 2: Chest X-ray 8/12/62.

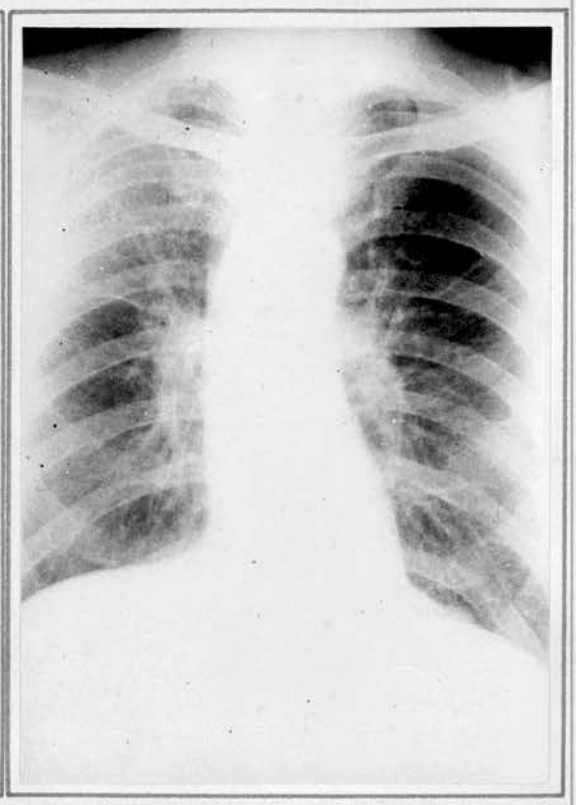


Fig. 3: Chest X-ray 24/2/63.

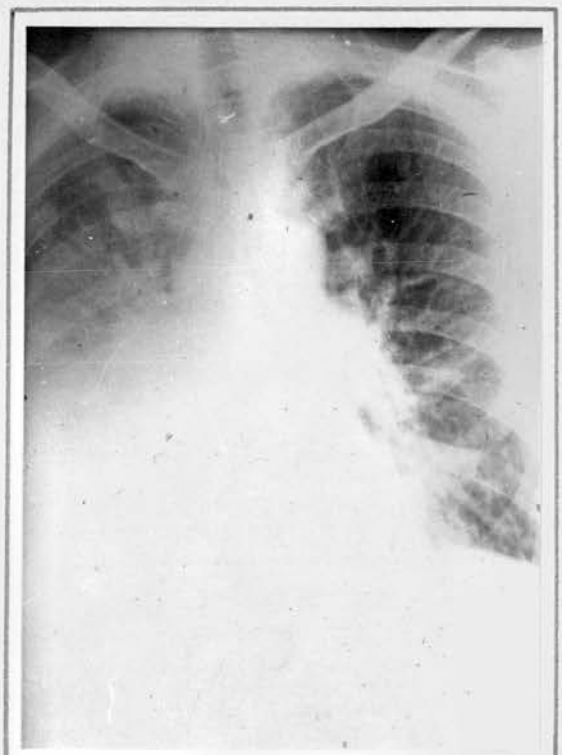
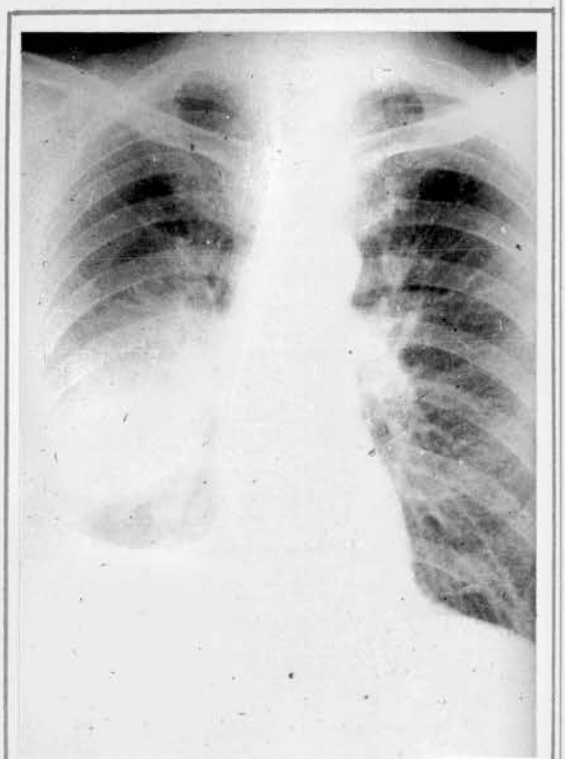
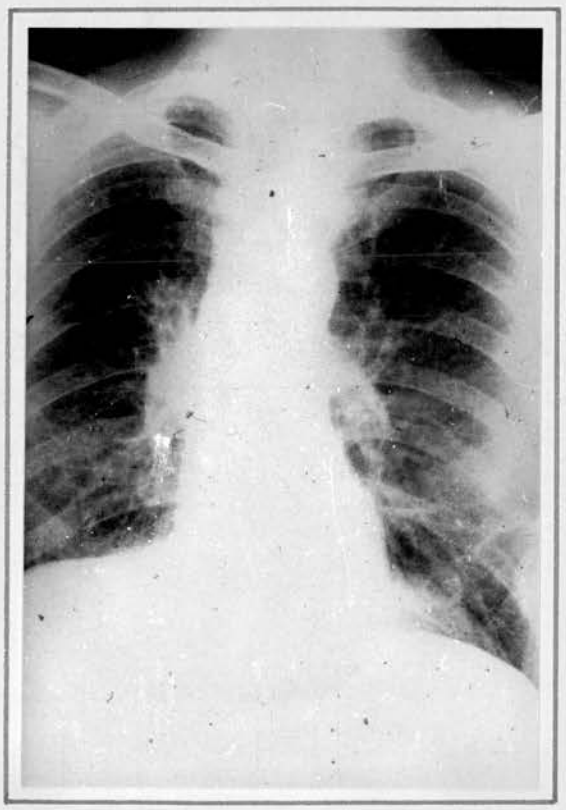


Fig. 4: Chest X-ray 15/4/63.



Case No. 30

Fig. 5: Chest X-ray 20/6/63.



GROUP F : CARCINOMA OF BREAST

Table 6a

Case: 31	E.B. 9/1/62 Age: 48 Sex: F	
Diagnosis:	Carcinoma of (L) breast with widespread skeletal metastases.	
History:	(L) radical mastectomy for Stage II carcinoma 1955, followed by postoperative radiotherapy. Well until September 1958 when developed pain in (R) chest. X-ray March 1959 showed a pathological fracture of (R) 9th rib. Complete relief from deca-durabolin. Then developed further rib and humeral deposits. Bilateral oophorectomy and two-stage adrenalectomy carried out without incident. Good response until September 1960, then given radiotherapy for re-activation of metastasis (L) humerus. Pathological fracture (L) humerus October 1961 but otherwise well until January 1962 when admitted with severe back pain and paralysis of leg from spinal metastases.	
Previous or concurrent treatment:	(1) (L) radical mastectomy:	July 1955
	(2) Radiotherapy: 4,100 r to internal mammary nodes 4,050 r to (L) supraclavicular nodes 3,250 r to anterior axilla	2/8/55-5/10/55
	(3) Durabolin: 25 mg. weekly x 4 by I.M.I.	March 1959
	(4) Bilateral oophorectomy and two-stage adrenalectomy:	June 1959
	(5) Radiotherapy: 2,000 r to (L) humerus	23/9/60-3/10/60
	(6) Cortisone acetate: 75-150 mg./day orally from time of adrenalectomy	
	(7) Durabolin and dianabol:	11/10/62-24/6/63
	(8) Radiotherapy: 2,800 r to lumbar spine 2,400 r to (L) humerus	September 1960
	(9) Radiotherapy: 3,600 r to lumbar spine	1/5/63-13/5/63
	(10) Analgesics: Wide variety at various times and often in considerable amount.	
Cytotoxic treatment:	(1) Cyclophosphamide: 18,000 mg. orally 3,000 mg. by I.V.I. 12,600 mg. orally 1,400 mg. by I.V.I. Grand total - 35,000 mg.	15/1/62-19/8/62 5/3/63-13/3/63 14/3/63-13/8/63 6/12/63-1/1/64
	(2) Vinblastine sulphate: 45 mg. by I.V.I.	13/9/63-17/11/63
Clinical/		

Table 6a (continued)

Clinical course and comments:	When readmitted in January 1962 was virtually bedridden due to back pain from metastases in lumbar spine; marked weakness in lower limbs. Commenced intravenous cyclophosphamide, rapidly experienced relief of back pain but developed severe electrolyte disturbances, became hypotensive and required high dosage of cortisone to restore balance. By 5/2/62 required antibiotics and barrier nursing because of very low W.B.C. (600/ccm). Marked alopecia 22/2/62 but feeling well and pain-free. Discharge home on 24/2/62 on maintenance dose of oral cyclophosphamide. 1 month later was fully mobile and symptom-free. Remained well for a total of six months and then readmitted with further severe low back pain but no other gross findings. Further radiotherapy to spine August 1962 but symptoms greatly aggravated and treatment stopped. Further response to anabolic steroids and cyclophosphamide. Remained reasonably well for further 6 months and then readmitted in constant severe pain from spinal metastases. Marked weakness and loss of sensation in lower limbs. Analgesics not controlling pain. Further dramatic response to cyclophosphamide, pain relieved and power improved in lower limbs. Hair regrowth. Home for further 2 months. Readmitted for review 20/8/63; general improvement continued but required radiotherapy for a new area of pain in mid-dorsal region. Started on vinblastine sulphate while on radiotherapy. Well enough to go home on 22/10/63 and at home for 2 months. Then readmitted with severe pain in neck and back - reactivation of widespread skeletal metastases. Now developed bladder and bowel symptoms, chest infection, congestive cardiac failure and finally died, after a distressing terminal phase, on 2/1/64.
Autopsy report:	Widespread hepatic and skeletal metastases from carcinoma of breast; relatively little lymph gland spread and lungs not involved. Bone marrow hypoplasia.
Result:	Remarkable and sustained regression on cyclophosphamide. Further long remissions obtained from repeated course of cyclophosphamide and altogether was at home for 16 of the 24 months on treatment.

Case No. 31: Carcinoma of Breast

Fig. 1: Chest X-ray 1/6/59.

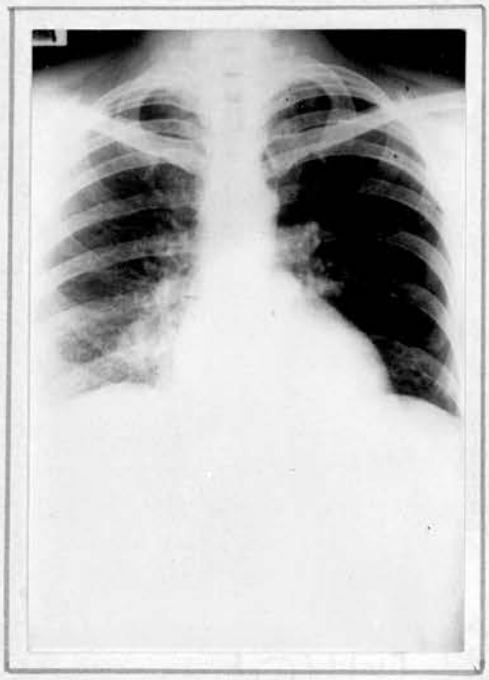


Fig. 2: Chest X-ray 2/10/63.

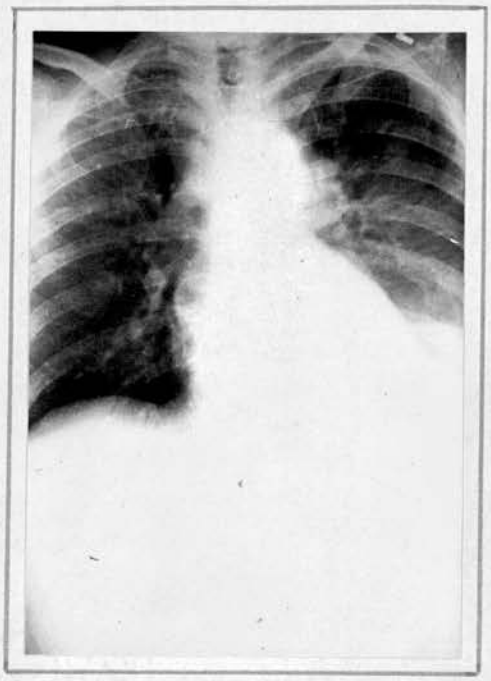


Fig. 3: Neck X-ray 1/6/59.

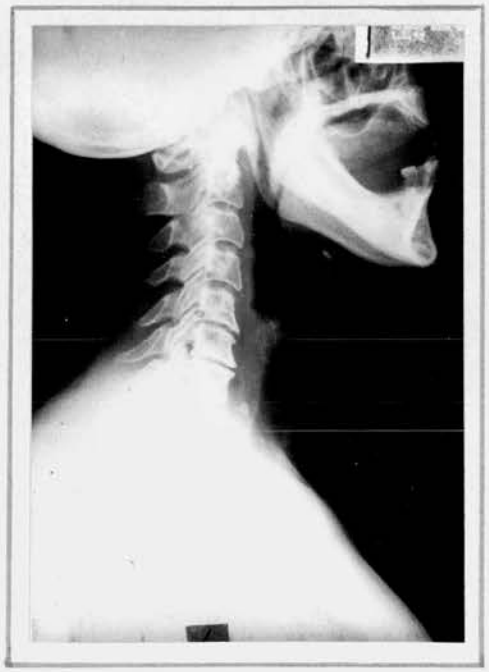
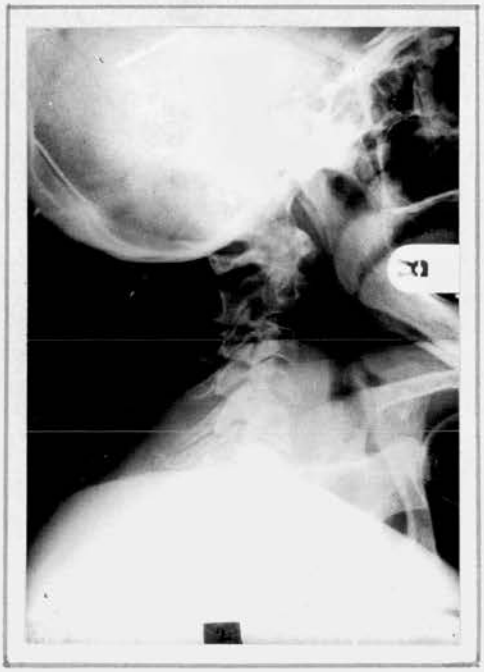


Fig. 4: Neck X-ray 5/12/63.



Case No. 31.

Fig. 5: (L) Humerus X-ray 4/9/60.

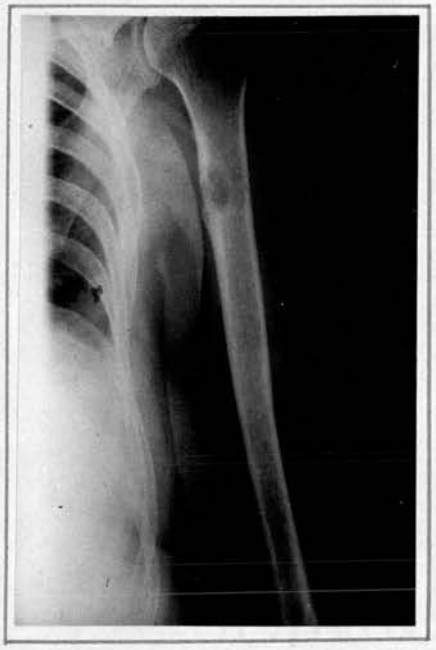


Fig. 6: (L) Humerus X-ray 2/10/63.

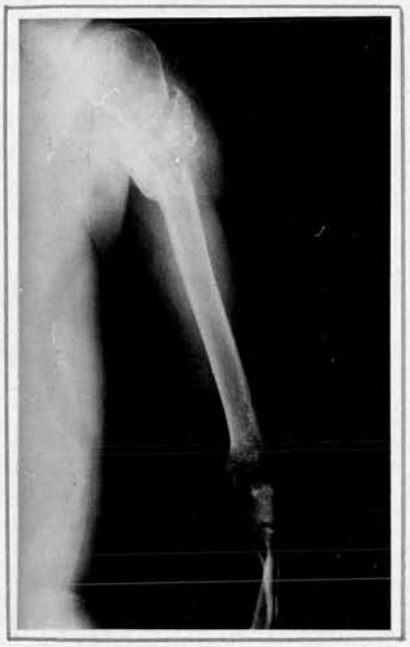


Fig. 7: Lumbar spine X-ray 1/6/59.

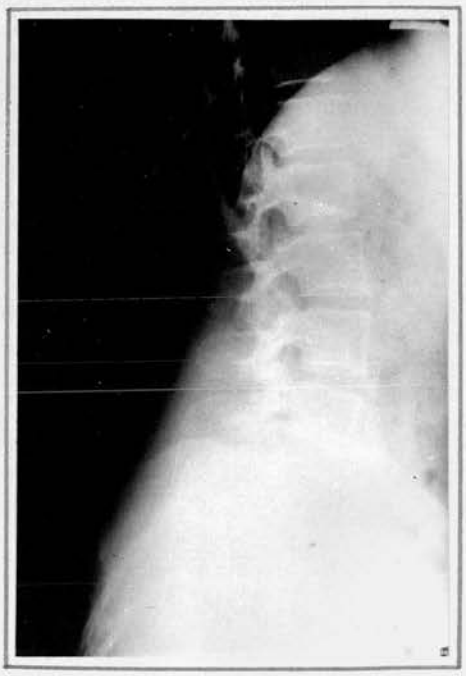
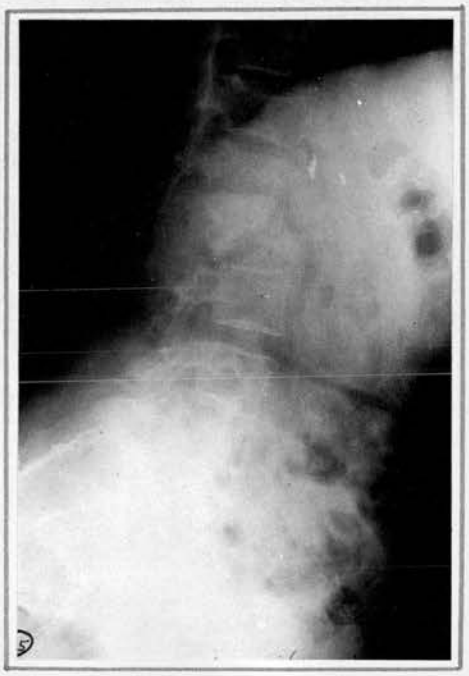


Fig. 8: Lumbar spine X-ray 2/10/63.



Case No.31.

Fig. 9: Lumbar spine X-ray 1/6/59.

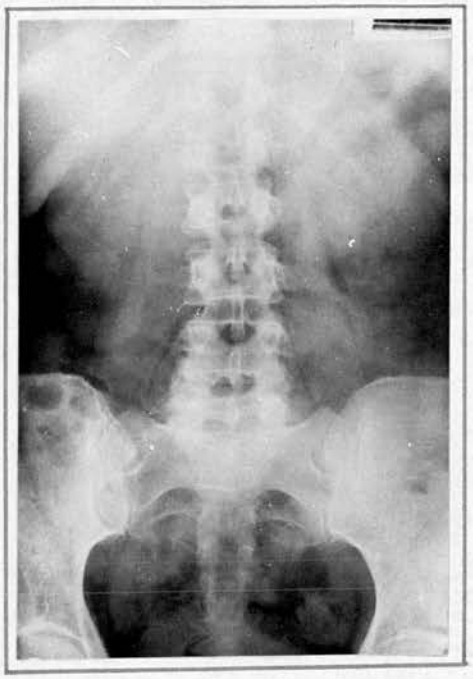


Fig. 10: Lumbar spine X-ray 2/10/63.

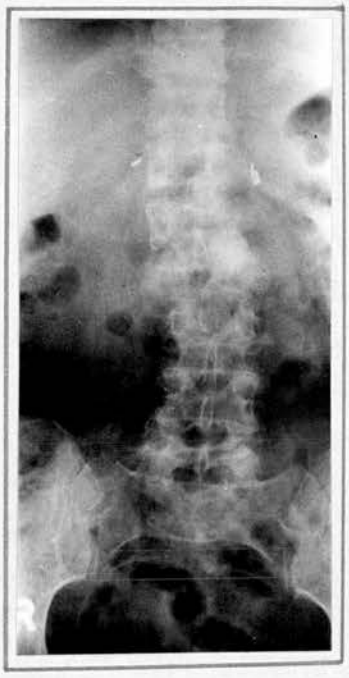


Fig. 11: Pelvis X-ray 1/6/59.

Fig. 12: Pelvis X-ray 2/10/63.

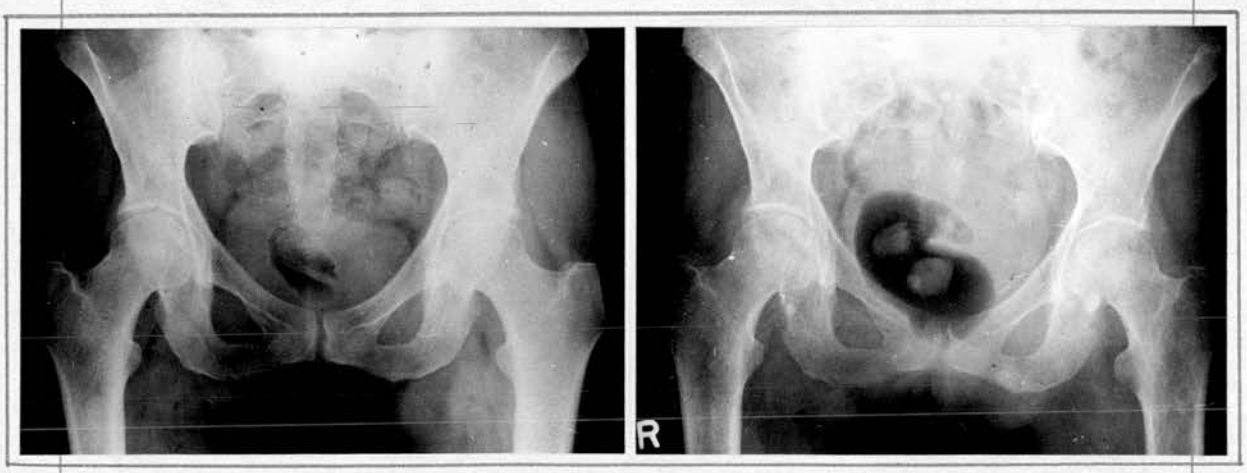


Table 6b

Case: 32	M.C. 9/8/62 Age: 36 Sex: F
Diagnosis:	Carcinoma of (L) breast Stage III. Anaplastic infiltrating duct carcinoma.
History:	Painless, non-tender lump in (L) breast for 1 month. No other relevant symptoms. Hard, irregular mobile mass 6 cm. in diameter.
Previous or concurrent treatment:	(1) Radiotherapy: 5,969r to tumour area (L) breast as pre-operative procedure 16/8/62-27/9/62 (2) Bilateral oophorectomy: 30/8/62 (3) (L) radical mastectomy: 6/11/62
Cytotoxic treatment:	(1) Cyclophosphamide: 300 mg. by intra-arterial infusion via (L) internal mammary artery during operation (2) Mannitol mustard: 300 mg. by I.V.I. 5/11/62-7/11/62
Clinical course and comments:	Large carcinoma of (L) breast treated by initial course of radiotherapy to maximum dose, followed by radical mastectomy. Operation carried out under cytotoxic cover. Postoperative course complicated by delayed wound healing and by necrosis of tips of (R) first and second toes. ? pressure effect. Discharged well on 16/12/62. Readmitted to another hospital as an emergency on 20/3/63 and died the same night. Had been well until 1 week before admission when became increasingly breathless, developed swelling of feet and ankles, was jaundiced and in peripheral circulatory failure on admission. Said to have an enlarged liver and left pleural effusion.
Autopsy report:	Post-mortem not carried out.
Result:	Patient given cytotoxins prophylactically. Total treatment prolonged and sudden unexplained deterioration 3 months after leaving hospital. ? septicaemia. ? myocarditis or cardiomyopathy.

Table 6c

Case: 33	D.B. 31/10/62	Age: 50 Sex: F
Diagnosis:	Carcinoma of (L) breast. Stage I. Infiltrating duct carcinoma.	
History:	Lump in (L) breast noted six months previously. Slight pain in breast. Periods still normal. No other significant symptoms.	
Previous or concurrent treatment:	(1) Biopsy of mass (L) breast:	11/12/62
	(2) (L) radical mastectomy:	18/12/62
	(3) Bilateral oophorectomy:	5/1/63
	(4) Radiotherapy: 4,400r to (L) axilla and (L) neck	17/1/63-18/2/63
	(5) Blood transfusion: 2 pints whole blood	17/12/62 and 4/1/63
Cytotoxic treatment:	(1) Mannitol mustard: 425 mg. by I.V.I. (100 mg. x 4, 25 mg. x 1)	16/12/62-20/12/62
Clinical course and comments:	Uninterrupted post-operative recovery but developed an indolent ulcer (L) antecubital fossa at site of injection of cytotoxin. No effects from course of radiotherapy. Remaining free of evidence of disease at last review in March 1964.	
Autopsy report:	-	
Result:	Cytotoxin given by intermittent intravenous injections as "cover" for operation period. Unable to assess result, but ulcer from extravasation of cytotoxin an important complication.	

Table 6/d

Case: 34	F.M.P. 4/2/63 Age: 43 Sex: F
Diagnosis:	Carcinoma of (L) breast Stage I. Intralobular duct carcinoma.
History:	Small lump first noted in (L) breast 2 months previously. No pain or nipple discharge. No other symptoms. Hysterectomy 1960 (preserving ovaries).
Previous or concurrent treatment:	(1) (L) radical mastectomy: 6/2/63
Cytotoxic treatment:	(1) Mannitol mustard: 500 mg. by I.V.I. (100 mg. x 5) 4/2/63-8/2/63 (2) Cyclophosphamide: 150 mg. by internal mammary arterial infusion during operation 6/2/63
Clinical course and comments:	Small carcinoma of (L) breast treated by radical mastectomy alone but under cytotoxic "cover". Developed oedema of (L) arm which responded to physiotherapy. Remaining free of evidence of disease at last review 14/2/64.
Autopsy report:	-
Result:	Cytotoxins used prophylactically as operation cover. No effects and result not possible to assess.

Table 6e

Case: 35	M.G. 8/2/63 Age: 52 Sex: F
Diagnosis:	Carcinoma of (L) breast with hepatic and skeletal metastases. Liver biopsy - infiltrating carcinoma and malignant cells in bone marrow.
History:	(L) radical mastectomy for Stage I carcinoma of breast 5 years previously in another hospital. No post-operative radiotherapy. Remained well thereafter and considered free of recurrence of disease. At laparotomy for suspected chronic duodenal ulcer in January 1963, however (in another hospital) was found to have malignant glands in porta hepatis and numerous small hepatic metastases. Main complaints had been gnawing epigastric pain for 3 years; poor appetite and loss of weight over 1½ years. 2 years post-menopausal.
Previous or concurrent treatment:	(1) Laparotomy: at another hospital - malignant glands at porta hepatis, small hepatic metastases. Pyloroplasty performed but no biopsy. 22/1/63 (2) Laparotomy: findings as above. No intra-abdominal primary. Biopsy of liver deposit. 12/2/63 (3) Radiotherapy: to metastases lumbar spine. Dose not known. November 1963 (4) Chlorpromazine: 25 mg. B.I.D. on same days as cyclophosphamide (5) Durabolin: 25 mg. by I.M.I. weekly from 9/1/64
Cytotoxic treatment:	(1) Mannitol mustard: 300 mg. by I.V.I. (operation cover) (100 mg. x 3) 11/2/63-13/2/63 (2) Cyclophosphamide: 1,000 mg. by I.V.I. 27/2/63-7/3/63 25,700 mg. orally 8/3/63-9/1/64
Clinical course and comments:	Apparently free of recurrence 5 years after radical mastectomy for Stage I carcinoma (L) breast. Long history of ulcer dyspepsia and at laparotomy for these symptoms 22/1/63 was found to have metastatic malignant disease. Second laparotomy carried out shortly after first to establish diagnosis. Slow postoperative improvement. Small pleural effusion clearing with physiotherapy. Started on cyclophosphamide orally after initial I.V. course. Discharged home 19/3/63 and remained extremely well until November 1963 when required radiotherapy for back pain from metastases. Further period of reasonably good health until January 1964 when readmitted for reassessment. Widespread skeletal metastases but almost free of symptoms. Chemotherapy suspended because of low W.B.C. but continued out-patient review and well at last review March 1964. Marked but incomplete hair loss initially but strong regrowth while on continued treatment.
Autopsy/	

Table 6e (continued)

Autopsy report:		-
Result:		Cytotoxic cover over second operation with mannitol mustard. Remarkably good subjective and objective response to cyclophosphamide maintained for 8 months. Further symptom-free period following radiotherapy to spine. Although increasing evidence of metastases remained free of symptoms after total of 12 months on treatment.

Table 6f

Case: 36	D.N. 1/3/63 Age: 36 Sex: F	
Diagnosis:	Carcinoma of (L) breast Stage I. Intraduct carcinoma.	
History:	Lump in (L) breast first noted 1 month previously. Associated with slight tenderness and milky discharge from nipple. Lump had decreased a little in size since first found. No other significant symptoms. No previous or family history of note.	
Previous or concurrent treatment:	(1) Biopsy of (L) breast:	14/2/63
	(2) (L) radical mastectomy:	4/3/63
	(3) Blood transfusion: 2 pints whole blood	5/3/63
Cytotoxic treatment:	(1) Mannitol mustard: 400 mg. by I.V.I. (4 x 100 mg.)	3/3/63-6/3/63
Clinical course and comments:	Small mobile tumour excised by biopsy. Uncomplicated recovery from operation. On oral iron for 1 month. No radiotherapy. Remaining well in all respects and free of evidence of recurrence of disease at last review 5/12/63.	
Autopsy report:	-	
Result:	Cytotoxins used as operation cover. Not possible to assess result. N.B. Attempt to perfuse cyclophosphamide at time of radical mastectomy failed.	

Table 6g

Case: 37	F.H. 17/6/63 Age: 42 Sex: F
Diagnosis:	Carcinoma of (L) breast with neck gland metastases. Biopsy of neck gland - metastatic carcinoma consistent with breast origin.
History:	(L) radical mastectomy for Stage I carcinoma of breast 1958 in another hospital. Free of recurrence until February 1963 when she noticed swelling in (L) side of neck. No other symptoms at that time. Reported to doctor in April 1963 and biopsy of neck glands carried out in another hospital in May 1963.
Previous or concurrent treatment:	(1) (L) radical mastectomy: September 1958 (2) Biopsy glands of neck: 26/4/63 (3) Bilateral oophorectomy 19/6/63 (4) Radiotherapy: 5980r to (L) supraclavicular area and (L) side of neck 1/7/63-8/8/63 (5) Aspiration of pleural effusion: 285 ml. 24/11/63; 240 ml. 28/11/63; 260 ml. 2/12/63; 300 ml. 6/12/63; 280 ml. 11/12/63
Cytotoxic treatment:	(1) Mannitol mustard: 300 mg. by I.V.I. (3 x 100 mg.) (operation cover) 25/4/63-27/4/63 (2) Cyclophosphamide: 800 mg. intrapleurally (2 x 400 mg.) 24/11/63-6/12/63 (3) Thiotepa: 60 mg. intrapleurally (4 x 15 mg.) 28/11/63-11/12/63 (4) Cyclophosphamide: 8,400 mg. orally 2/12/63-27/2/63
Clinical course and comments:	Appearance of neck gland metastases five years after radical mastectomy for Stage I carcinoma of (L) breast. Biopsy of neck gland under cytotoxic cover followed by bilateral oophorectomy in June 1963. Completed course of radiotherapy to neck glands in August 1963 with marked shrinkage of glands. Remained well for 3 months and, although free of symptoms, was then found to have a malignant pleural effusion (L) November 1963. Intrapleural and systemic chemotherapy commenced November 1963 with gradual control of effusion. At last review on 27/2/63 the effusion had cleared, patient well and no evidence of other metastases.
Autopsy report:	-
Result:	Cytotoxins employed initially as "cover" for neck gland biopsy. Subsequently required for control of malignant pleural effusion after radiotherapy to neck glands. Good control of effusion for 3 months to final review. No side effects.

Table 6h

Case: 38	M.M.D. 17/6/63. Age: 53 Sex: F	
Diagnosis:	Carcinoma of breast (R) Stage I. Muco-epidermoid carcinoma.	
History:	Small, painless lump first noted 3 weeks previously. Menstruation becoming irregular but no other symptoms. No previous or family history of note.	
Previous or concurrent treatment:	(1) Excision biopsy of lump (R) breast:	18/6/63
	(2) (R) radical mastectomy:	22/6/63
	(3) Blood transfusion: 2 pints whole blood	22/6/63
Cytotoxic treatment:	(1) Mannitol mustard: 450 mg. by I.V.I. (operation cover) (50 mg. x 1, 100 mg. x 4)	20/6/63-24/6/63
Clinical course and comments:	Small primary tumour treated by radical mastectomy; no postoperative radiotherapy. Uncomplicated recovery. Remaining well and free of evidence of disease at last review 7/11/63.	
Autopsy report:	-	
Result:	Cytotoxin given as operation cover and result cannot be assessed. No complications. N.B. Attempt to perfuse cyclophosphamide via (R) internal mammary artery at time of operation failed.	

Table 6i

Case: 39	M.P. 19/8/63 Age: 42 Sex: F
Diagnosis:	Carcinoma of (R) breast Stage II. Infiltrating duct carcinoma with involvement of axillary glands.
History:	First noted large, painful red swelling in upper outer part of (R) breast 2 years previously. Regarded as mastitis and treated with penicillin followed by short-wave diathermy. 2 months after onset symptoms and signs largely resolved but firm nodular mass remained. Residual mass was kept under observation and subsequently a discharge from the nipple was noted. Patient finally reported in August 1963 with small swelling in (R) axilla present for 3 weeks. Mass in breast now much larger and harder.
Previous or concurrent treatment:	(1) Penicillin and short-wave diathermy to (R) breast 1961 (2) Wide excision biopsy of mass in (R) breast: 28/8/63 (3) (R) radical mastectomy: 29/8/63 (4) Radiotherapy: 6,000r to (R) chest wall, axilla and supraclavicular region 1/10/63-5/11/63 (5) Blood transfusion: 2 pints whole blood 29/8/63 (6) Penicillin: for wound infection
Cytotoxic treatment:	(1) Mannitol mustard: 500 mg. by I.V.I. (100 mg. x 5) 26/8/63-30/8/63 450 mg. orally 16/9/63-27/9/63
Clinical course and comments:	Remarkable delay in establishing diagnosis despite patient being continuously under review. Tumour advanced before treatment commenced. Postoperative course complicated by necrosis of axillary flap, wound infection and wound dehiscence in its middle two-thirds protracted healing preventing commencement of radiotherapy until 1/10/63 - delay of 5 weeks. Discharged home 7/11/63. Remaining well and free of evidence of recurrence of disease at last review 5/1/64
Autopsy report:	-
Result:	Cytotoxins given as operation "cover" and final result cannot be assessed. Further oral mannitol mustard given because of delay in commencing radiotherapy. Cytotoxins may in part have been responsible for delayed wound healing but no other side effects.

Table 6j

Case: 40	F.S. 20/8/63 Age: 39 Sex: F
Diagnosis:	Carcinoma of (R) breast Stage III. Poorly differentiated carcinoma of breast with invasion of axillary glands.
History:	First seen at another hospital on 4/7/65 with a mass in (R) breast noted 2 months previously. Examination at that time revealed a hard, irregular tumour in lower medial quadrant of breast, fixed to skin and with clinically involved glands in axilla. Simple mastectomy was carried out on 8/7/65 and patient referred for further treatment. No other symptoms and no previous history of note.
Previous or concurrent treatment:	(1) Simple mastectomy: 8/7/63 (2) Radiotherapy: 6,000r to (R) axilla, chest wall and supraclavicular region 16/9/63-21/10/63 (3) Blood transfusion: 1 pint whole blood postoperatively (4) Completion of (R) radical mastectomy: 27/8/63
Cytotoxic treatment:	(1) Cyclophosphamide: 200 mg. by internal mammary artery perfusion 27/8/63 (2) Mannitol mustard: 500 mg. by I.V.I. (5 x 100 mg.) 26/8/63-30/8/63
Clinical course and comments:	Incomplete initial treatment for locally advanced carcinoma of breast. Uninterrupted postoperative recovery, primary wound healing. Completed radiotherapy without incident. Remaining well and free of evidence of disease at last review 26/2/64.
Autopsy report:	-
Result:	Cytotoxins given as prophylactic measure and final assessment not possible. No complications from cytotoxins.

Table 6k

Case: 41	B.S. 3/9/63 Age: 43 Sex: F
Diagnosis:	Carcinoma of (L) breast. Stage I. Infiltrating duct carcinoma.
History:	First noted stabbing pain in (L) breast 2 months previously - on examining breast patient felt a small lump in upper inner quadrant. Lump increased in size but no discharge from nipple. Generalised tenderness in (L) breast and (L) axilla. Had previously experienced symptoms of fibrocystic disease in (L) breast over period of 2 years. No other symptoms and no previous or family history of note.
Previous or concurrent treatment:	(1) Excision biopsy mass (L) breast: 6/9/63 (2) (L) radical mastectomy: 7/9/63 (3) Radiotherapy: 5,000r to (L) axilla, chest wall and supraclavicular area (4) Aspiration of fluid from beneath skin flaps: 280 ml. 18/9/63 40 ml. 23/9/63 20 ml. 24/9/63 65 ml. 18/11/63
Cytotoxic treatment:	(1) Mannitol mustard: 300 mg. by I.V.I. (3 x 100 mg.) 5/9/63-7/9/63
Clinical course and comments:	Small primary tumour. Primary wound healing but recurrent effusion beneath flaps requiring repeated aspiration. Initially worried about being pregnant; initially tests equivocal, subsequently negative. Otherwise remaining well and free of recurrence of disease at last review March 1964.
Autopsy report:	-
Result:	Cytotoxin given as operation "cover" and final result cannot be assessed. No side effects. N.B. Failed to attempt to infuse (L) internal mammary artery with cyclophosphamide at time of operation.

Table 61

Case: 42	I.F. 19/11/63 Age: 53 Sex: F
Diagnosis:	Carcinoma of (R) breast Stage II. Infiltrating duct carcinoma.
History:	Mass in (R) breast noticed 1 year previously - not reported and found by own doctor during examination for a certificate of medical fitness. No pain in breast and no nipple discharge. No previous history but one relative had died of breast cancer.
Previous or concurrent treatment:	(1) (R) radical mastectomy: with cannulation of (R) internal mammary artery 23/11/63 (2) Radiotherapy: 4,400r to (R) axilla, chest wall and supraclavicular area 16/1/64-6/2/64
Cytotoxic treatment:	(1) Cyclophosphamide: 400 mg. by I.V.I. (2 x 200 mg.) 22/11/63-24/11/63 200 mg. by internal mammary artery infusion during operation
Clinical course and comments:	Long delay before tumour of breast found during examination for other reasons. Postoperative course complicated by delayed wound healing and formation of large eschar. Postoperative radiotherapy therefore postponed for 3 weeks but course ultimately completed without incident. Discharged 7/2/64 and was remaining free of evidence of her disease at last review 6 months postoperative.
Autopsy report:	-
Result:	Cytotoxins given as operation "cover" and final result cannot be assessed. Delayed wound healing thought more likely due to use of diathermy than to cytotoxins.

Table 6/m

Case: 43	V.L. 28/11/63 Age: 67 Sex: F
Diagnosis:	Carcinoma of (R) breast Stage I. Intra-duct carcinoma.
History:	Accidentally noted small lump in (R) breast 1 month previously. No pain in breast or nipple discharge. Menopause 6 years previously No previous history of note but distant relative died of cancer of breast.
Previous or concurrent treatment:	(1) Biopsy of (R) breast: in another hospital 7/11/63 (2) (R) radical mastectomy: with cannulation of (R) internal mammary artery 30/11/63 (3) Blood transfusion: 2 pints whole blood 30/11/63
Cytotoxic treatment:	(1) Cyclophosphamide: 200 mg. by internal mammary artery infusion at time of operation
Clinical course and comments:	Small tumour; some initial doubt over histology and hence delay in definitive operation. No postoperative radiotherapy. Uncomplicated recovery and remaining free of recurrence of disease 6 months post-operatively.
Autopsy report:	-
Result:	Cytotoxin given as "cover" during operation and final result cannot be assessed.

Table 6n

Case: 44	M.McD. 9/12/63 Age: 47 Sex: F
Diagnosis:	Carcinoma of (L) breast Stage II. Invasive intra-duct carcinoma with involvement of glands.
History:	Small lump in upper outer quadrant of (L) breast for 3 months, with associated pain, tenderness and swelling in breasts, particularly the (L), for same period. No nipple discharge. Periods scanty and irregular for 3 months. No other relevant symptoms. N.B. 2 years previously a small lump had been removed from (L) breast; reported as intra-duct carcinoma but no further action taken at that time. Mother died of carcinoma of mouth.
Previous or concurrent treatment:	(1) Excision biopsy of lump (L) breast: under cytotoxic "cover" 27/11/63 (2) (L) radical mastectomy: under cytotoxic "cover" 28/11/63 (3) Bilateral oophorectomy: under cytotoxic "cover" 17/12/63 (4) Radiotherapy: 5,000r to (L) axilla, chest wall and supraclavicular area 2/1/64-21/1/64 (5) Blood transfusion: 1 pint of whole blood 28/11/63 (6) Aspiration of fluid from beneath skin flaps: 9/12/63; 17/12/63 and 31/12/63
Cytotoxic treatment:	(1) Mannitol mustard: 600 mg. by I.V.I. (6 x 100 mg.) as operation "cover" 27/11/63-2/12/63 (2) Cyclophosphamide: 600 mg. by I.V.I. (3 x 200 mg.) as operation "cover" 16/12/63-18/12/63
Clinical course and comments:	Small primary tumour (L) breast with invasion of axillary lymph glands. Uninterrupted recovery from radical mastectomy and bilateral oophorectomy. No effects from cytotoxins. Remained well and free of evidence of recurrence of disease at last review March 1964.
Autopsy report:	-
Result:	Cytotoxins given as operation "cover" and final result cannot be assessed. No untoward effects produced.

Table 6o

Case: 45	L.B. 18/3/63 Age: 38 Sex: F
Diagnosis:	Carcinoma of (L) breast with widespread bone, skin and cerebral metastases. Anaplastic carcinoma.
History:	Radical mastectomy for Stage II carcinoma of breast 6/4/62 - 8 months post-partum. Admitted 28/12/62 with 6-week history of headaches and vomiting. Re-admitted 18/3/63 with severe pain in (L) side of face and widespread metastases. Nausea and vomiting.
Previous or concurrent treatment:	(1) (L) radical mastectomy - in another hospital 6/4/62 (2) Radiotherapy: 6,000r to (L) chest wall and axilla - post-operative (3) Radiotherapy: 3,700r to skull 8/1/63-25/1/63 1,230r to pelvis 8/1/63-15/1/63 (4) Testosterone proprionate: 100 mg. daily by I.M.I. 24/2/63-11/3/63 (5) Prednisone: 30 mg. daily by mouth reducing to 20 mg. daily by mouth 20/3/63-22/12/63
Cytotoxic treatment:	(1) Perfusion of internal mammary and axillary arteries at operation - cyclophosphamide 200 mg. 6/4/62 (2) Cyclophosphamide: 2,600 mg. by I.V.I. 31/3/63-15/4/63 22,800 mg. by mouth 16/4/63-27/11/63 Total - 25.6 G. (3) Vinblastine sulphate: 45 mg. by I.V.I. 2/10/63-27/11/63
Clinical course and comments:	First evidence of skin and skeletal metastases developed 7 months after mastectomy. Headaches, facial pain, nausea and vomiting from cranial and bone metastases, incompletely relieved by radiotherapy to skull and hormone therapy. Complete relief of all symptoms and marked tumour regression with cyclophosphamide. Regression maintained for 7 months and then gradual decline to death in hospital 22/12/63.
Autopsy report:	Widespread bone, skin and glandular metastases from breast primary. Severe oedema of legs and bilateral pleural effusions. Marked bone marrow hypoplasia.
Result:	1-3 for 9 months. For period of 7 months, response to cytotoxins was dramatic.

Case No. 45: Carcinoma of Breast

Fig. 1: Chest X-ray 30/4/63.

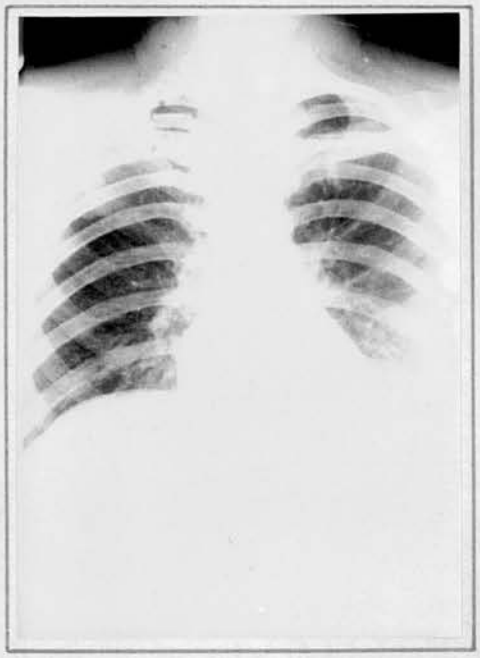


Fig. 2: Chest X-ray 8/1/63.

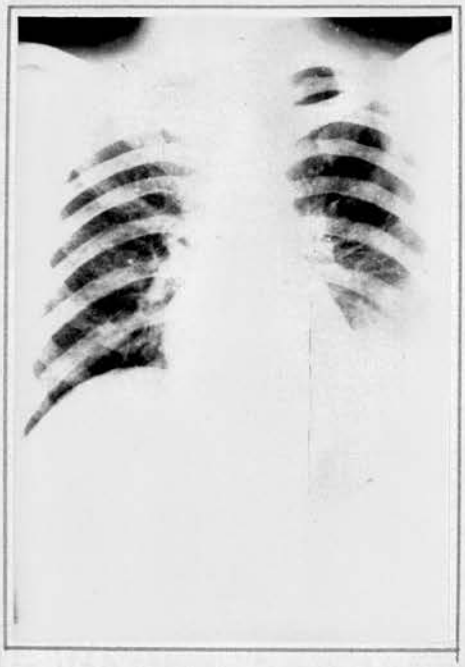


Fig. 3: Skull X-ray 28/12/62.

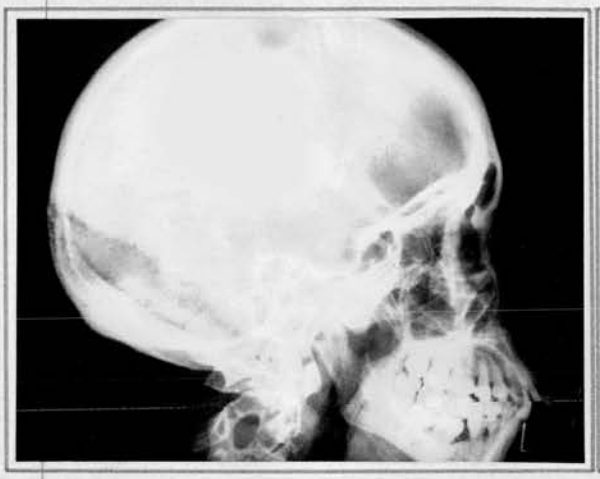
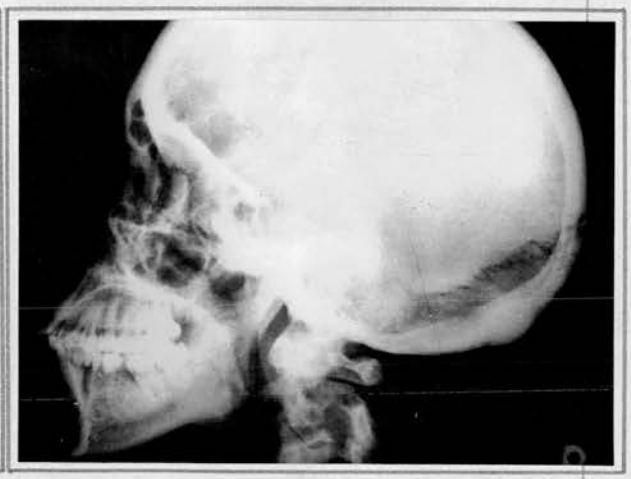


Fig. 4: Skull X-ray 24/9/63.



Case No.45.

Fig. 5: (L) Shoulder X-ray
16/4/63.

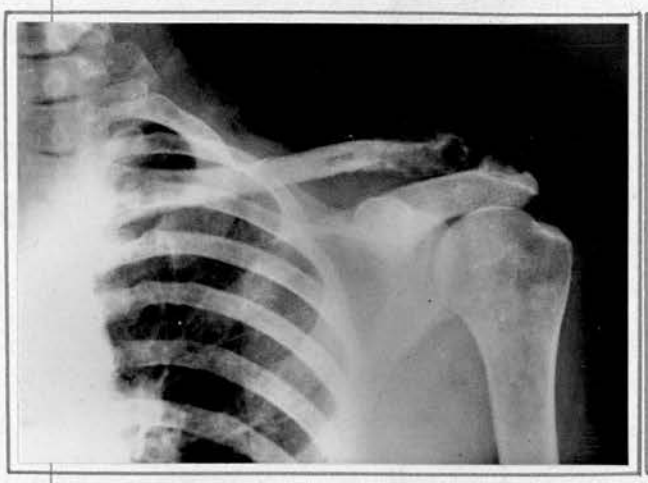


Fig. 6: (L) Shoulder X-ray
12/9/63.

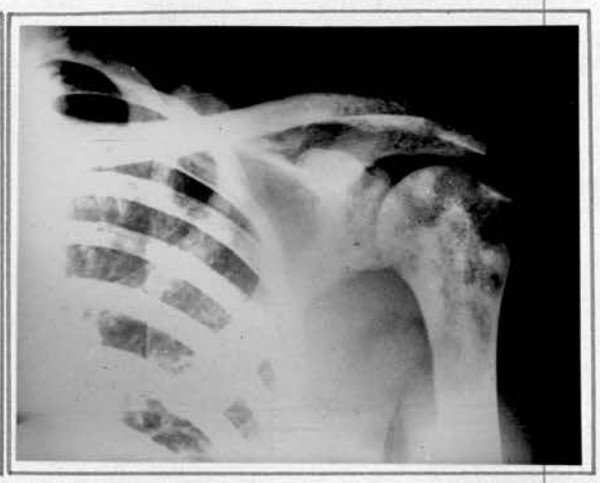


Fig. 7: Lumbar spine X-ray
29/12/62.

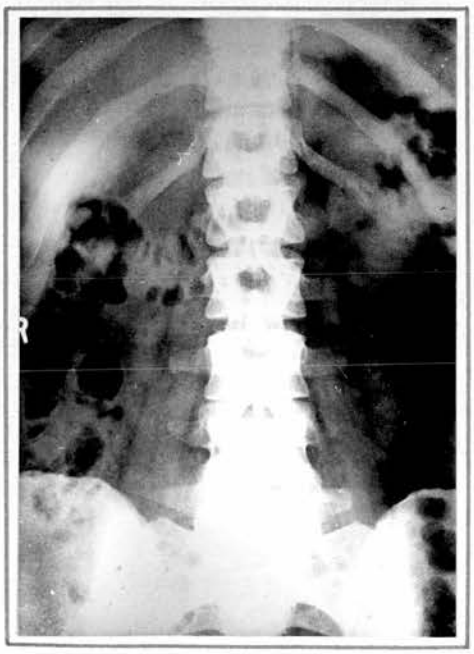
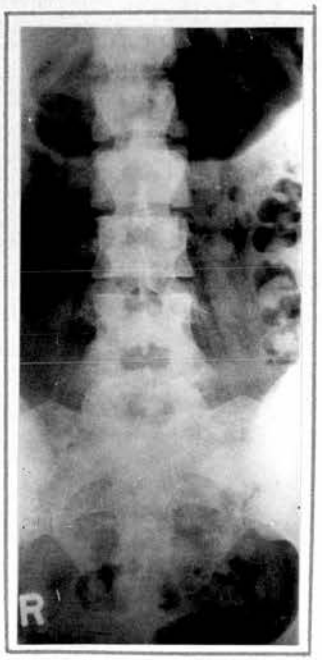


Fig. 8: Lumbar spine X-ray
14/8/63.



Case No.45.

Fig. 9: Pelvis X-ray 29/12/62.

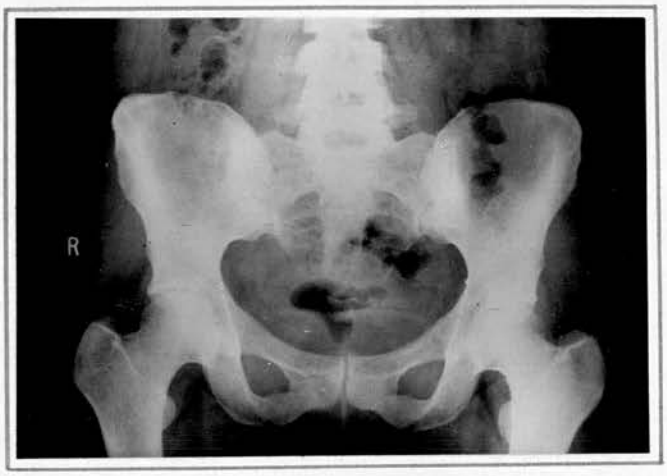


Fig. 10: Pelvis X-ray 14/8/63.

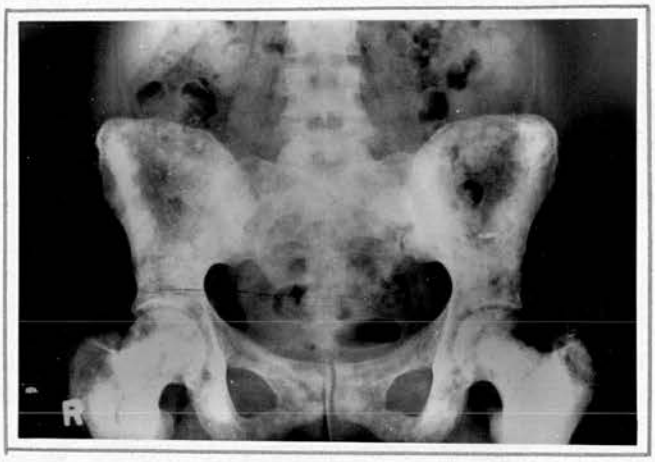


Table 6p

Case: 46	B.K. 15/3/64 Age: 42 Sex: F
Diagnosis:	Local recurrence of carcinoma (R) breast. Anaplastic carcinoma.
History:	Radical mastectomy was carried out in another hospital in March 196 for anaplastic Stage II carcinoma of (R) breast. No post-operative radiotherapy given but radiation menopause induced in May 1962. Remained well until November 1963 when she noticed a small swelling over (R) anterior chest wall. Gradual increase in size of swelling with mild aching discomfort over it. Rapid increase in size and local tenderness over 1 month. No other symptoms. Pulmonary tuberculosis 1949 with flare-up in 1954 and 1961; no further troubl since then.
Previous or concurrent treatment:	(1) (R) radical mastectomy: elsewhere March 1962 (2) Radiation menopause: elsewhere May 1962 (3) Bilateral oophorectomy: 10/3/64 (4) Cannulation of (R) internal mammary artery - for infusion 10/3/64
Cytotoxic treatment:	(1) Cyclophosphamide: 2,000 mg. by intra-arterial infusion (R) internal mammary artery 10/3/64-18/3/64 (1,000 mg. x 1, 200 mg. x 2, 100 mg. x 6)
Clinical course and comments:	Clinical examination revealed a 3" x 3" mass of recurrent tumour beneath the medial skin flap and 1" from the mid-line. There was no evidence of metastases elsewhere. Rapid and dramatic response to intra-arterial infusion of cyclophosphamide with loss of tension an discomfort after 24 hours and marked reduction in size of tumour after 6 days. Regression continued until tumour had virtually disappeared within 3 weeks. Slow recurrence of lesion with local discomfort, moderate hair loss and decline in general condition ove period of 6 months.
Autopsy report:	-
Result:	2-3 for 7 months.

Table 6c

Case: 47	M.G. 1/9/65 Age: 67 Sex: F
Diagnosis:	Carcinoma of (R) breast with local recurrence, glandular, skeletal and pleural metastases.
History:	Stage IV carcinoma of (R) breast treated by radiotherapy in 1958. Recurrent disease in October 1959 controlled by stilboestrol until September 1961. This slow increase in size of local tumour with axillary gland involvement. Bilateral ovariectomy 4/3/64 with slight benefit. Also given prednisone and testosterone. Despite slowly spreading disease patient remained reasonably well and activ until 1/9/65 when she was re-admitted complaining of increasing breathlessness, listlessness and chronic non-productive cough. Now considered for cytotoxic therapy.
Previous or concurrent treatment:	(1) Radiotherapy: for Stage IV carcinoma of (R) breast 1958 - details not known. (2) Hormone therapy: (a) stilboestrol - October 1959-September 196 then losing effect. (b) bilateral ovariectomy - 10/3/64 (c) testosterone proprionate and prednisone - from 1/7/64 - 22/10/64, thereafter testos erone continued alone until 1/9/65. (3) Aspiration of pleural effusion: 1000 ml - 3/9/65 700 ml - 13/9/65 600 ml - 4/11/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1300 mg. intrapleurally 3/9/65-18/11/65 400 mg x 2 300 mg x 1 200 mg x 1 1800 mg. by I.V.I. 9/9/65-21/10/65 400 mg x 2 300 mg x 2 200 mg x 2 300 mg. by mouth 100 mg x 3 Total = 3400 mg.
Clinical course and comments:	When re-admitted on 1/9/65 was found to have a large (R) pleural effusion. Area of locally recurrent ulcerated tumour (R) chest wall 5 cm x 5 cm.. Single large gland (L) axilla, glands in (R) side of neck and in groins, ribs invaded. Pleural effusion aspirated and cyclophosphamide commenced intrapleurally and intra-venously 3/9/65. Effusion controlled for 2 months after a second aspiration/

Table 6g (continued)

	aspiration on 13/9/65. No obvious change in local tumour or gland masses during this time. Patient remained reasonably well and active, but stopped oral cyclophosphamide after only 3 days because of nausea and vomiting. Was making good progress when collapsed and died suddenly at home 25/11/65 one hour after onset of severe, constricting chest pain.
Autopsy report:	Died at home. No post-mortem, but clinically death due to acute myocardial infarction
Result:	Pleural effusion controlled for 2 months to time of sudden death, but no obvious effect on recurrent and metastatic tumour mass. 2-3 for 2 months.

Table 6r

Case: 48	A.W. 9/3/65 **Age:** 63 **Sex:** F
Diagnosis:	Carcinoma of (R) breast with (L) pleural effusion
History:	Stage III carcinoma of (R) breast treated by radical mastectomy followed by radiotherapy in another hospital in 1962. Glandular recurrence (R) axilla treated by excision on 14/6/64. Severe herpes zoster in distribution of (L) 10th nerve, 2 years previously and still complaining of severe post-hepatic pain resistent to all therapy. Found at review in February 1965 to have (L) pleural effusion; started stilboestrol, but with no effect. Referred for consideration of cytotoxins on 9/3/65 because of increasing breathlessness and severe pain in (L) side of chest.
Previous or concurrent treatment:	(1) Radical Mastectomy and Post-operative Radiotherapy: 1962 in another hospital. (2) Excision gland (R) axilla: 14/6/64. (3) Hormone Therapy: Stilboestrol - 1 mg. b.i.d. from 16/2/65-10/6/65 (4) Aspiration of Pleural Effusion: 1100 ml. - 11/3/65 1300 ml. - 13/11/65 1200 ml. - 15/12/65 600 ml. - 3/1/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1800 mg. intrapleurally 11/3/65-15/11/65 600 mg. by I.V.I. 16/9/65-7/10/65
Clinical course and comments:	Large (L) sided pleural effusion present when patient first seen in chemotherapy clinic. Main complaint, however, was of severe constant pain in (L) lower chest present for two years and not relieved by any kind of analgesic - March 1965. Treated by aspiration of pleural effusion and instillation of cyclophosphamide. Effusion controlled for 8 months, during which time patients' general condition remained good. Continued, however, to complain of unrelenting pain in (L) side although metastatic bone or soft tissue lesion never established. In November, 1965 reaccumulation of effusion requiring further aspiration. Partial control with cytotoxins intrapleurally and intravenously, but condition slowly deteriorated. Admitted to a medical ward in March 1966 mainly as social problem, but thereafter declined to death at home on 22/4/66 1 year after commencing chemotherapy.
Autopsy report:	Died at home- no post-mortem obtained.
Result:	Although pleural effusion controlled for 8 months with small amounts of cyclophosphamide, but pain never relieved. Terminal illness long drawn-out and little further benefit from cytotoxins. No side-effects and total dose moderate only. 1-2 for 1 year.

Table 6 s

Case: 49	M.O. 12/1/65 Age: 44 Sex: F
Diagnosis:	Carcinoma of breast with widespread metastases and gross ascites. Hepatic metastases.
History:	Stage III carcinoma of (L) breast treated by simple mastectomy and radiotherapy in 1960. Radiation menopause in July 1963 for recurrent tumour in (L) axilla and chest wall. Temporary control of disease with disappearance of recurrent nodes (L) axilla. Further recurrences in skin of chest wall and (R) breast in June 1964 with gross ascites and bilateral pleural effusions. Also known to have rheumatic heart disease and significance of this uncertain. Dramatic response to prednisolone which was maintained until December 1964 when admitted to a medical ward with gross ascites palpable masses in abdomen and recurrent tumours in (R) breast, glands and skin. Referred for consideration of chemotherapy.
Previous or concurrent treatment:	(1) Simple mastectomy and Radiotherapy: 1960 for stage III carcinoma of (L) breast. Details not known. (2) Radiation to ovaries: July 1963. (3) Digoxin and diuretics: intermittently from January 1963. (4) Steroids: Prednisolone: 15-30 mg. daily by mouth 16/6/64-31/1/65 (5) Abdominal paracentesis: Two occasions in July 1964 - details not known. 4+ litres - 14/1/65 2100 ml. - 16/1/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1000 mg. by I.V. infusion over 24 hours 14/1/65 200 mg. by I.V.I. 19/1/65 Total = 1200 mg.
Clinical course and comments:	Patients' general condition was poor when cytotoxic therapy was commenced on 14/1/65, but it was hoped to control her rapidly accumulating ascites and to lessen severity of symptoms. Widespread tumour masses were present in abdomen and elsewhere. Patient remained listless and anorexia began to deteriorate by 25/1/65 and treatment suspended. Died in the ward on 2/2/65.
Autopsy report:	Not obtained.
Result:	Insufficient dosage given at too late a stage to obtain any benefit. 0 for 2 weeks.

Table 6t

Case: 50	M.S. 15/12/64 Age: 63 Sex: F
Diagnosis:	Carcinoma (R) breast with widespread deposits in bone, liver, adrenals and glands. Poorly differentiated scirrhous carcinoma of breast.
History:	First seen as out-patient in December 1964 with thrombophlebitis of (R) arm. No other symptoms at that time and no evidence of overt malignancy. Again seen in September 1965 with swelling of (R) arm, palpable glands in (L) supraclavicular area and distended veins over (R) breast. Bronchoscopy, chest X-ray, negative, but biopsy of neck gland revealed anaplastic carcinoma. ? bronchogenic or breast. Admitted to ward for investigation and treatment 9/9/65. Now complaining of subcostal and back pain, swelling of abdomen and ankles. N.B. No primary breast lesion found but evidence of widespread metastases. General state remained very good.
Previous or concurrent treatment:	(1) Bronchoscopy and neck gland biopsy: 14/9/65 (2) Radiotherapy: Lumbar spine, (R) axilla, dorsal spine and (L) supraclavicular region - palliative only 12/11/65-19/11/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1,800 mg. by I.V.I. (200 mg. x 3, 400 mg. x 3) 21/9/65-21/10/65
Clinical course and comments:	Although general condition was good at commencement of chemotherapy, symptoms were marked and disease already widespread. Primary site not known at this stage. Symptoms less marked within 1 week of starting treatment and after 1 month was able to do housework, etc. without pain. Appetite normal. Remained well until 5/11/65 when re-admitted with severe pain in (L) hip and back due to collapse of L.V.3. General condition remaining good and given radiotherapy to spine and (L) supraclavicular areas. Following radiotherapy general condition deteriorated; no further chemotherapy was given and patient died in hospital on 5/1/66 - 1 year from first episode of thrombophlebitis and 4 months after overt malignant disease discovered.
Autopsy report:	Primary tumour not detected in life but P.M. revealed 2 x 1 x 1 cm. scirrhous carcinoma of (R) breast. Widespread deposits in vertebrae, liver, adrenals and lymph glands with microscopic deposits in lungs. (R) pulmonary embolism with thrombosis in (R) femoral and iliac veins. No other significant findings.
Result:	Initial response to cyclophosphamide was rapid and symptoms relieved for 2 months. Recurrence of severe back pain from vertebral collapse No further benefit from radiotherapy. 1-3 for $3\frac{1}{2}$ months. No significant side effects from cytotoxic therapy.

Table 6u

Case: 51	M.K. 8/8/63 and 13/4/65 Age: 50 Sex: F
Diagnosis:	Carcinoma of (R) breast with skin, glandular, pleural, skeletal and hepatic metastases. Poorly differentiated carcinoma of breast.
History:	Radical mastectomy for stage three carcinoma of (R) breast, August 1963. Previous ovariectomy in 1941 and hysterectomy 1958. Local chest wall recurrence January 1964 and at same time developed a pre-malignant rectal polyp subsequently treated by diathermy excision. Skin recurrences treated by radiotherapy April, 1964, but further recurrences chest wall and (R) axilla by July, 1964 with gradual appearance of skeletal metastases (R) hip, (R) ilium and ribs between September and December 1964. Further radiotherapy to recurrences December, 1964. Re-admitted 20/1/65 with pain in (L) leg chest and back; (R) pleural effusion, commenced treatment with steroids 24/1/65 and pleural effusion aspirates. Condition reasonable for two months and then re-admitted because of increasing breathlessness, oedema and pain.
Previous or concurrent treatment:	(1) Radical Mastectomy: Stage III carcinoma of breast 12/8/63 (2) Excision of nodules mastectomy scar: 12/8/63 (3) Excision of rectal polyp: 13/2/64 and 16/11/64 (4) Radiotherapy: (a) to (R) chest wall April 1964 (b) to chest wall, (R) acilla, (R) hip and (L) 9th rib. December 1964. (5) Hormone therapy: (a) testosterone mg. 100 by I.M.I. daily, 24/1/65-1/2/65 then 100 mg. weekly. (b) cortisone acetate 100 mg. by mouth reducing to 12.5 mg. by mouth from 24/1/65 (c) analgesics. (6) Blood transufsion:
Cytotoxic treatment:	(1) Thiotepa: 48 mg. by I.V.I. 12/8/63-15/8/63 (4x12 mg. daily) (2) Cyclophosphamide: 2,100 mg. by intrapleural instillation 13/4/65-8/10/65. 8000 mg. by mouth 10/6/65-8/10/65 Total = 10,100 mg.
Clinical course and comments:	When treatment with cytotoxins commenced in April 1965 the patient had already received surgery, radiotherapy and hormone therapy in an attempt to control advancing metastatic disease. Main symptoms due to pleural effusion and anaemia. Symptoms rapidly improved by intrapleural cyclophosphamide subsequently controlled reasonably well with oral therapy and occasional pleural aspiration. Moderate alopecia. General condition remained good, required occasional blood transfusion and iron therapy to maintain haemoglobin. Managed at home for 6 months and was then re-admitted to ward because of breathlessness, weakness and upper abdominal pain. No longer able to manage at home. Symptoms improved and discharged to nursing home where she became acutely paranoid and required admissi to/

Table 6u (continued)

	to a mental hospital. General condition slowly deteriorated and she died there on 20/12/65.
Autopsy report:	Carcinoma of (R) breast with metastases to regional lymph nodes, pleura, lungs, pericardium, liver, suprarenal glands and bones. Polypoid tumours of rectum - carcinoma in situ. Effusion in all serous cavities with large collection in (R) pleural and complete collapse of (R) lower lobe. Thyroiditis and pituitary hyperplasia
Result:	Case of interest from "prophylactic" use of thiotepa at time of mastectomy and rapid recurrence of tumour. Symptomatic control for 7 months with cyclophosphamide. Moderate alopecia and terminal mental illness as significant side effects. 1-2 for 7 months.

Table 6v

Case: 52	S.O. 28/8/64 Age: 64 Sex: F
Diagnosis:	Carcinoma of breast; skin nodules and pleural effusion. Clumps of neoplastic cells in pleural fluid.
History:	(R) radical mastectomy for carcinoma in 1947. Local skin recurrences in flaps on 4 occasions treated by radiation or local excision. Remained in good general health, however, until July 1964 when she reported with increasing breathlessness found to be due to a large (R) pleural effusion, and further skin nodules. The effusion was aspirated on 2 occasions and patient then considered for cytotoxic therapy.
Previous or concurrent treatment:	(1) (R) radical mastectomy: 1947 (2) Excision of recurrent skin nodules: on 4 occasions between 1949 and 1963. (3) Pleural aspiration: 700 ml. 29/7/64; 700 ml. 14/8/64; 600 ml. 28/8/64; 500 ml. 1/9/64; 500 ml. 18/9/64; 400 ml. 5/10/64 (4) Abdominal paracentesis: 5 litres 2/12/65
Cytotoxic treatment:	(1) Thiotepa: 45 mg. intrapleural 28/8/64-5/10/64 30 mg. intraperitoneal 2/12/65
Clinical course and comments:	Despite repeated appearance of small nodules in mastectomy flaps, the patient's general condition remained good for 17 years following operation. Then developed a large (R) pleural effusion which responded to a short course of thiotepa and did not require aspiration for the last 15 months. She remained remarkably well and active until 1/12/65 (18 months after appearance of pleural effusion) when readmitted to ward with anorexia, vomiting and gross ascites. Remained well for a further short period following abdominal paracentesis, but then rapidly deteriorated to death at home on 24/1/66.
Autopsy report:	Died at home - no post-mortem obtained.
Result:	Nineteen year survival following radical mastectomy for carcinoma of (R) breast. Complete control of pleural effusion for 15 months with cytotoxins and no side effects. 2-3 for 15 months.

GROUP G : CARCINOMA OF OVARY

Table 7a

Case: 53	J.M.H. 26/6/62 Age: 41 Sex: F
Diagnosis:	Mucus-secreting adenocarcinoma of ovaries with peritoneal and neck-gland metastases. Initial biopsy of gland (L) side of neck.
History:	Increasing lassitude and epigastric "fullness" after meals for 1 year. Swelling in (L) side of neck for 6 months. Previous health normal but treated for a "mental illness" in 1950. Biopsy of gland in (L) side of neck 5 weeks previously in another hospital - mucus secreting adenocarcinoma. Thought to have a primary neoplasm of stomach or colon.
Previous or concurrent treatment:	(1) Laparotomy: large soft tumours replacing both ovaries, peritoneal metastases and in stomach wall - partial gastrectomy and biopsy of ovarian masses. 11/7/62 (2) Radiotherapy: 4,500 r to (L) side of neck 11/3/63-1/4/63 (3) Blood transfusion: 2 x 2 pints of whole blood on 11/7/62 and 25/8/62
Cytotoxic treatment:	(1) Thiocolciran: 60 mg. by I.V.I. operation cover 9/7/62-14/7/62 260 mg. by I.V.I. 8/8/62-26/10/62 (2) Cyclophosphamide: 9,900 mg. orally 5/11/62-28/2/63 3,000 mg. by I.V.I. 30/4/63-8/5/63 (3) Vinblastine sulphate: 40 mg. by I.V.I. 12/3/63-30/4/63
Clinical course and comments:	Patient presented with malignant glands in neck thought to be from primary lesion in stomach or colon. Laparotomy and subsequent histological examination confirmed ovaries as the primary site. Laparotomy carried out under cytotoxic "cover". Post-operative course complicated by recurrent abdominal distension and development of a chronic subphrenic abscess. Some initial response to cytotoxins and home for short periods. Experienced recurrent bouts of depression, abdominal pain and backache requiring repeated re-admission. Short-lived response to radiotherapy and cyclophosphamide but terminal phase prolonged with increased pain, alopecia and depression. Died 20/6/63.
Autopsy report:	Permission for post-mortem not obtained.
Result:	Minimal subjective response only over total period of 1 year mainly in hospital.

Table 7b

Case: 54	A.E. 7/8/62 Age: 39 Sex: F	
Diagnosis:	Carcinoma of ovary with widespread omental and peritoneal deposits. Biopsy of omental deposit, ovary and Fallopian tube.	
History:	Perfectly well until last month of her first pregnancy (May 1962) then experienced nausea and vomiting thought to be due to hiatus hernia. Noted post-partum to have ascites - ? tuberculous. Laparotomy at another hospital in July 1962 revealed carcinomatosis peritonei from primary lesion of ovaries. Biopsy only carried out.	
Previous or concurrent treatment:	(1) Anti-tuberculous chemotherapy: Streptomycin and P.A.S. for brief period	June-July 1962
	(2) Laparotomy: Biopsy of omentum, ovary and Fallopian tube	July 1962
	(3) Radiotherapy: 3,300r to whole abdomen and pelvis	10/8/62-13/9/62
	(4) Laparotomy: Subtotal hysterectomy, bilateral oophorectomy with removal of omentum	25/9/62
	(5) Blood transfusion: 14 pints whole blood between 21/8/62 and 23/7/63	
	(6) Paracentesis: Aspiration of ascitic fluid	11/5/63, 12/6/63 and 27/6/63
Cytotoxic treatment:	(1) Thiocolciran: 130 mg. by I.V.I. 20 mg. intraperitoneally	14/8/62-28/10/62 29/10/62-4/11/62
	(2) Cyclophosphamide: 13,500 mg. orally 4,650 mg. by I.V.I.	17/1/63-30/5/63 3/7/63-12/9/63
	(3) Thiotepa: 45 mg. intraperitoneally	11/5/63
	(4) Vinblastine sulphate: 22 mg. by I.V.I.	30/5/63-12/8/63
Clinical course and comments:	Thought initially to have tuberculous ascites but no response to short period of anti-tuberculous chemotherapy and at laparotomy July 1962 found to have carcinomatosis peritonei. Following a course of radiotherapy to the abdomen and I.V. thiocolciran a subtotal hysterectomy and oophorectomy was carried out. Postoperative course was stormy but cytotoxic therapy continued and patient was discharged home on 21/11/63. Progress thereafter was rapid and weight increased by 1 stone. Further weight gain by January 1963 but appetite decreasing and masses palpable in abdomen - commenced cyclophosphamide. Good clinical response for 4 months and then readmitted May 1963 with backache, ascites, increasing abdominal masses and cystitis. Slow progressive downhill course with ascites requiring aspiration on 3 occasions. Herpes Zoster in June 1963. Increasing abdominal pain, large tumour masses. Short periods at home but died 25/9/63.	
Autopsy/		

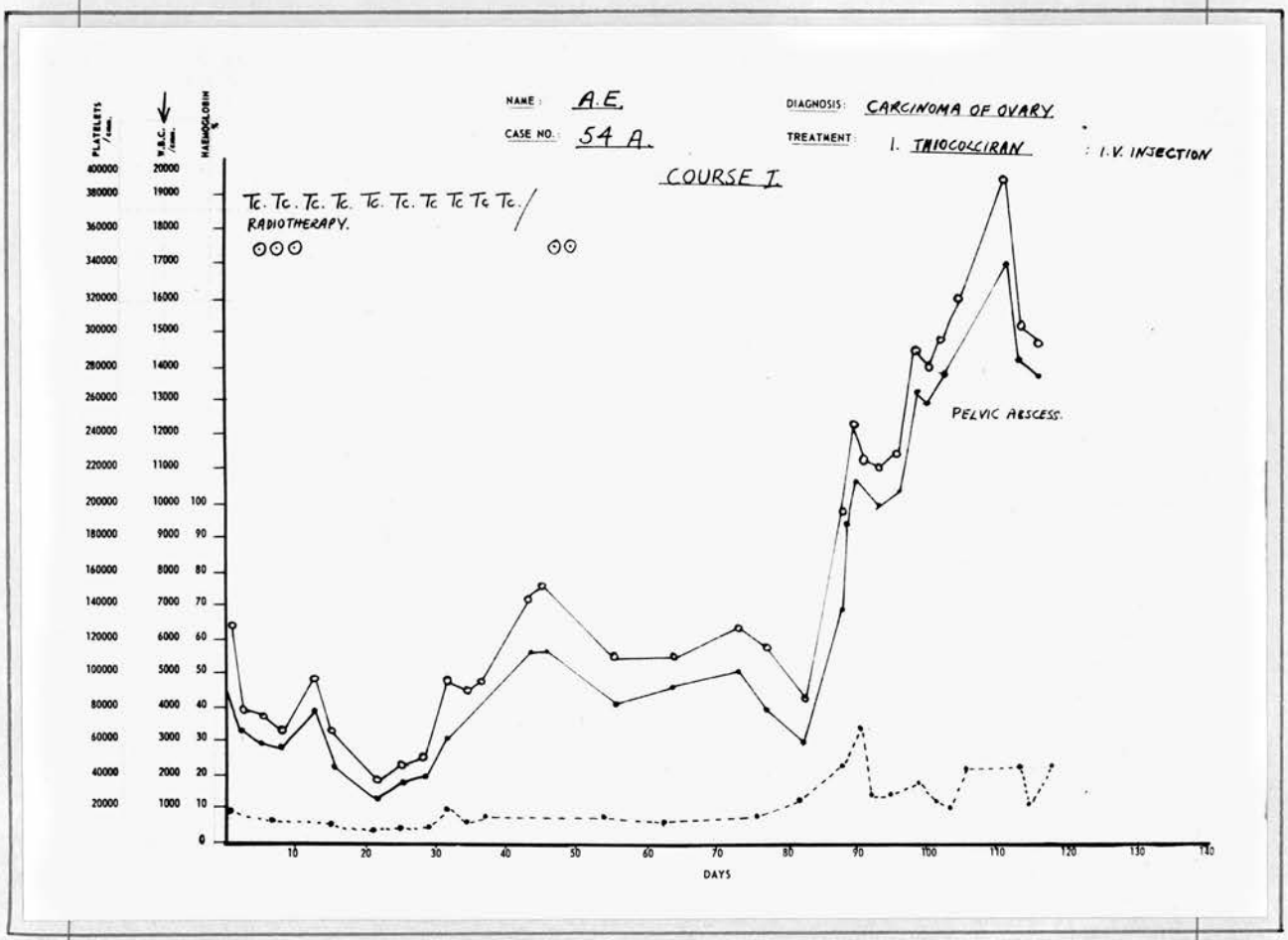
Table 7b (continued)

Autopsy report:	Peritoneal cavity almost obliterated by dense adhesions in which were multiple seedling metastases. Small subphrenic abscess. Liver not grossly involved by metastases. Invasion posterior wall of bladder by residual tumour. Few pleural but no pulmonary metastases and no significant metastases elsewhere.
Result:	Good subjective and objective response maintained for 8 months. Short periods of subjective response only for further 4 months. Long periods at home.

CASE NO. 54

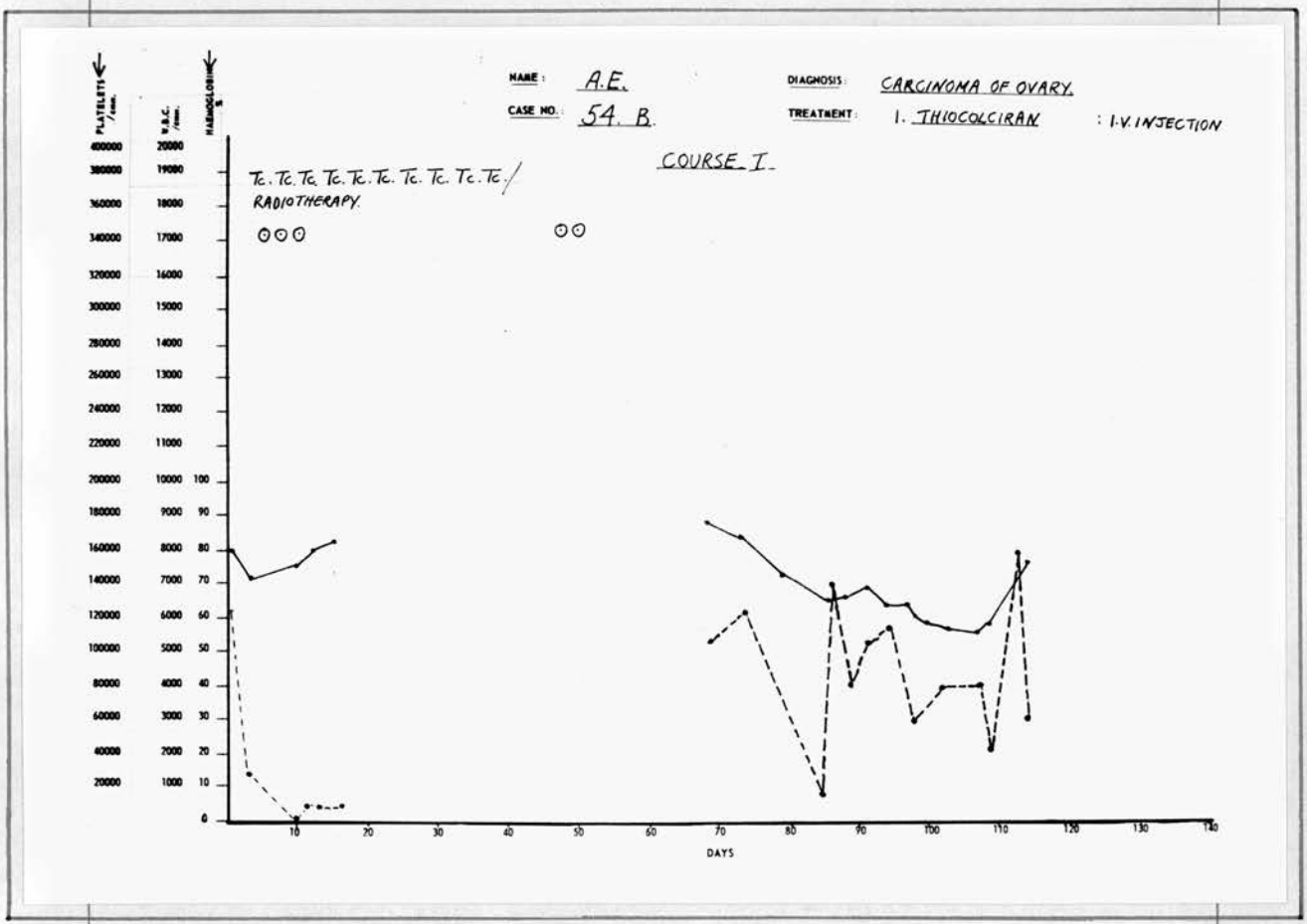
PERIPHERAL BLOOD COUNTS

GRAPH A COURSE I



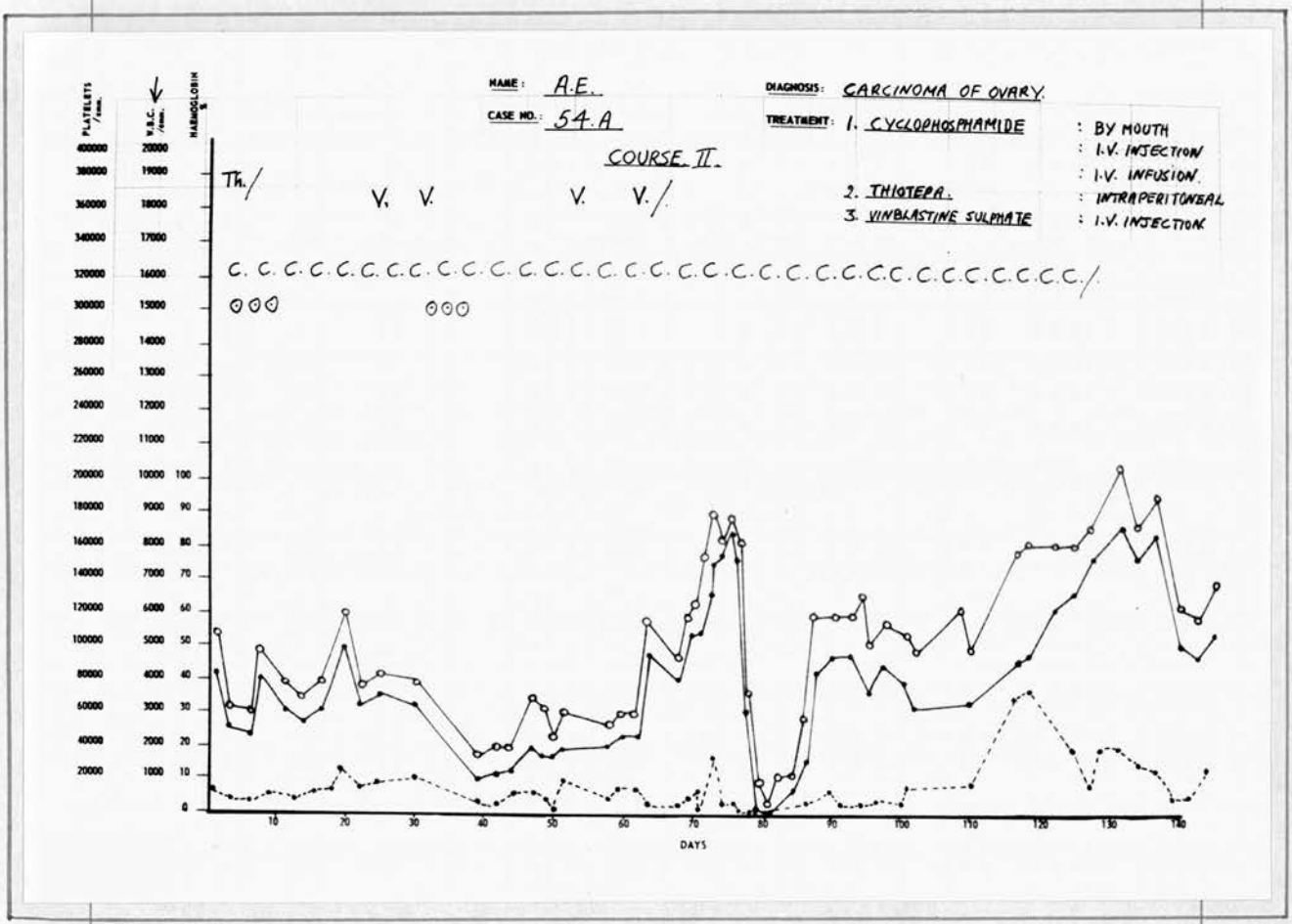
CASE NO. 54 PERIPHERAL BLOOD COUNTS

GRAPH B COURSE I



CASE NO. 54 PERIPHERAL BLOOD COUNTS

GRAPH A COURSE II



CASE NO. 54 PERIPHERAL BLOOD COUNTS

GRAPH B COURSE II

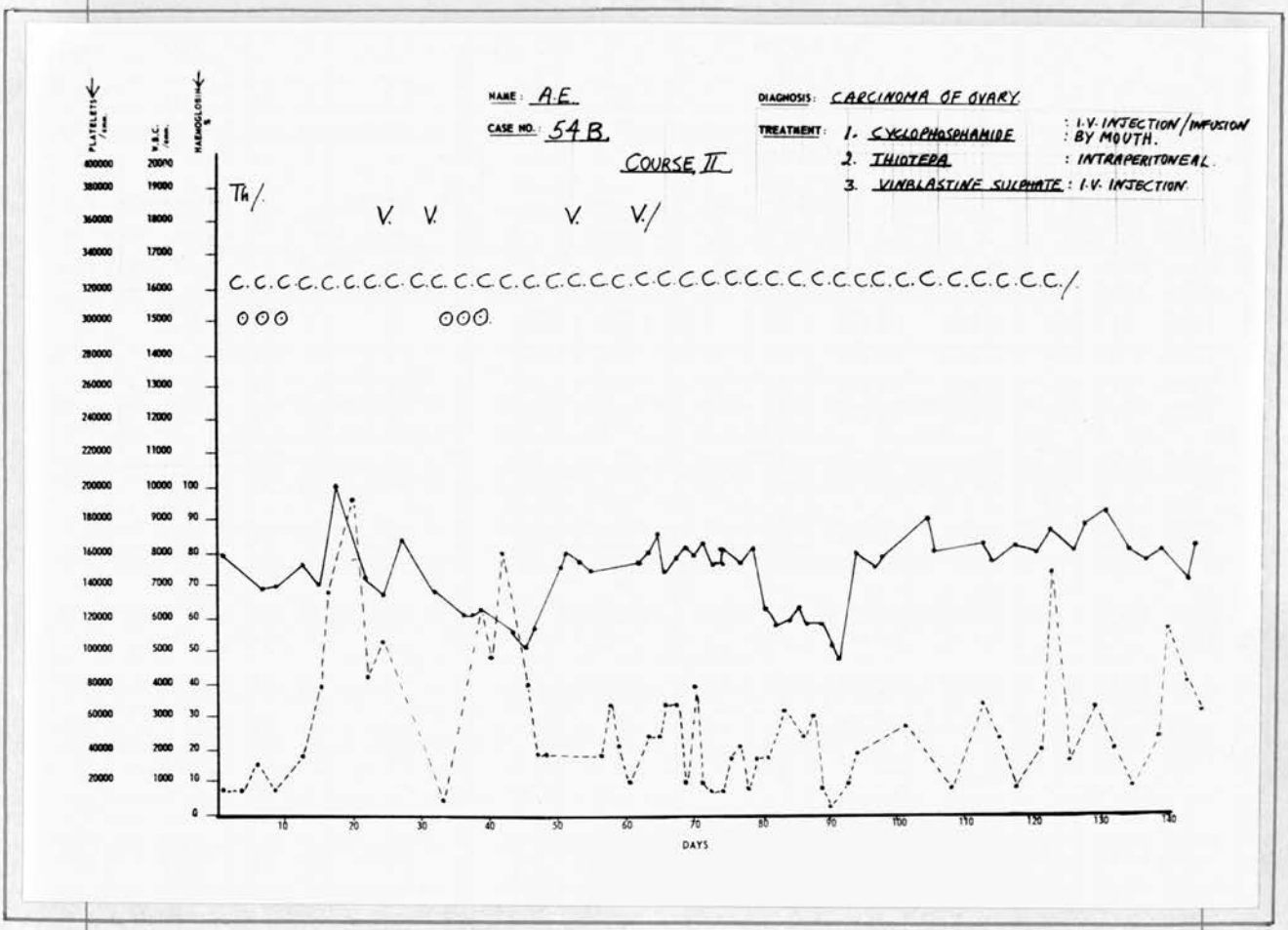


Table 7c

Case: 55	D.M. 19/12/62 Age: 46 Sex: F
Diagnosis:	Adenocarcinoma of ovary with peritoneal metastases. Biopsy of omental deposit and pelvic mass.
History:	Admitted to another hospital 21/11/62 with history of diarrhoea and bilateral groin pain for 6 days and increasing abdominal distension for 3 days. Influenzal illness one month previously. Laparotomy 5/12/62 revealed mass (R) ovary and tube with omental nodules ? metastases. 2 litres of ascitic fluid removed; biopsy of pelvic mass. No other procedure. Transferred 14 days postoperatively - no significant symptoms.
Previous or concurrent treatment:	(1) Laparotomy: Mass (R) ovary and tube. ? omental metastases. Ascites. Biopsy only — 5/12/62 (2) Blood transfusion: 2 pints whole blood — 7/1/63 (3) Laparotomy: Bilateral tubo-ovarian masses; thickened omentum but no other peritoneal masses. Ascites. Biopsy only — 8/1/63 (4) Radiotherapy: 4,590 r to pelvis and lower abdomen — 24/1/63-1/3/63 (5) Chlorpromazine, folic acid, B_{12} and iron: December 1962-January 1963 (6) Paracentesis: Repeated aspiration of ascites — 23/9/63-28/10/63
Cytotoxic treatment:	(1) Cyclophosphamide: 26,700 mg. orally — 22/12/62-10/10/63 (2) Thiotepa: 50 mg. intraperitoneally — 25/9/63-9/10/63 (3) Vinblastine sulphate: 12 mg. by I.V.I. — 8/10/63-21/10/63
Clinical course and comments:	Tumour could not be excised at secondary laparotomy (8/1/63) which was carried out after 2 weeks of oral cyclophosphamide therapy. Following laparotomy a radical course of radiotherapy was given to pelvis and abdomen and cyclophosphamide was continued. Complete remission was maintained for 8 months. During this time almost complete alopecia required a wig but subsequent strong regrowth of hair while still on treatment. Readmitted 23/9/63 with ascites, palpable mass P.V., but no other evidence of spread. Ascites aspirated and thiotepa instilled intraperitoneally. No significant benefit with increasing abdominal discomfort, nausea and vomiting. Developed pain and swelling (L) leg - massive thrombosis. Condition static for short period on velbe and then deteriorated to death on 27/11/63.
Autopsy/	

Table 7c (continued)

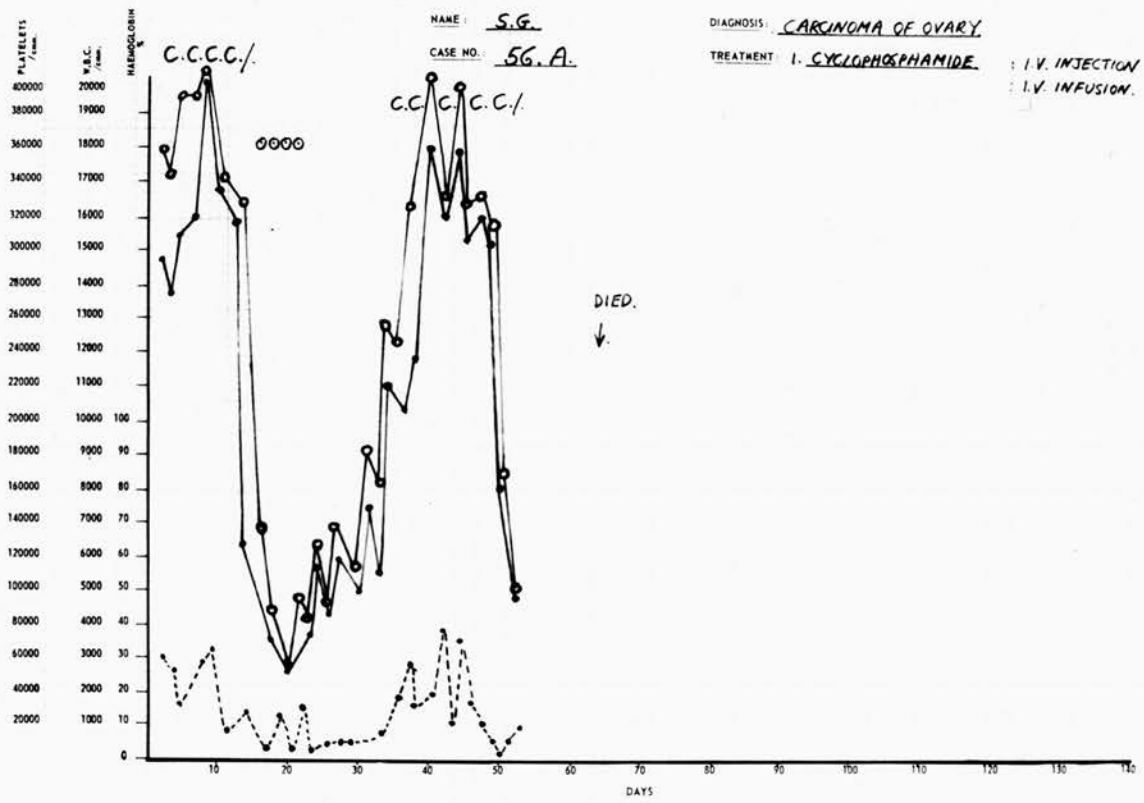
Autopsy report:	3 litres ascitic fluid. No discrete peritoneal nodules but whole peritoneum appeared to be infiltrated by malignant tissue. No obvious liver nodules but involved microscopically. Malignant mass in pelvis binding down and embedding bladder, ovaries and uterus. No metastases outside the abdomen.
Result:	Complete objective and subjective remission for 8 months then only intermittent subjective response for further 2 months.

Table 7d

Case: 56	S.G. 30/8/63 Age: 42 Sex: F
Diagnosis:	Papillary-cystadeno-carcinoma of ovary. Biopsy of omentum.
History:	Increasing (R) sided abdominal pains for 3 months with awareness of a lump in (R) abdomen and increasing malaise. Constipated and marked urinary symptoms; no menstrual symptoms. N.B. Previously complained of (R) sided abdominal pain at intervals for 8 years; variously investigated in 3 other hospitals and finally referred to a psychiatrist who found a large, tender mass in (R) side of abdomen! Examination under anaesthesia on 23/8/63 revealed large masses in pelvis and (R) upper abdomen.
Previous or concurrent treatment:	(1) Laparotomy: Peritoneal cavity obliterated by grossly thickened omentum infiltrated by tumour. Pelvis and upper abdomen "frozen" with adhesions and tumour deposits. 2 litres of bloodstained glairy fluid. Biopsy of omentum only. 26/8/63 (2) Blood transfusion: 4 pints whole blood 16/9/63 (3) Antibiotics: Furadantin and penbritin for urinary infection
Cytotoxic treatment:	(1) Cyclophosphamide: 3,200 mg. by I.V.I. and I.V. drip 5/9/63-13/9/63 2,900 mg. orally 28/9/63-16/10/63
Clinical course and comments:	Rapid refilling of abdomen with viscid, glairy fluid following laparotomy. Became dehydrated, drowsy and in gross electrolyte imbalance. Marked peripheral oedema. No improvement from cytotoxins, developed bedsores and ran a downhill course to death on 18/10/63.
Autopsy report:	Confirmed laparotomy findings of peritoneal cavity "frozen" by adhesions and widespread tumour deposits. Liver, lymph gland in abdomen involved. Pelvic and abdominal viscera ensheathed and obscured by large amounts of tumour tissue. Bilateral pleural effusions but no metastases outwith the abdomen. Histology confirmed primary cystadenocarcinoma of ovaries.
Result:	No benefit from cytotoxins

CASE NO. 56 PERIPHERAL BLOOD COUNTS

GRAPH A



CASE NO. 56 PERIPHERAL BLOOD COUNTS

GRAPH B

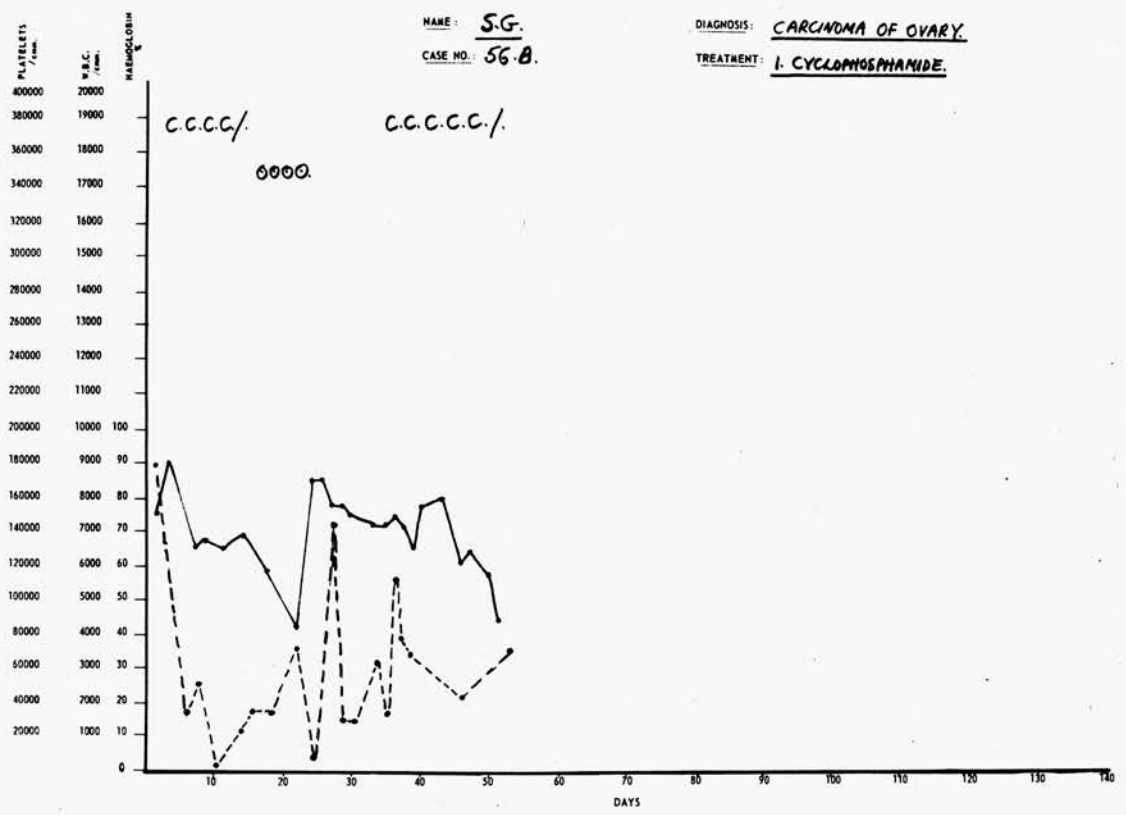


Table 7e

Case: 57	M.C. 24/6/65 Age: 70 Sex: F
Diagnosis:	Carcinoma of ovaries with ascites and omental deposits. Papillary adenocarcinoma.
History:	Laparotomy on 17/3/65 in another hospital for a 1 year history of increasing abdominal distension and constipation. Clinical diagnosis of ovarian malignancy made. When first seen here three months post-operatively general condition was good and only complaint was of mild lassitude and listlessness. No relevant previous or family history.
Previous or concurrent treatment:	(1) Laparotomy: removal of uterus and appendages; biopsy of omental deposit - in another hospital 17/3/65 (2) Blood transfusion: 1 litre 5/11/65; 1 litre 31/1/66 (3) Abdominal paracentesis: 5 litres 12/12/65; 5 litres 29/1/65; $2\frac{1}{2}$ litres 5/3/66 (4) Diuretics: Neo Naclex and lasix from 7/10/65
Cytotoxic treatment:	(1) Thiotepa: 60 mg. intraperitoneally at time of operation (2) Cyclophosphamide: 2,200 mg. by I.V.I. 24/6/65-26/8/65; 2,200 mg. orally 9/9/65-11/11/65; 900 mg. intraperitoneally 13/12/65-1/2/66
Clinical course and comments:	Patient with advanced ovarian malignancy when first diagnosed. Well for 8 months and at home. Then developed rapidly re-accumulating ascites, nausea, anorexia, occasional epistaxis and mild to moderate alopecia. Platelet count low throughout possibly due to initial thiotepa. Slow but progressive deterioration over last three months of illness during which time only small amounts of cytotoxins were used and repeated aspiration of ascites was necessary despite diuretics and low-salt diet. Died at home 21/3/66 - 1 year after initial diagnosis.
Autopsy report:	Died at home - no post-mortem.
Result:	Good subjective and objective response maintained for 8 months then slow deterioration. Low platelet count throughout with occasional mild epistaxis. Mild to moderate alopecia after 3 months of cyclo-phosphamide. 2-3 for 8 months.

Table 7f

Case: 58	E.H. 29/6/64 Age: 60 Sex: F
Diagnosis:	Carcinoma of (R) ovary with peritoneal metastases and ascites. Pleomorphic anaplastic carcinoma of ovary.
History:	Emergency admission thought to have intestinal obstruction. History was of increasing abdominal distension with backache for 1 week, mild general malaise and mild anorexia for 6 weeks. No symptoms referable to specific systems. "Pleurisy" two years previously but no other past history of note. Married but no children; no other relevant family or social history.
Previous or concurrent treatment:	(1) Laparotomy: large amount of ascitic fluid; widespread deposits from apparent primary in (R) ovary. Biopsy only. 7/7/64 (2) Low-salt diet and diuretics: from 11/7/64 (3) Blood transfusion: 1½ litres of whole blood 4/9/64 (4) Aspiration of (R) pleural effusion: 3 litres 3/9/64; 1 litre 6/9/64; 700 ml. 21/10/64 (5) Prednisone: 20 mg./day by mouth from 21/10/64
Cytotoxic treatment:	(1) Thiotepa: 90 mg. intraperitoneally (3 x 30 mg.) 11/7/64-20/7/64 (2) Cyclophosphamide: 2,600 mg. by I.V.I. 13/7/64-29/7/64 (3) Thiotepa: 60 mg. intrapleural (4 x 15 mg.) 3/9/64-19/9/64 (4) Cyclophosphamide: 300 mg. intrapleural 21/10/64; 200 mg. by I.V.I. 31/10/64
Clinical course and comments:	Presented with obvious ascites and a clinical diagnosis of ovarian malignancy was made on day of admission. Diagnosis confirmed at laparotomy and treatment commenced with cytotoxins, low-salt diet and diuretics. Marked diarrhoea following intraperitoneal thiotepa and diuretics. Settled and apart from superficial wound breakdown progress was satisfactory. Remained well for 1 month then developed (R) pleural effusion which required repeated aspiration. Epilation was marked and from second month general condition steadily deteriorated. Anorexia was main complaint with intermittent bouts of vomiting and diarrhoea, listlessness and weight loss. Died at home 16/11/64, 5 months from diagnosis.
Autopsy report:	Died at home - post-mortem not obtained.
Result:	Cytotoxins given in 2 courses with an interval of 5 weeks between. Initial course for intra-abdominal metastases and control of ascites. This was effective and ascites did not require further aspiration over 5 months. Second course given for pleural effusion but this much less effective. Side effects from initial course were marked with diarrhoea and alopecia. 1-2 for 5 months.

GROUP H : TESTICULAR TUMOURS

Table 8a

Case: 59	D.H. 5/10/62 Age: 30 Sex: M
Diagnosis:	Teratoma of left testis (intra-abdominal).
History:	First reported 4/10/62 with a two-week history of frequency of micturition, lassitude and cramp-like pain in (R) leg, worse on sitting down. N.B. (L) testis had never been in the scrotum.
Previous or concurrent treatment:	(1) Radiotherapy: 976r to midline of pelvis between 29/10/62 and 2/11/62 (2) Laparotomy and removal of large left testicular tumour, intra-abdominal and freely mobile on cord 12/11/62 (3) Radiotherapy: 3,476r to para-aortic glands 26/11/62-2/1/63 (4) Blood transfusion: 2 pints whole blood 12/11/62
Cytotoxic treatment:	(1) Mannitol mustard: 500 mg. by I.V.I. operation cover 10/11/62-14/11/62
Clinical course and comments:	Large abdominal mass arising from pelvis tentatively diagnosed as a testicular tumour and confirmed at laparotomy. Cytotoxins used as prophylactic cover two days before operation, on day of operation and two days after operation. Completed radiotherapy without incident. Remained free of recurrence of tumour when last seen on 13/2/64.
Autopsy report:	-
Result:	3 P. for 15 months to period of follow-up.

Table 8b

Case: 60	T.T. 7/6/63 Age: 30 Sex: M	
Diagnosis:	Terato-carcinoma of left testis, with pulmonary metastases. Histology: terato-carcinoma with chorio-carcinomatous elements.	
History:	Pain, swelling and tenderness of left testis for 5 weeks. Aching pain in left loin for 5 months. No symptoms referable to other systems.	
Previous or concurrent treatment:	(1) Left orchiectomy:	11/6/63
	(2) Radiotherapy: 5,000r to abdominal gland fields	1/7/63-5/8/63
	3,550r to deposit left upper chest	29/11/63-20/12/63
	3,000r to left hilum and mediastinum	31/12/63-27/1/64
	(3) Blood transfusion: 3 pints whole blood	15/8/63
	(4) Bone marrow extraction: modest yield only	12/8/63
Cytotoxic treatment:	(1) Mannitol mustard: 500 mg. by I.V.I. operation cover	10/6/63-14/6/63
	(2) Vinblastine sulphate: 38.5 mg. by I.V.I.	13/8/63-16/9/63
	(3) Methotrexate: 12.5 mg. by mouth	13/8/63-17/8/63
	60 mg. by I.V.I.	18/8/63-29/8/63
	115 mg. by mouth	30/8/63-28/9/63
	Total = 187.5 mg.	
Clinical course and comments:	Uncomplicated recovery following (L) orchiectomy. Carried out under cytotoxic cover. Completed postoperative radiotherapy without incident. Small haemoptysis 6/8/63 and chest X-ray revealed a small metastasis in left upper lobe. Commenced cytotoxic therapy on 13/8/63 after bone marrow extraction and storage. Remained reasonably well with occasional small haemoptyses and transient chest pains. Metastasis in (L) upper lobe remained static but further metastases developed at (L) hilum - both areas of metastasis being treated by radiotherapy with gradual resolution of the lesions. At last review 13/2/64 was remaining well with normal weight and good appetite; no further spread of tumour at this stage.	
Autopsy report:	-	
Result:	3 P. for 6 months to period of follow-up.	

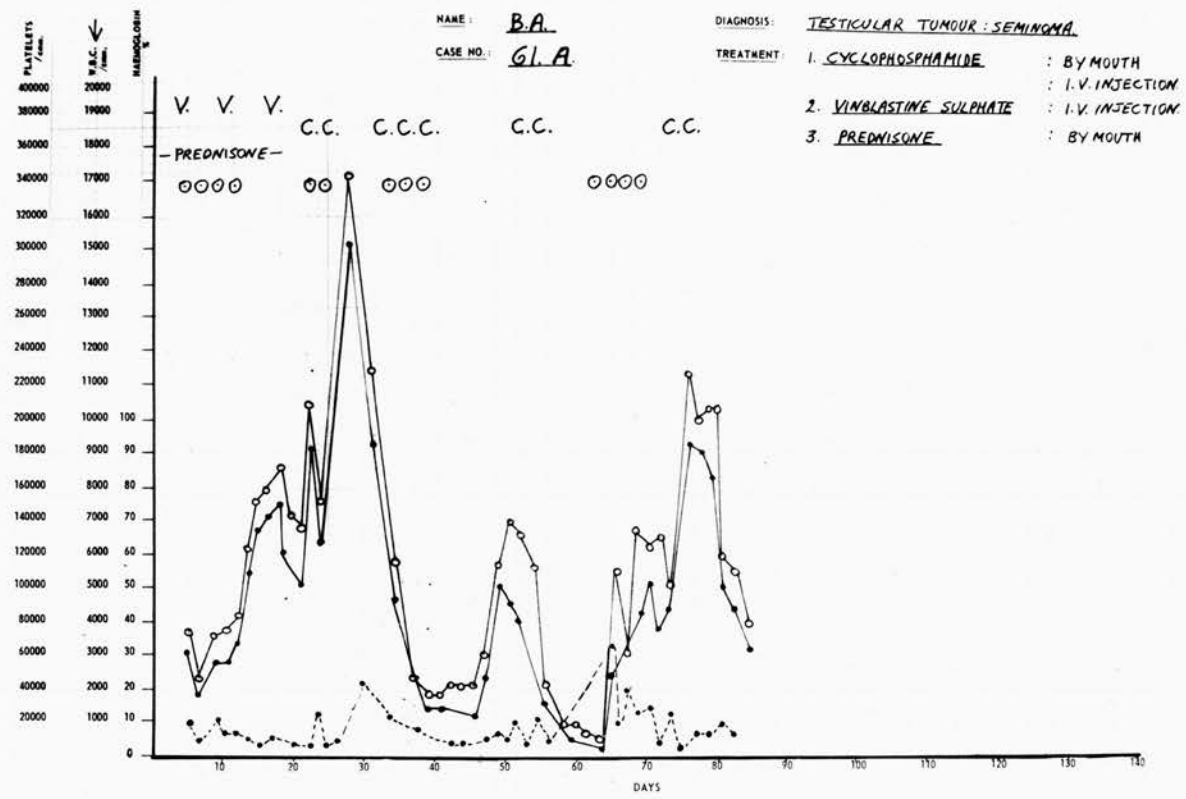
Table 8c

Case: 61	B.A. 17/7/63 Age: 49 Sex: M
Diagnosis:	Seminoma of left testis, with widespread skeletal, pulmonary and lymph node metastases.
History:	(L) orchiectomy carried out in Singapore for histologically proven seminoma on 10/9/62. Postoperative radiotherapy to (L) inguinal region and para-aortic chains. Remained well until 8/4/63 when he developed a metastasis in his (R) ischial tuberosity. By 17/5/63 had developed a cauda equina lesion and pulmonary metastases. Lesions treated by radiotherapy with temporary improvement. Patient developed haemoptysis in June 1963 and received further radiotherapy to the mediastinum. Increasing bone and mediastinal lesions with severe pain in (R) hip and leg. Returned to this country for further treatment.
Previous or concurrent treatment:	(1) Radiotherapy: 2,670r to para-aortic glands and 3,150r to left inguinal region 25/9/62-6/11/62 (2) Radiotherapy: 4,200r to posterior sacral area 21/5/63-21/6/63 1,950r to mediastinum 9/7/63-11/7/63 1,100r to right pubic region (3) Blood transfusion: total of 13 pints between 18/7/63 and 29/8/63 (4) Antibiotics: Erythromycin Penbritin 28/8/63-3/9/63 (5) Prednisone: 30 mg./day by mouth 22/7/63-2/8/63
Cytotoxic treatment:	(1) Cyclophosphamide: 3,200 mg. by mouth over 3 weeks prior to admission 4,600 mg. by I.V.I. 1/8/63-7/9/63 (2) Vinblastine sulphate: 14 mg. by I.V.I. 19/7/63-29/7/63
Clinical course and comments:	General condition was very poor on admission; improved by blood transfusion, prednisone and diet. Severe pain in (R) hip and leg controlled for 6 weeks by cyclophosphamide but course interrupted by recurrent haematemesis. Pulmonary metastases demonstrated regression and by 3/9/63 was feeling well with good appetite and free of pain. Sudden, rapid deterioration with pyrexia and falling blood count; became dyspnoeic, pain again severe. Died 13/9/63.
Autopsy report:	Not obtained
Result:	2-3 for 2 months

CASE NO. 61

PERIPHERAL BLOOD COUNTS

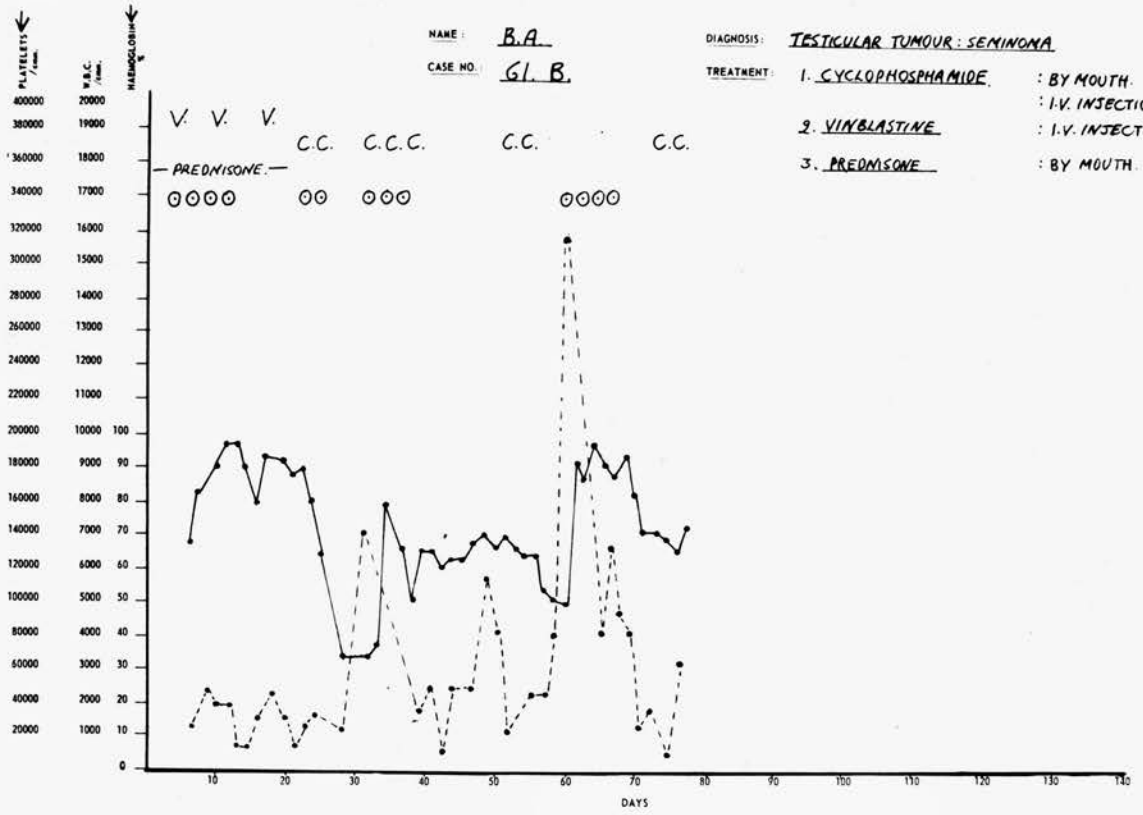
GRAPH A



CASE NO. 61

PERIPHERAL BLOOD COUNTS

GRAPH B



Case No. 61: Testicular Tumour-Seminoma

Fig. 1: Chest X-ray 12/8/63.

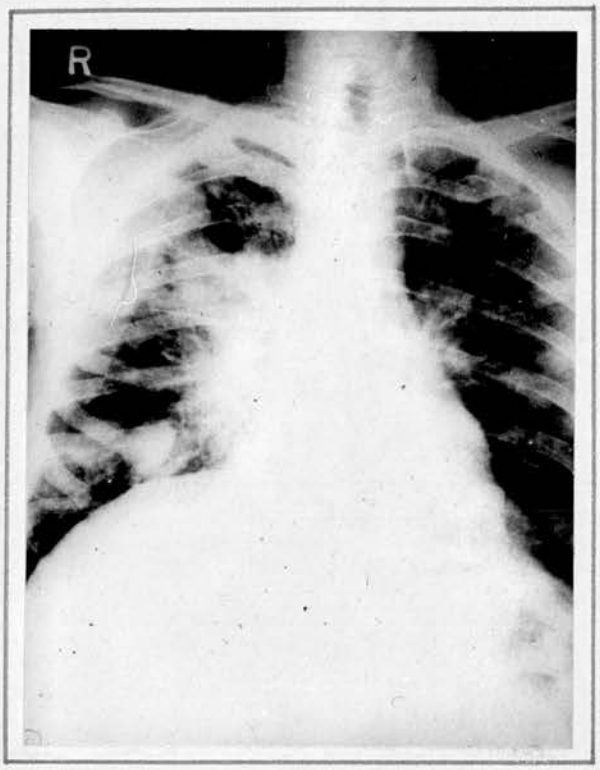


Fig. 2: Chest X-ray 28/8/63.

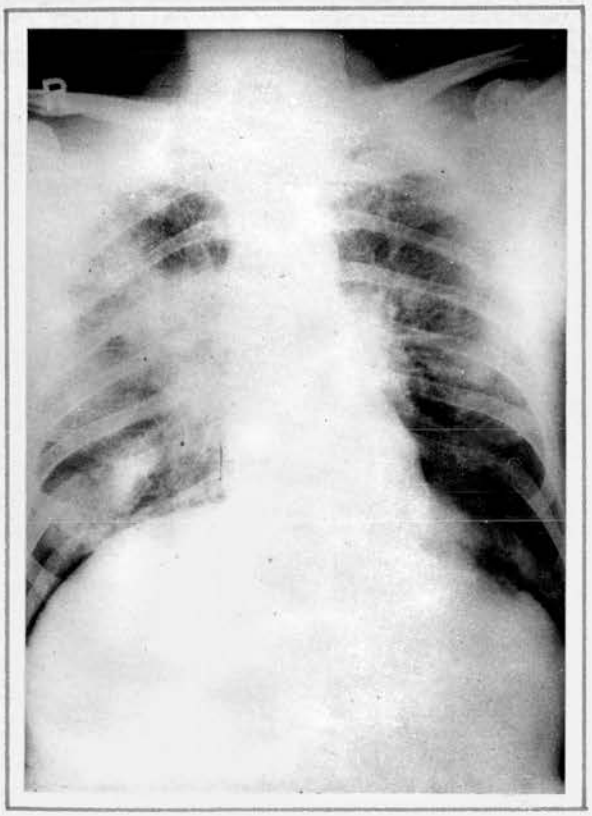


Table 8d

Case: 62	A.J.I. 17/9/63 Age: 22 Sex: M
Diagnosis:	Terato-chorio-carcinoma of (R) testis - with skin, lung and lymph gland metastases.
History:	Admitted 17/9/63 for incision of a supposed abscess (infected haematoma) over (L) upper arm said to have resulted from a motor cycle accident 6 weeks previously. Lesion recognised clinically as a skin deposit from an enormous tumour of the (R) testis. Patient admitted to a progressive, painless swelling of (R) testis for 17 months after initial acute symptoms were thought to be due to epididymo-orchitis. Also complained of increasing malaise for previous few months, anorexia, and loss of $2\frac{1}{2}$ stones in wt. with aching pain in (R) upper arm for 3-4 weeks.
Previous or concurrent treatment:	(1) Physiotherapy: for leg injury following motor cycle accident. (2) Antibiotics: Penbritin, 250 mg. 6-hourly from 27/9/63 (3) Blood transfusion: Total of 24 pints whole blood between 19/9/63 and 16/12/63 (4) (R) orchiectomy: and excision of cord under cytotoxic cover 19/9/63
Cytotoxic treatment:	(1) Mannitol mustard: 100 mg. by I.V.I. as operation cover 19/9/63 (2) Methotrexate: 50 mg. by I.V. drip over 72 hr. 19/9/63-21/9/63 (3) Cyclophosphamide: 3,800 mg. by I.V.I. 28/9/63-21/10/63 (4) Methotrexate: 30 mg. by mouth 25/10/63-6/11/63 (5) Cyclophosphamide: 2,000 mg. by I.V.I. 13/11/63-8/12/63 (6) Vinblastine sulphate: 40 mg. by I.V.I. 2/11/63-8/12/63
Clinical course and comments:	Patient demonstrated widespread malignant disease on admission but removal of the primary tumour was considered reasonable to prevent further dissemination from source and to provide histological confirmation of tumour type. Uncomplicated postoperative course despite commencement of cytotoxins on day of operation. Within 5 days of methotrexate infusion was feeling generally improved with return of appetite and disappearance of pain in (R) upper arm. Commencing regression of skin metastases and abdominal glands by 28/9/63 and improvement maintained for 3 wks. Thereafter developed deep vein thrombosis in (L) leg and increasing skin and abdominal glandular metastases. General condition fluctuating but over-all deterioration with intermittent gastro-intestinal bleeding, vomiting and rapid increase in size and number of metastases. Died 24/12/63.
Autopsy report:	Terato-chorio-carcinoma of (R) testis with large necrotic ulcerating deposit over (L) humerus and similar but smaller lesions over (L) clavicle and sternum. The lungs were heavily infiltrated with massive involvement of mediastinal and retroperitoneal glands. There were multiple petechial haemorrhages throughout G.I. tract but liver free of metastases. Death due to progress of disease and bronchopneumonia.
Result:	0-1 for 3 months

Table 8e

Case: 63	M.W.F. 5/11/63 Age: 25 Sex: M	
Diagnosis:	Embryonal-cell carcinoma of (R) testis, with pulmonary metastases.	
History:	Four months' history of painless swelling of (R) testis. Chest X-ray taken at time of first reporting revealed a mass in the (L) hilum and multiple peripheral opacities.	
Previous or concurrent treatment:	(1) (R) orchiectomy: for malignant tumour of testis, under cytotoxic cover	11/9/63
	(2) Radiotherapy: 2,038r to both lung fields	11/11/63-27/11/63
	(3) Radiotherapy: 3,000r to (R) inguinal and para-aortic areas	16/1/64-18/2/64
	(4) Blood transfusion:	
Cytotoxic treatment:	(1) Mannitol mustard: 300 mg. by I.V.I.	10/9/63-12/9/63
	(2) Methotrexate: 50 mg. by I.V. drip	16/10/63
	(3) Cyclophosphamide: 2,600 mg. by I.V.I. 3,200 mg. by I.V.I.	16/10/63-1/11/63 23/12/63-12/1/64
	(4) Vinblastine sulphate: 87 mg. by I.V.I.	12/11/63-12/2/64
Clinical course and comments:	Although pulmonary metastases were present at first diagnosis removal of the primary tumour was carried out to reduce further dissemination. In view of widespread nature of disease and poor general condition cytotoxic therapy was continued with methotrexate and cyclophosphamide intravenously. General condition improved and some regression of pulmonary metastases produced. Radiotherapy commenced on 11/11/63 when evidence of new metastases seen on chest X-ray. Following initial treatment general condition deteriorated, lost 10 lb. in weight and became nauseated and anorexic. Further glands in abdomen treated by radiotherapy. General state poor despite combining radiotherapy with vinblastine, but at last review 12/2/64 was improving slightly.	
Autopsy report:	-	
Result:	1-2 for 5 months	

GROUP I: RENAL CARCINOMA (HYPERNEPHROMA)

Table 9a

Case: 64	H.F.S. 3/10/63 Age: 40 Sex: M	
Diagnosis:	Hypernephroma (R) kidney: pulmonary metastases.	
History:	First reported 29/8/63 with increasing breathlessness, productive cough, intermittent pyrexia, anorexia and weight loss ($1\frac{1}{2}$ stone) over the previous 8 months. At laparotomy (at another hospital) 19/9/63 a (L) hypernephroma was found and removed. No relevant previous or family history.	
Previous or concurrent treatment:	(1) Laparotomy: (L) nephrectomy	19/9/63
	(2) Radiotherapy: 4,990r to (L) hypochondrium	14/10/63-14/11/63
Cytotoxic treatment:	(1) Cyclophosphamide: 1,300 mg. by I.V.I.	24/9/63-2/10/63
	2,000 mg. by I.V. drip	17/12/63-19/12/63
	2,100 mg. by I.V.I.	20/12/63-10/1/64
	(2) Vinblastine sulphate: 38 mg. by I.V.I.	16/12/63-20/1/64
	(3) Cyclophosphamide: 1,800 mg. orally	16/1/64-31/1/64
	2,400 mg. orally	13/2/64-12/3/64
Clinical course and comments:	Originally thought to have carcinoma stomach and hypernephroma only discovered at laparotomy. Noted to have small metastases in (R) lower lung fields but radiotherapy given to (L) renal area in view of local extent of tumour. General condition remained reasonable but cytotoxic therapy commenced on 17/12/63 because of increase in size of pulmonary metastases. Remained in good health and returned to work for 4 months. Weight steady and appetite fair. Mild loss of hair. Thereafter slow deterioration and at last review 12/5/64 the pulmonary metastases were steadily increasing in size and number; he complained of a persistent, productive cough and tired easily.	
Autopsy report:	-	
Result:	2-3 for 6 months	

GROUP I : RENAL CARCINOMA (HYPERNEPHROMA)
(continued)

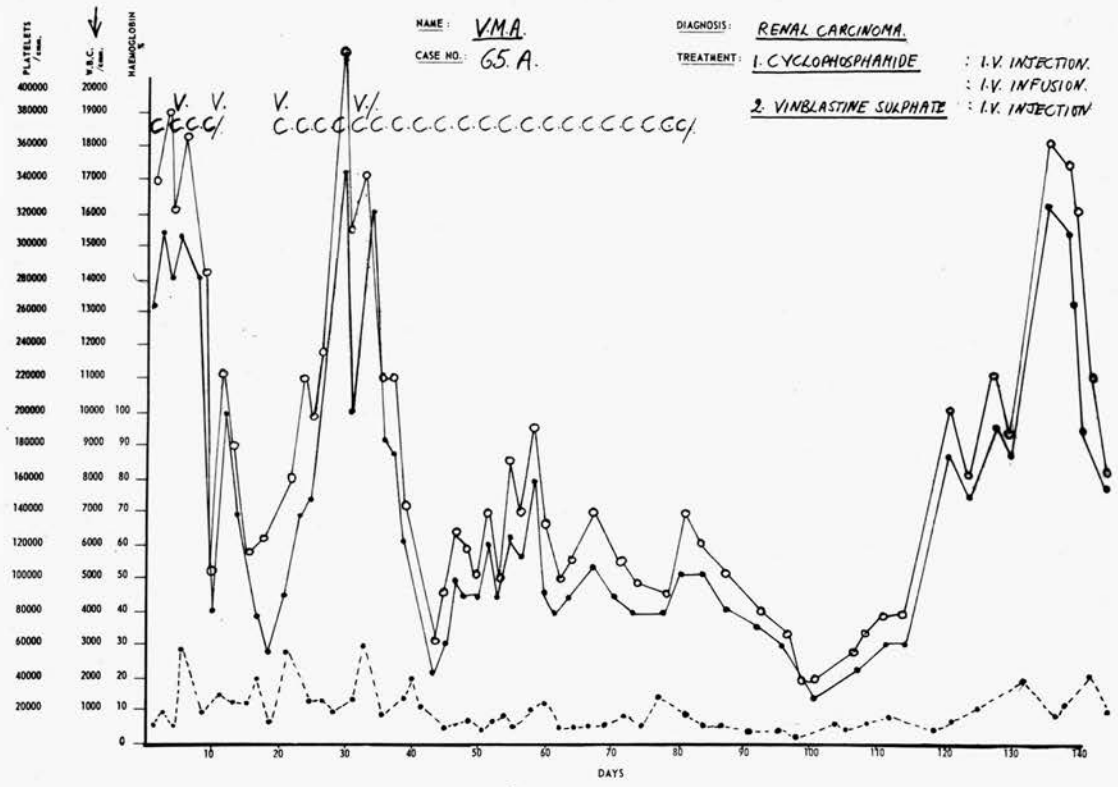
Table 9b

Case: 65	V.M.A. 28/5/63 Age: 49 Sex: F
Diagnosis:	Hypernephroma (R) kidney: extensive local recurrence, pulmonary and skeletal metastases.
History:	(R) nephrectomy for histologically proven hypernephroma at another hospital August 1962 for 10-month history of backache, haematuria and (R) loin pain. Found in May 1963 to have lung and bone metastases and was in considerable pain. Thereafter increasingly severe pain in (R) loin, hip and thigh, numbness and weakness in legs. Marked weight loss, anorexia and insomnia. Mother died of carcinoma breast.
Previous or concurrent treatment:	(1) Analgesics: (2) Radiotherapy: 400r to abdominal mass 31/7/63-2/8/63 Course interrupted because of falling W.B.C. (3) Blood transfusion: total of 24 pints whole blood 11/6/63-2/9/63
Cytotoxic treatment:	(1) Cyclophosphamide: 2,400 mg. by I.V.I. and I.V. drip 1/6/63-20/6/63 6,200 mg. orally 24/6/63-12/8/63 (2) Vinblastine sulphate: 18 mg. by I.V.I. 4/6/63-23/6/63
Clinical course and comments:	Ill and extremely distressed on admission with an enormous mass in the (R) side of the abdomen, extensive pulmonary metastases and metastases in (R) femur. Severe intractable pain, unrelieved by any form of analgesic. Maintained pain relief with cyclophosphamide and clearing of pulmonary metastases. Minimal change in size of abdominal mass. Required repeated blood transfusion to maintain haemoglobin. Complete epilation - wig fitted. Three months after admission condition began to deteriorate, and abdominal mass increased rapidly in size. Patient remained free of pain and distress until she died on 27/9/63.
Autopsy report:	Emaciated. Large mass in (R) loin extending into (R) iliac fossa; mass fixed to retroperitoneal structures. Liver grossly enlarged and widely infiltrated by tumour deposits. $2\frac{1}{2}$ x 2 cm. tumour deposit in (R) lung but no other obvious metastases in lung. Microscopy confirmed presence of widespread carcinoma consistent with renal primary.
Result:	1-2 for 4 months

CASE NO. 65

PERIPHERAL BLOOD COUNTS

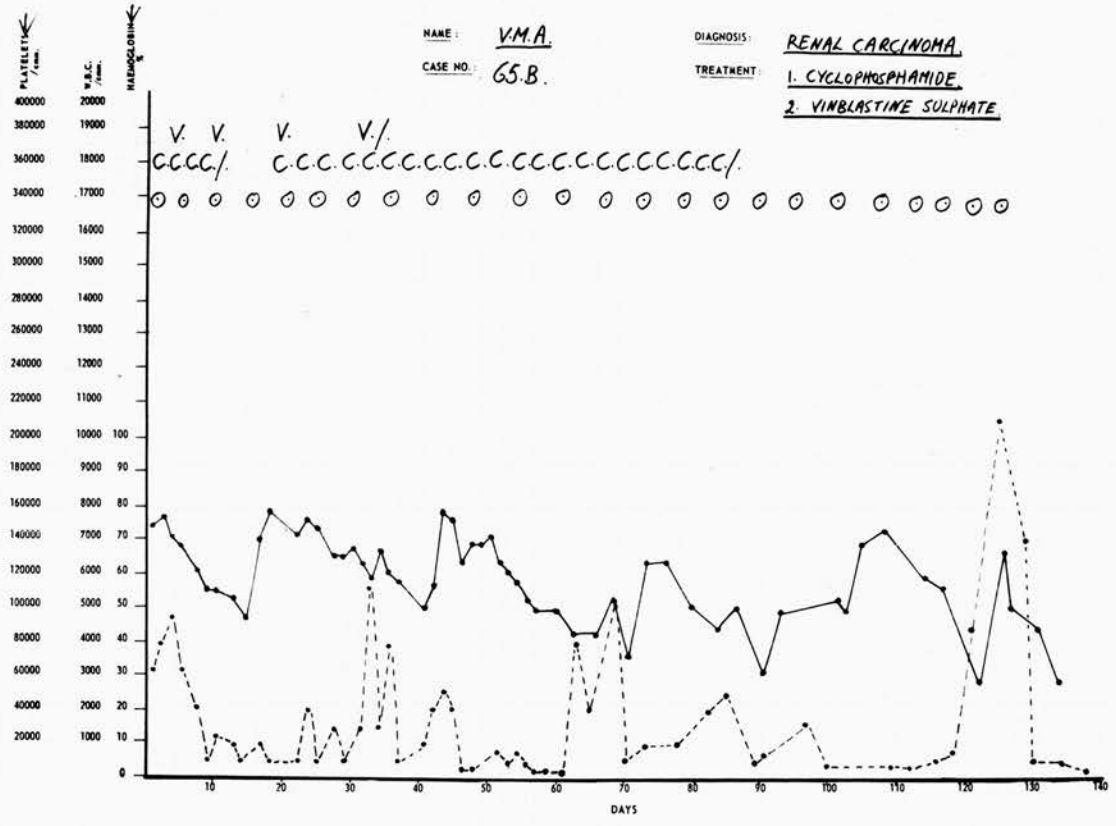
GRAPH A



CASE NO. 65

PERIPHERAL BLOOD COUNTS

GRAPH B



Case No. 65: Renal Carcinoma

Fig. 1: Chest X-ray 29/5/63.

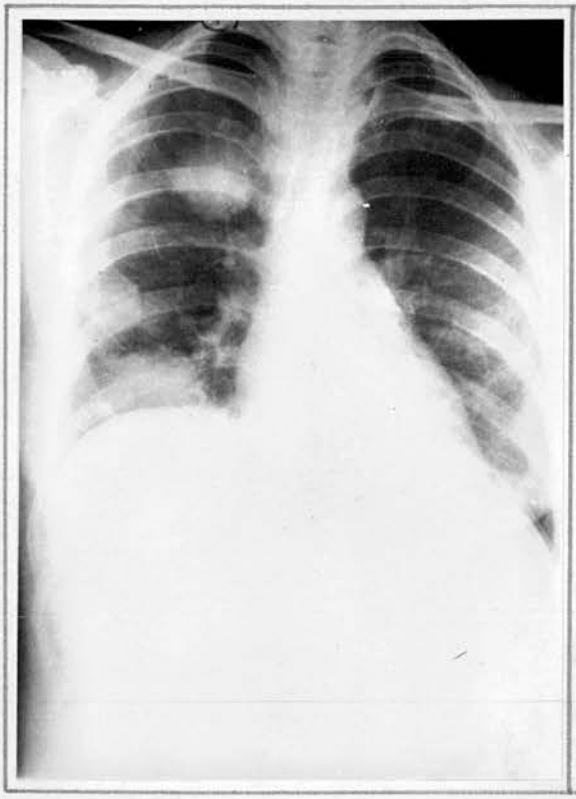


Fig. 2: Chest X-ray 21/6/63.

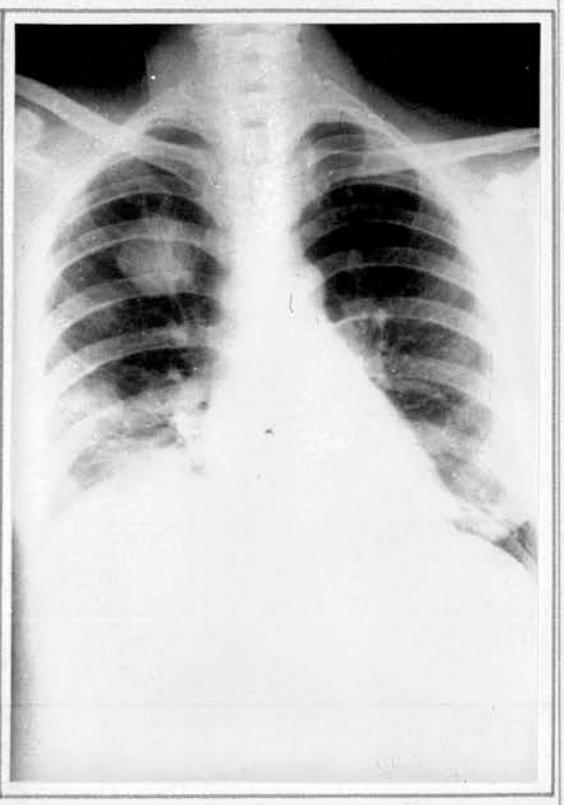


Fig. 3: Chest X-ray 12/8/63.

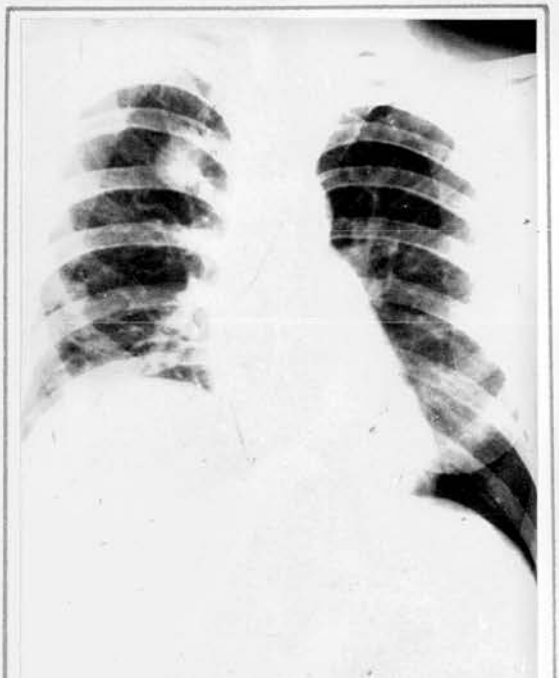


Table 9c

Case: 66	J.W. 9/3/65 Age: 66 Sex: M
Diagnosis:	(R) hypernephroma. No histology obtained.
History:	Admitted as a transfer from a medical ward with a 4-month history of nausea, vomiting, anorexia, diarrhoea and the loss of 1 stone in weight. There had been one brief episode of haematuria 3 weeks previously, but no other urinary symptoms. Had previously been under care of cardiology unit since September 1962 following an episode of myocardial infarction and congestive failure. Known to be severely hypertensive and on treatment for this. Initially symptoms thought to be due to cardiovascular state or its treatment, but investigation established presence of an advanced (R) sided hypernephroma.
Previous or concurrent treatment:	(1) Medical treatment for hypertension and cardiac failure. (a) Aldomet 250 mg. t.i.d. (b) Digoxin 0.25 mg. b.i.d.
Cytotoxic treatment:	(1) Cyclophosphamide: 3,000 mg. by intra-arterial injection (R) renal artery (3 x 1,000 mg.) 600 mg. by I.V.I. (3 x 200 mg.) 19/3/65-23/3/65
Clinical course and comments:	Patient with known severe hypertensive heart disease presenting an unusual history of nausea, vomiting and diarrhoea due to an advanced hypernephroma of (R) kidney. Symptoms initially ascribed to medical condition and to medical treatment. Operation was not considered feasible and despite the lack of histological proof, it was agreed to try the effects of cytotoxins. Given by intra-arterial and intravenous injection, cyclophosphamide produced a rapid and complete relief of principal symptoms. Patient remained well and at home for 5 weeks, but was then re-admitted to a medical ward with rapid deterioration to death from staphylococcal pneumonia on 18/5/64.
Autopsy Report:	Permission not obtained.
Result:	Rapid and complete relief of vomiting and diarrhoea with cyclophosphamide, but little significant effect on tumour itself. Benefit lasting 5 weeks only, but side effects limited to moderate leucopaenia only. 1-2 for 5 weeks.

Case No. 66: Renal Carcinoma

Fig.1: Inferior vena cavagram: tumour invasion: A.P. view.

Fig.2: Inferior vena cavagram: tumour invasion: lateral view.

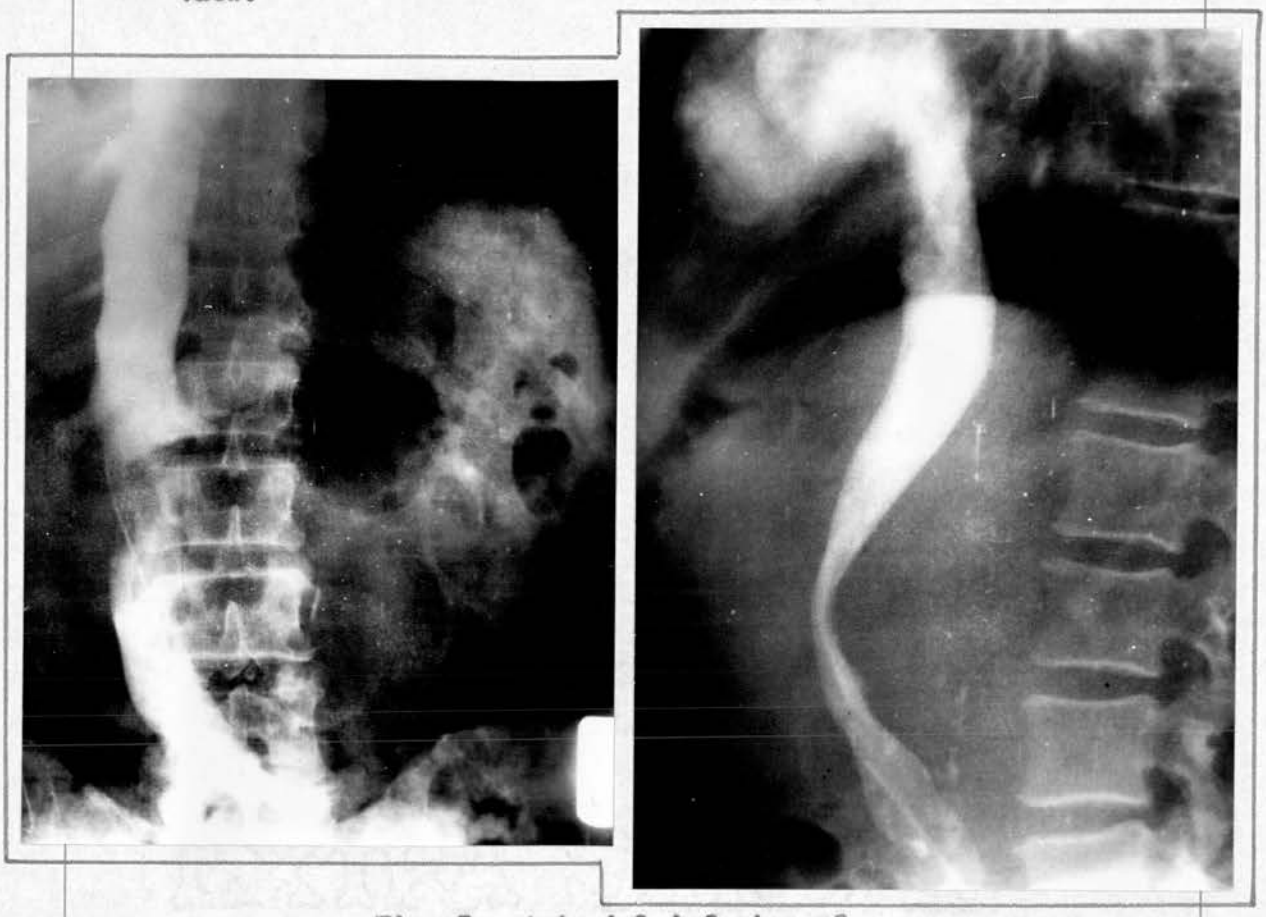
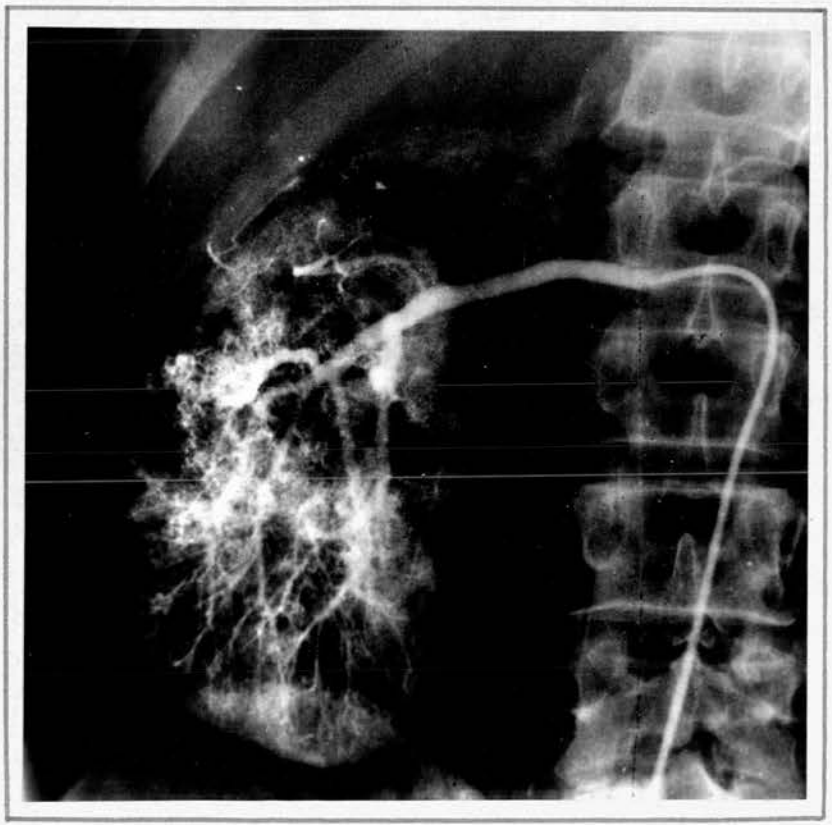


Fig. 3: Arterial infusion of cyclophosphamide 16/3/65.



Case No. 66.

Fig. 4: Arterial infusion of cyclophosphamide 16/3/65.

Fig. 5: Second arterial infusion of cyclophosphamide 25/3/65.

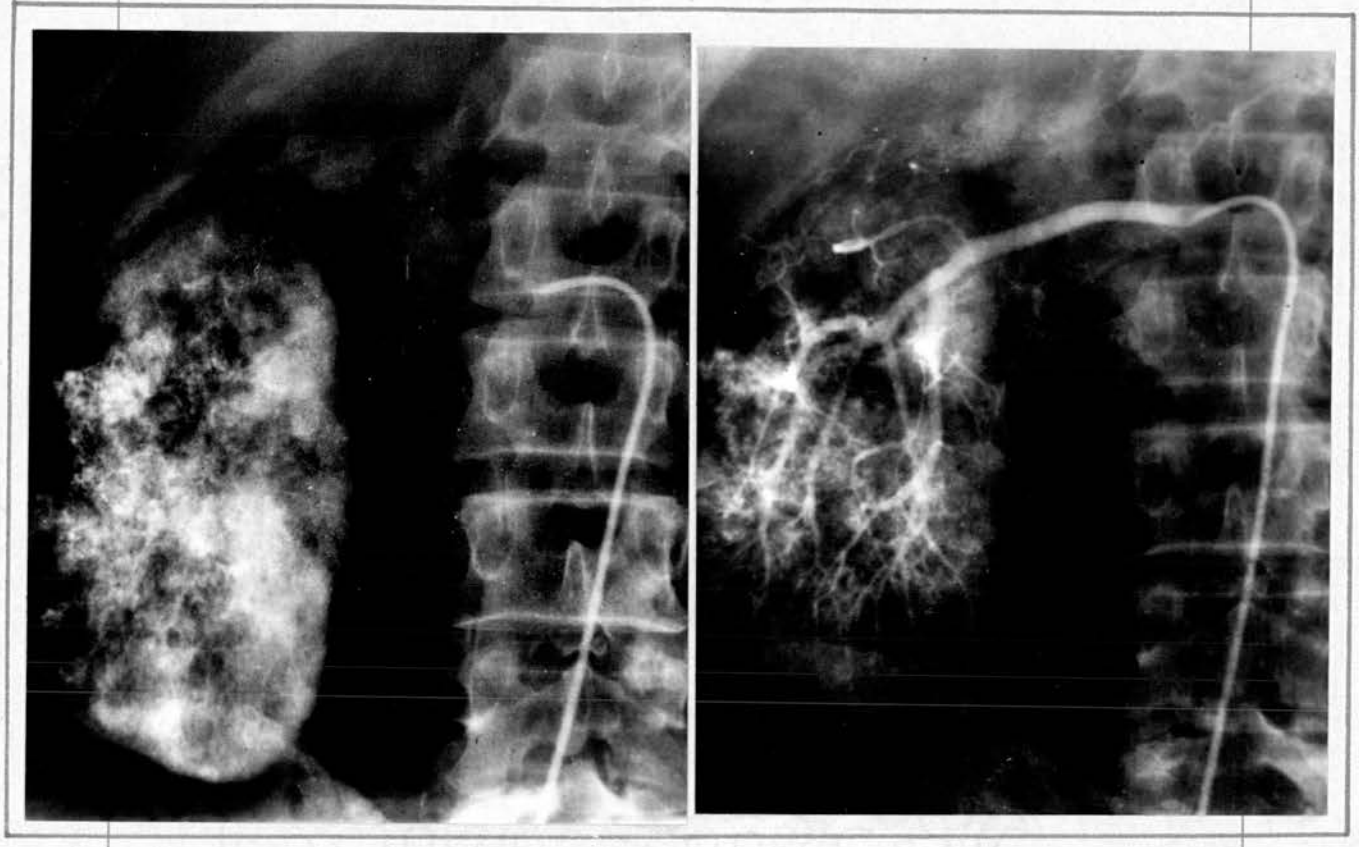
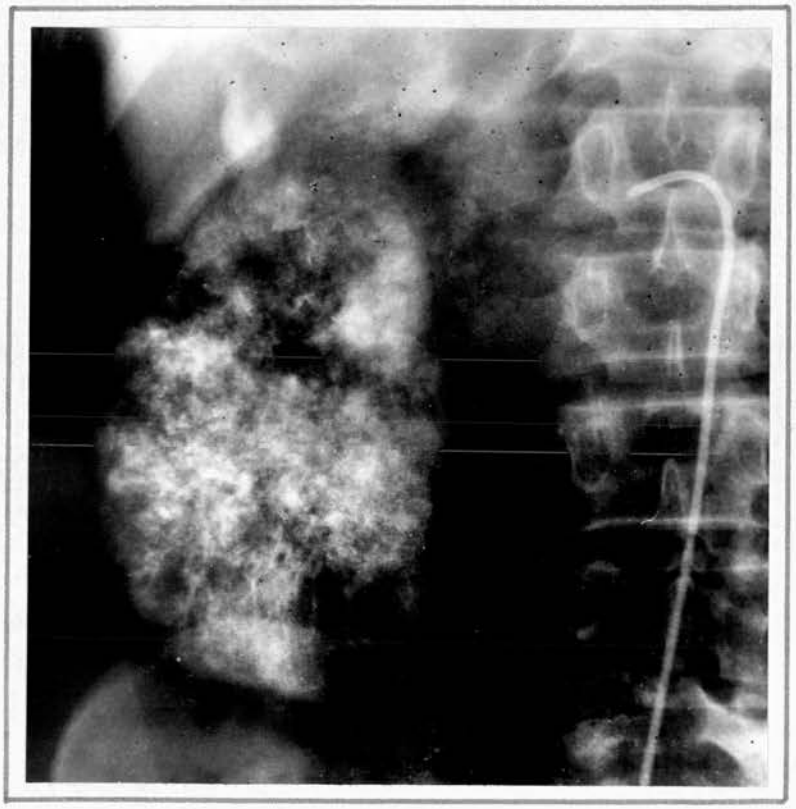


Fig. 6: Second arterial infusion of cyclophosphamide 25/3/65.



Case No. 66.

Fig. 7: Third arterial infusion of cyclophosphamide 12/4/65.

Fig. 8: Third arterial infusion of cyclophosphamide 12/4/65.

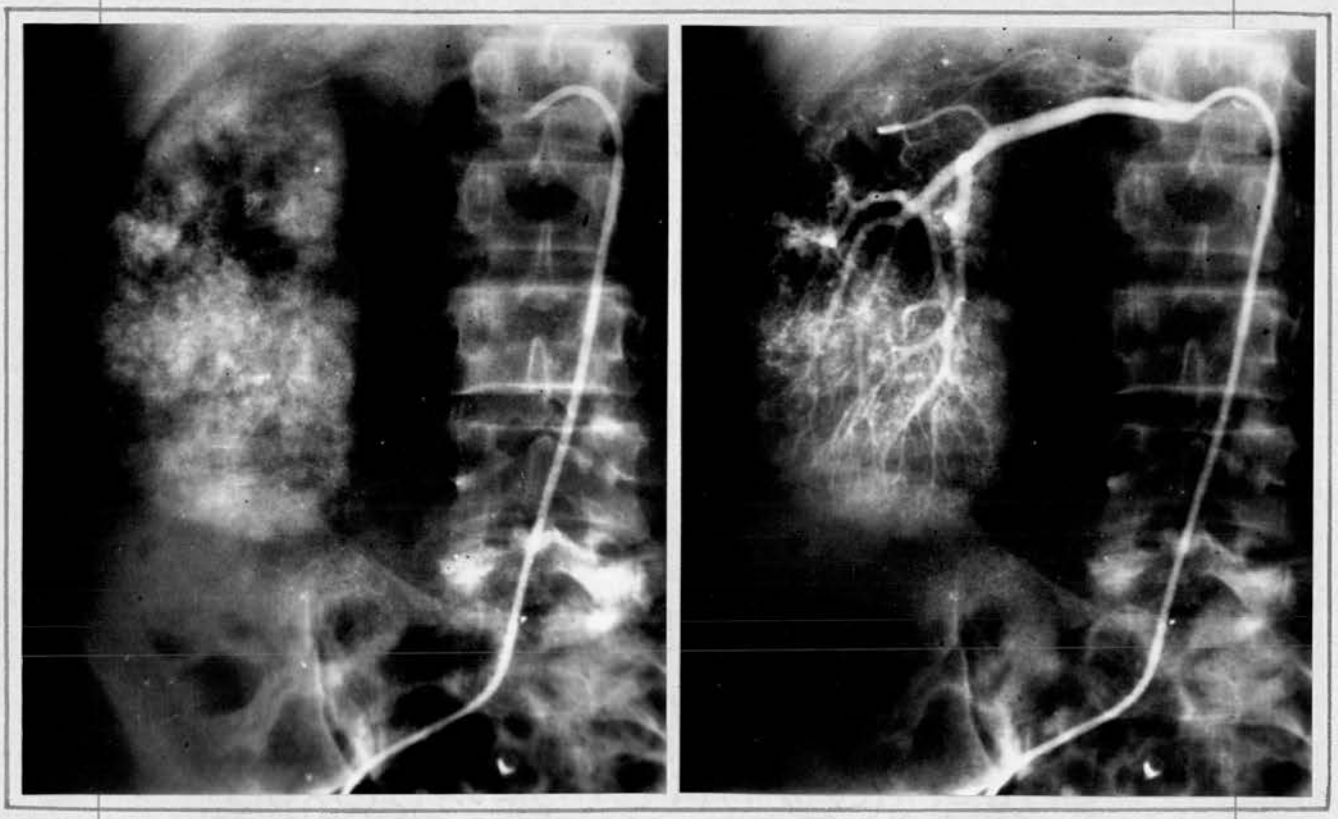


Fig. 9: Chest X-ray: (L) ventricular aneurysm: 12/4/65.

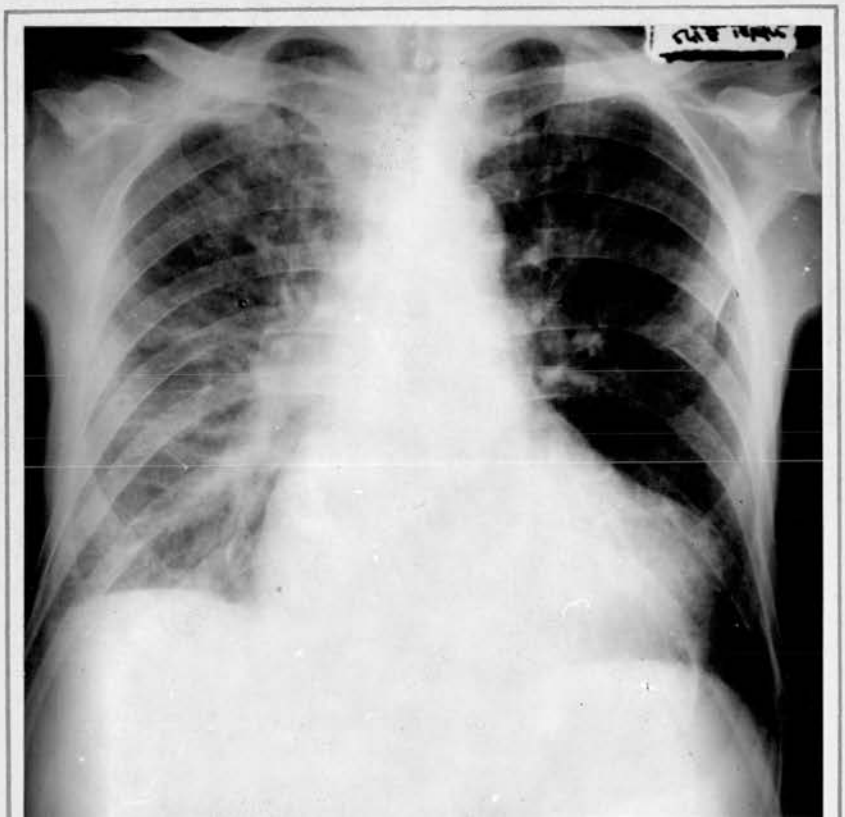


Table 9d.

Case: 67	J.C. 10/11/62 and 15/6/64 Age: 60 Sex: M
Diagnosis:	Hypernephroma (R) kidney - massive local recurrence and pulmonary metastases. Typical renal carcinoma.
History:	First admitted 10/11/62 as a transfer from a medical ward with a 3-month history of intermittent gnawing pain in (R) loin. An I.V.P. had revealed a tumour of (R) kidney. At operation on 13/11/62 a large hypernephroma was found extending along renal vein and into inferior vena cava with invasion of peri-renal tissues. Excision known to be incomplete. Remained well, relatively symptom-free and at work until 3/10/63 when a palpable mass was felt beneath scar. By 15/1/64 patient was himself aware of the mass but had few symptoms. At review on 9/5/64, however, was experiencing considerable local pain with pain and paraesthesiae down back of (R) leg. Given 1 week's palliative radiotherapy 13/5/64 to 20/5/64 but with relief of leg symptoms only. In view of severe local pain use of cytotoxins was considered at review on 15/6/64.
Previous or concurrent treatment:	(1) (R) nephrectomy for large carcinoma of (R) kidney. Excision known to be incomplete. 13/11/62 (2) Radiotherapy: to (R) renal area - details of dosage not known. 13/5/64-20/5/64 (3) Analgesics: Various - from April 1964. (4) Blood transfusion: 2 litres of whole blood 22/6/66
Cytotoxic treatment:	(1) Cyclophosphamide: 3,000 mg. by I.V.I. and I.V. infusion 20/6/64-9/7/64 4,200 mg. by mouth 13/7/64-20/8/64
Clinical course and comments:	At the stage of starting cytotoxic therapy the patient was complaining of severe pain in relation to large tumour mass in (R) side, despite a palliative course of radiotherapy 5 weeks previously. He had lost weight following radiotherapy and appetite was just beginning to return. 10 days after starting cyclophosphamide pain was definitely less marked, but had had some mild haematuria. Reduced need for analgesics. 1 month later was virtually free of pain in tumour, but leg pain and paraesthesiae had returned. Mass larger and pulmonary metastases extending. Oral cyclophosphamide increased, but no further benefit and general condition steadily declined to death at home 25/8/65 - 2 months after starting treatment.
Autopsy report:	Died at home. No post-mortem obtained.
Result:	Definite pain relief from use of cytotoxins but maintained for 6 weeks only. N.B. Cystitis from ? cyclophosphamide but no other side effects. 1-2 for 2 months.

Table 9e

Case: 68	H.S. 29/9/65 Age: 53 Sex: F
Diagnosis:	Hypernephroma of (R) kidney. Typical renal carcinoma.
History:	First admitted to another hospital in September 1965 with a large swelling which she had noticed in (R) side of her abdomen for the previous 6 weeks. Denied any other symptoms at this time. No previous or family history of significance. Investigations, including aortography, established a diagnosis of (R) hypernephroma and this was confirmed at laparotomy on 30/9/65.
Previous or concurrent treatment:	(1) Laparotomy: in another hospital. Extensive, invading hypernephroma of (R) kidney. Inoperable. N.B. Cytotoxins first given 2 days before operation. 30/9/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1,500 mg. by intra-arterial infusion via (R) renal artery, i.e. percutaneous femoral puncture and seldinger catheterisation of renal artery on 3 occasions, viz.: 400 mg. 29/9/65 500 mg. 21/10/65 600 mg. 6/1/66 1,400 mg. by I.V.I. 4/11/65-23/12/65 4,200 mg. by mouth 18/11/65-17/1/66 Total - 7,100 mg.
Clinical course and comments:	Patient presented with an enormous mass in (R) side of abdomen, but was curiously free of other symptoms. At laparotomy the mass proved to be an extensive inoperable hypernephroma. It was considered proper to treat this tumour with cytotoxins and on 3 occasions cyclophosphamide was infused via the (R) renal artery. At the same time intravenous and oral therapy were continued. Over a period of 5 months the mass in (R) side of abdomen slowly increased in size but the patient remained active, reasonably well and entirely free of pain. She became mildly anaemic by mid-January and thereafter gradually deteriorated with occasional vomiting and increasing lethargy. Re-admitted to original hospital on 3/3/66 with vomiting, weakness and depression. Hb 64%. Vomiting settled but two large rectal haemorrhages on 10/3/66 and 12/3/66 resulted in death on 13/3/66.
Autopsy report:	Massive carcinoma of (R) kidney infiltrating abdominal wall anteriorly and laterally with penetration into colon. Metastases to both lungs. Massive haemorrhage into colon due to penetrating carcinoma. Large areas of necrosis in primary tumour.
Result:	Cytotoxins exhibited over period of 5 months. Probably little effect on tumour until later stages. No significant side effects. 1-2 for 5 months.

Case No. 68: Renal Carcinoma

Fig. 1: Arterial infusion of Cyclophosphamide 28/9/65.

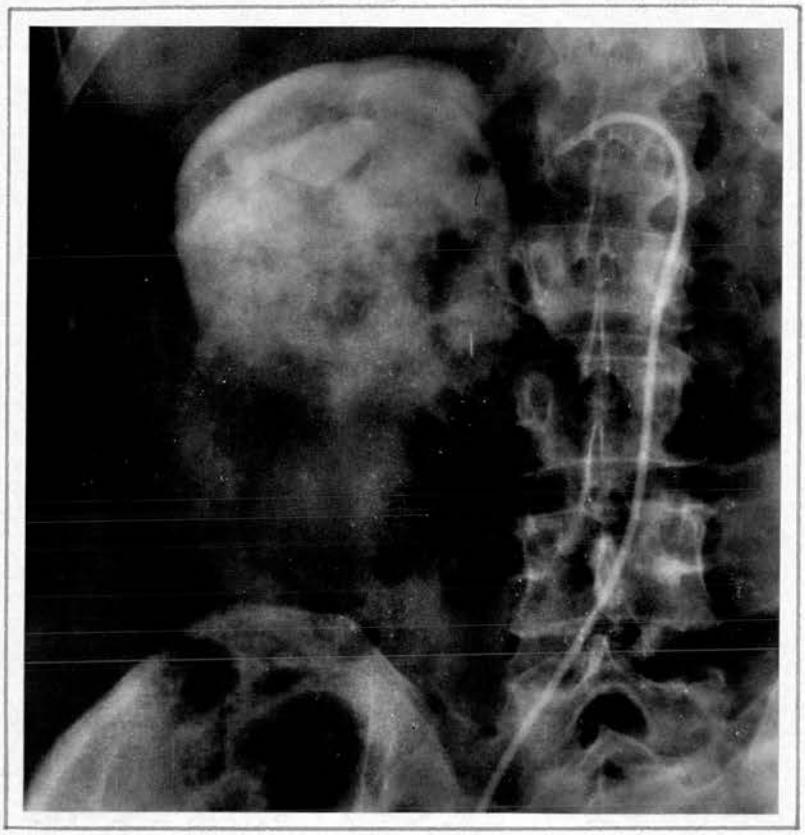
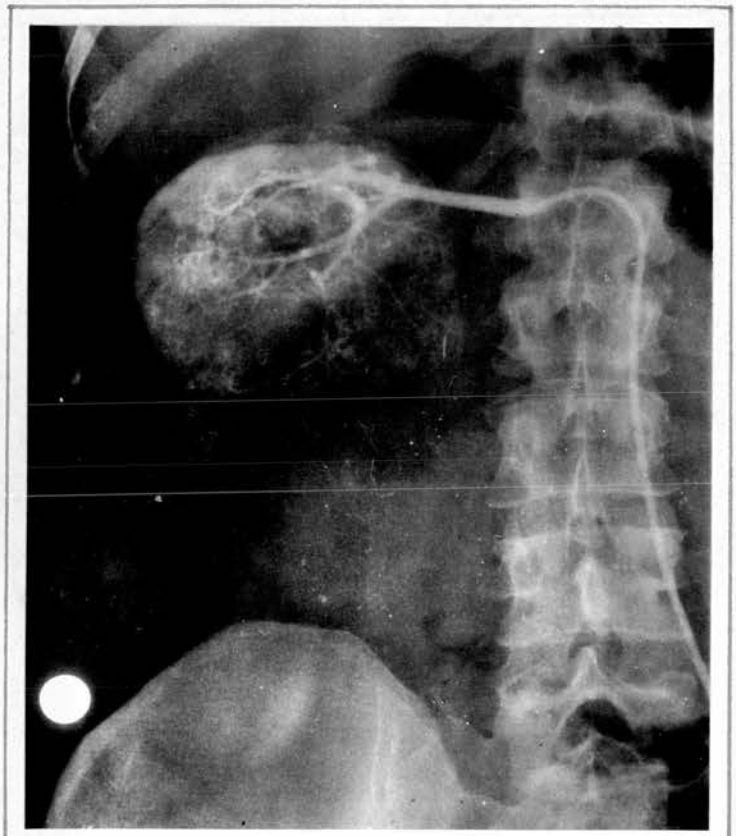


Fig. 2: Second arterial infusion of Cyclophosphamide 6/1/66.



GROUP J : CARCINOMA OF BLADDER

Table 10a

Case: 69	W.K. 12/2/64 Age: 70 Sex: M
Diagnosis:	Carcinoma of base of bladder with local infiltration, glandular and hepatic metastases. Undifferentiated infiltrating squamous carcinoma.
History:	First treated in February 1962 for a (L)-sided renal cyst giving rise to aching discomfort in (L) loin. For the next 12 months the patient complained of increasing frequency, supra-pubic pain, dysuria and nocturia. Symptoms subsequently attributed to an infiltrating carcinoma of base of bladder although initially the prostate had been thought the site of origin. No response to treatment with oestrogens and not considered suitable for radio-therapy since site and extent of tumour could not be defined accurately. No previous or family history of note.
Previous or concurrent treatment:	(1) Hormone therapy: (a) Honvan - 300 mg./day 25/3/65-15/4/65 (b) Stilboestrol - 90 mg./day 18/4/65-18/5/65 (2) Antibiotics: Various - for recurrent urinary tract infection. (3) Uretero-colic anastomosis: Widespread deposits in liver and abdominal glands; hard infiltrating tumour bladder neck and prostate. 28/6/65 (4) Blood transfusion: 1½ litres of whole blood 30/6/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1,000 mg. by I.V. infusion over 24 hours 13/6/65-14/6/65 (2) 5-fluorouracil: 1,050 mg. by I.V.I. 16/6/65-18/6/65
Clinical course and comments:	Despite treatment with antibiotics and hormones, patient's symptoms remained unchanged. Persistent, severe supra-pubic and (L) lower abdominal pain resulted in patient being virtually bedridden. Cytotoxins started in hope of relieving severity of pain and of supporting proposed uretero-colic anastomosis. Within 10 days of starting treatment pain relief was virtually complete, but frequency and incontinence persisted. Uretero-colic anastomosis carried out without incident on 28/6/65, but general condition remained poor. No further cytotoxin therapy given and patient survived in reasonable comfort until 13/8/65.
Autopsy report:	Died in Nursing Home and post-mortem not obtained.
Result:	Although cytotoxins given for only short period and in moderate dose pain relief was marked. No significant side effects. 0-1 for 2 months.

GROUP K : CARCINOMA OF PROSTATE

Table 11a

Case: 70	T.P. 6/9/62 and 27/8/63 Age: 59 Sex: M	
Diagnosis:	Carcinoma of prostate with skeletal metastases.	
History:	First admitted 6/9/62 with 1-month history of backache, constipation and marked weight loss. (Had previously been investigated in another hospital in 1957 for weight loss and general malaise but cause found.) Now presented with clinically obvious carcinoma of prostate with widespread skeletal metastases, particularly in lumbar spine and pelvis. Apart from above, no previous or family history of significance.	
Previous or concurrent treatment:	(1) Bilateral orchiectomy:	17/9/62
	(2) Steroids: (a) Hydrocortisone 500 mg. I.V.I.	30/7/63
	(b) Cortisone acetate 100 mg. IM. 1 x 2	1/8/63
	(c) Cortisone acetate 25 mg. t.i.d. orally	from 2/8/63
	(3) Oestrogens:	
	(a) T.A.C.E. 12 mg. t.i.d. by mouth	15/8/63-28/8/63
	(b) Ethinyloestradiol 0.6 mg./day from	29/8/63
	(4) Blood transfusion: 1 litre of whole blood	21/8/63
Cytotoxic treatment:	(1) Cyclophosphamide: 2,500 mg. by I.V.I. (500 mg. x 5)	11/9/63-15/9/63
Clinical course and comments:	Marked remission of symptoms following bilateral orchiectomy 17/9/63 with healing of skeletal lesions. Remained well and at work until 30/7/63 when he was admitted to another hospital with sudden onset of severe backache, fatigue, lethargy and dehydration. Examination at this stage revealed a waxy pallor (although Hb 78%), premature senility, dehydration, a firm, irregular prostate and a large hard mass occupying hollow of sacrum. X-rays revealed extensive reactivation of metastases. Transferred for further management. On admission was unfit for any further surgery although bowel almost obstructed from tumour mass in pelvis. Started cyclophosphamide 11/9/63 and general condition improved by 18/9/63. White blood count and platelets then dropped to very low levels and patient barrier-nursed. By 21/9/63 was weak and deteriorating. Small melaena 22/9/63 - transferred and same day collapsed with severe hypotension. Despite I.V. hydrocortisone and blood transfusion, profound collapse persisted and patient died same day.	
Autopsy/		

Table 11a (continued)

Autopsy report:	Oedema and early decomposition of face and trunk. Large black or deep red blobs in skin. Abdomen distended and early gangrenous changes of scrotum. Pronounced hiss of escaping gas on reflecting scalp. Culture of Cl. Welchii and gram negative coliforms from exudates and tissues. Death due to ?gram negative septicaemia due to carcinoma of prostate.
Result:	Cytotoxins exhibited late in disease process. Produced profound bone marrow depression within one week of commencement and patient died of haemorrhage and ?gram negative septicaemia. 0 for 2 weeks.

Case No. 70: Carcinoma of Prostate

Fig. 1: Chest X-ray 28/8/62.

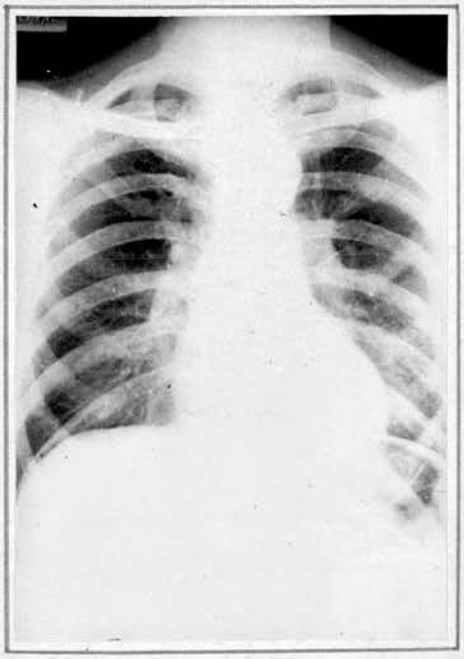


Fig. 2: Chest X-ray 10/9/63.

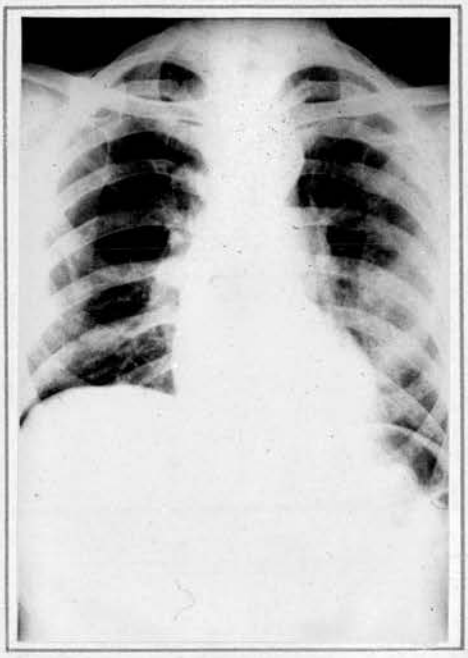
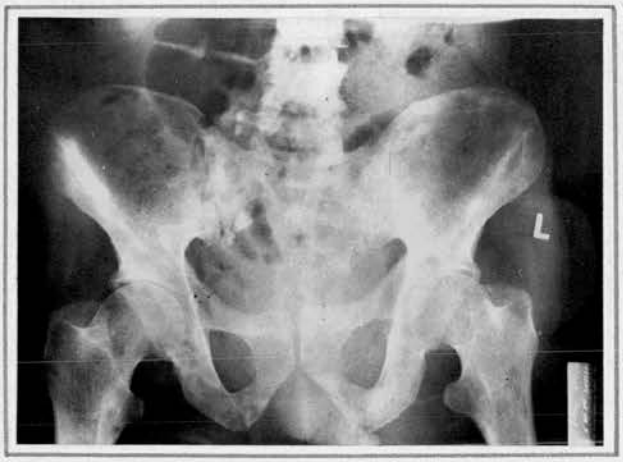


Fig. 3: X-ray of pelvis 28/8/62.



GROUP L : ADRENAL CARCINOMA

Table 12a

Case: 71	J.R. 13/2/62 **Age:** 43 **Sex:** M
Diagnosis:	Adrenal carcinoma. (Mediastinal, bone and skin metastases.) (Biopsy of abdominal mass.)
History:	Laparotomy August 1960 for history of persistent backache, weight loss and anorexia over previous 3 months. Biopsy of a large irremovable retroperitoneal mass above (L) kidney revealed an adrenal carcinoma. Lesion treated by irradiation with marked benefit. Mediastinal metastases were also treated by irradiation one year later. Remained well and at work until February 1962 when he was admitted with increasing listlessness, dysphagia, weight loss, anorexia and further metastases in mediastinum and (L) buttock.
Previous or concurrent treatment:	(1) Radiotherapy: 5,700r to primary tumour 24/8/60-17/10/60 4,300r to mediastinal metastases 12/10/61-10/11/61 (2) Analgesics: (3) Blood transfusion: total of 14 pints 9/3/63-21/11/63 (4) Haematinics: (5) Radiotherapy: 3,967r to mediastinum 5,240r to (L) buttock } 29/7/63-28/8/63 5,340r to (R) knee
Cytotoxic treatment:	(1) Nitrogen mustard: 40 mg. by I.V.I. 24/2/62-26/2/62 40 mg. by I.V.I. 16/5/62-18/5/62 (2) Cyclophosphamide: 1,000 mg. by I.V.I. 28/2/62-4/3/62 1,000 mg. by I.V.I. 19/3/62-23/3/62 1,000 mg. by I.V.I. 21/5/62-25/5/62 18,300 mg. orally 26/6/62-19/2/63 1,000 mg. by I.V.I. 1/3/63-8/3/63 10,600 mg. orally 9/3/63-18/7/63 1,500 mg. by I.V.I. 13/9/63-17/9/63 2,700 mg. orally 5/10/63-22/10/63 1,000 mg. by I.V.I. 2/11/63-18/11/63 550 mg. orally 19/11/63-29/11/63 Grand total = 38,650 mg.
Clinical/	

Table 12a (continued)

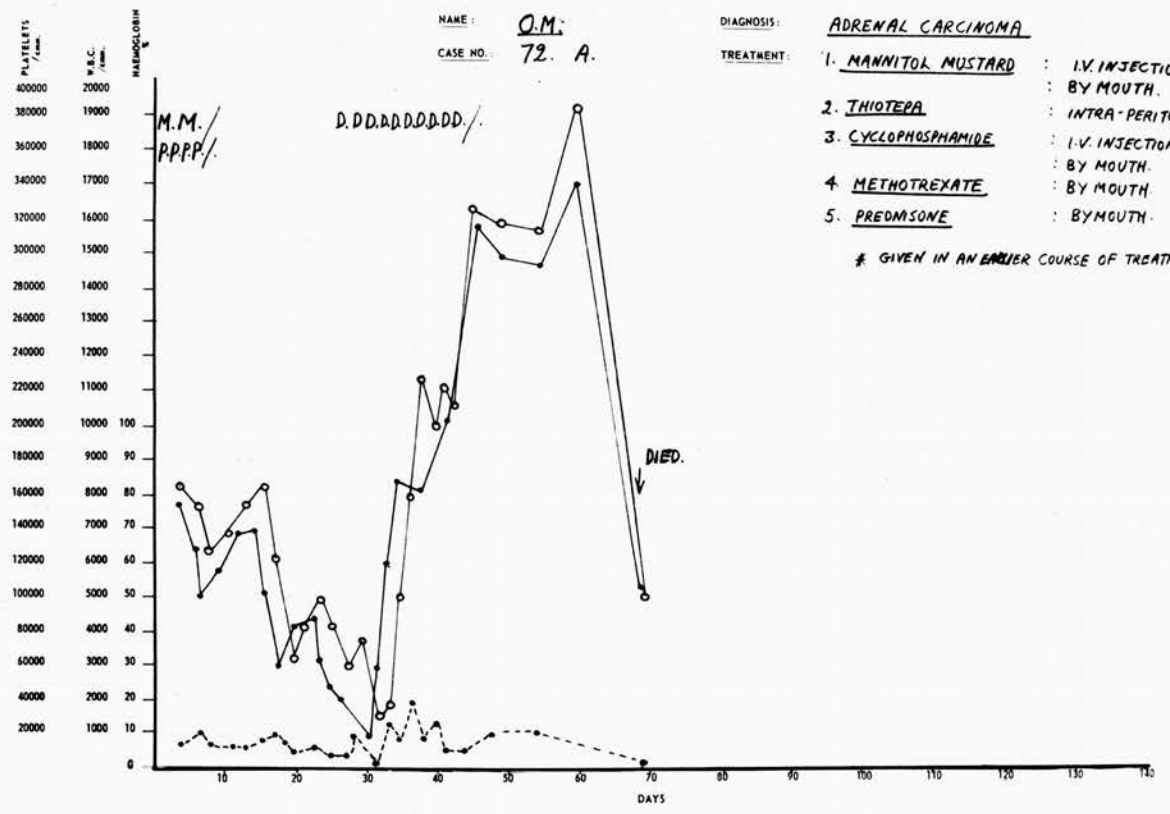
Clinical course and comments:	When admitted in February 1962 patient was unwell with anorexia, weight loss, dysphagia and a palpable mass in (L) buttock. Within two weeks of starting chemotherapy with nitrogen mustard and cyclophosphamide there was a marked improvement both objectively and subjectively and the patient returned to work on 18/4/62. Remained well for 4 months and was then readmitted following an episode suggesting an epileptiform convulsion. No obvious lesion on examination and discharged after a few days, on continued treatment. On 19/2/63 he was readmitted with similar symptoms to those in February 1962, but now had pain in (L) tibia also. Again made a rapid and dramatic response to cyclophosphamide intravenously. Discharged symptom-free 11/3/63. Thereafter, however, periods of remission were short and by 18/7/63 symptoms were again severe. Further radiotherapy was given to mediastinum, buttock and (L) knee and symptoms stopped. Reasonably well for 6 weeks but in severe pain thereafter in (R) loin and (L) knee. Again responded dramatically to cyclophosphamide but maintained for 1 month only. Thereafter relentless downhill course to death on 17/12/63. Case of especial interest from point of view of rapid response to cyclophosphamide intravenously on at least 4 occasions but with ever decreasing periods of remission.
Autopsy report:	Death from acute pulmonary oedema secondary to carcinomatosis, secondary to carcinoma ? from (L) adrenal. Widespread intra-abdominal deposits with considerable necrosis. Glands of mediastinum and abdomen widely infiltrated. Both kidneys embedded in a mass of tumour tissue. Mass of necrotic tumour tissue in site of adrenals.
Result:	2-3 for 18 months

Table 12b

Case: 72	O.M. 17/9/62 Age: 26 Sex: F
Diagnosis:	Carcinoma of adrenal gland with pulmonary metastases. (Biopsy of abdominal mass.)
History:	One year increasing weight loss, listlessness and breathlessness on exertion. Increasing abdominal pain, vomiting, fever and weakness for 6 months - following birth of second child. Initially thought to have a polycystic (L) kidney and recurrent pyelitis, but increasingly severe symptoms finally raised the question of malignant disease.
Previous or concurrent treatment:	(1) Blood transfusion: at birth of second child — March 1962 Also total of 7 pints whole blood — 8/10/62-23/10/62 (2) Laparotomy: Large tumour mass confluent with upper pole of (L) kidney found and resected — 23/10/62 (3) Radiotherapy: 5,766r to (L) kidney region — 15/11/62-2/1/63 (4) Prednisone: 25-30 mg./day by mouth — 6/4/63-25/7/63
Cytotoxic treatment:	(1) Mannitol mustard: 400 mg. by I.V.I. operation cover — 22/10/62-24/10/62 (2) Thiotepa: 7.5 mg. intra-abdominal -at operation — 23/10/62 (3) Cyclophosphamide: 1,000 mg. by I.V.I. — 28/3/63-4/3/63 2,400 mg. orally — 5/3/63-6/4/63 N.B. Refused to take further cyclophosphamide because of fear of hair falling (4) Methotrexate: 50 mg. by I.V. drip — 11/5/63 (5) Mannitol mustard: 1,000 mg. orally — 25/5/63-5/6/63
Clinical course and comments:	Following operation and radiotherapy patient gained weight, was free of abdominal pain and felt generally well. Remained well until 28/2/63 when pain recurred in (L) hypochondrium and chest X-ray revealed metastases in (L) lower lung fields and in (R) upper lobe. Readmitted and cyclophosphamide commenced. Allowed home 6/3/63 still experiencing aching pain in (L) hypochondrium. Readmitted 4/4/63 with severe back pain, anorexia, vomiting and weight loss. Widespread metastases in lung, liver and spine. Thereafter developed increasing weakness of legs, bladder dysfunction and finally paraplegia. Progressive downhill course to death on 27/7/63, unaffected by cyclophosphamide.
Autopsy report:	Not obtained
Result:	3 for 2 months

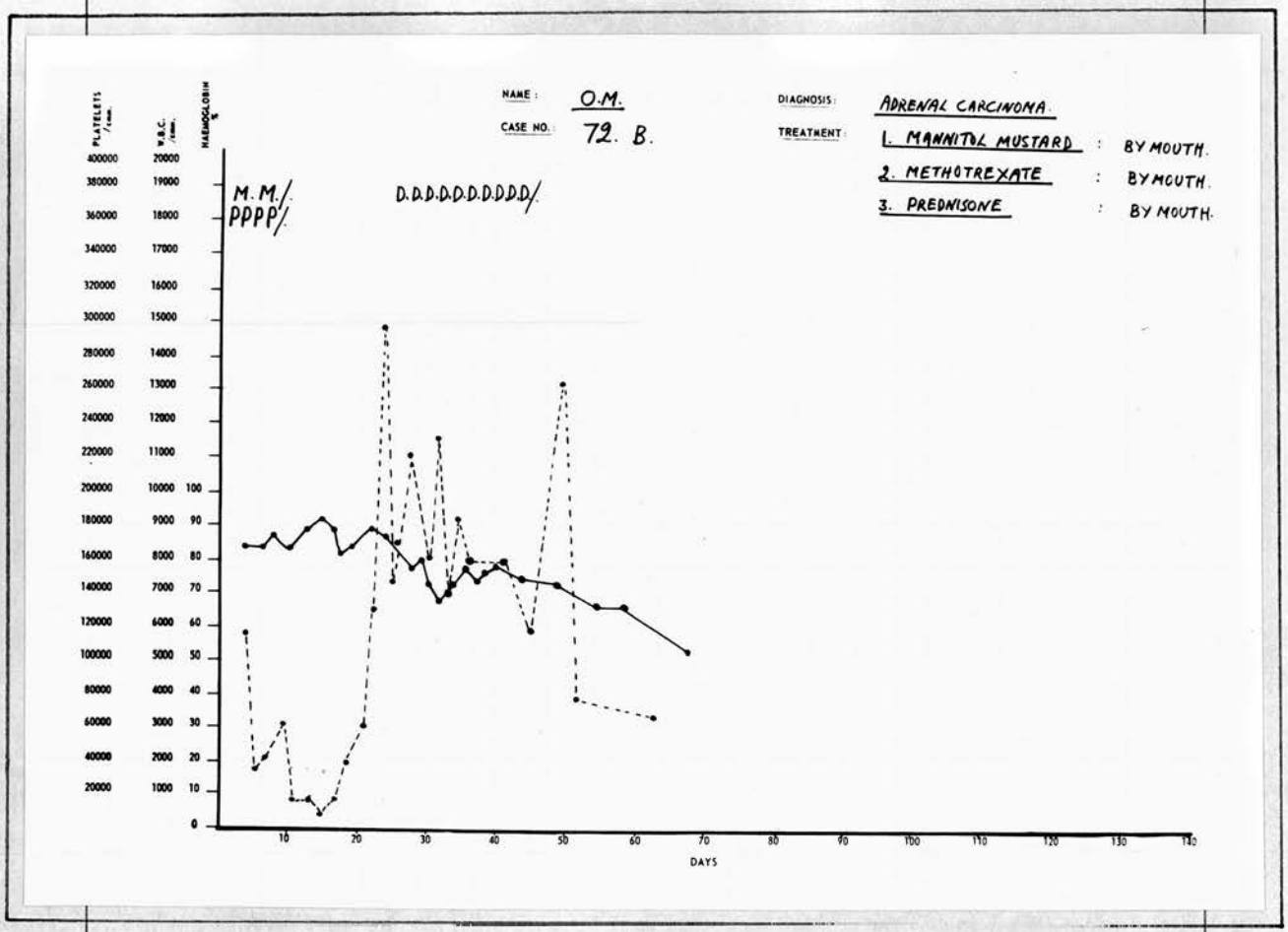
CASE NO. 72 PERIPHERAL BLOOD COUNTS

GRAPH A



CASE NO. 72 PERIPHERAL BLOOD COUNT

GRAPH B



Case No. 72: Adrenal Carcinoma

Fig. 1: Chest X-ray 10/10/62.

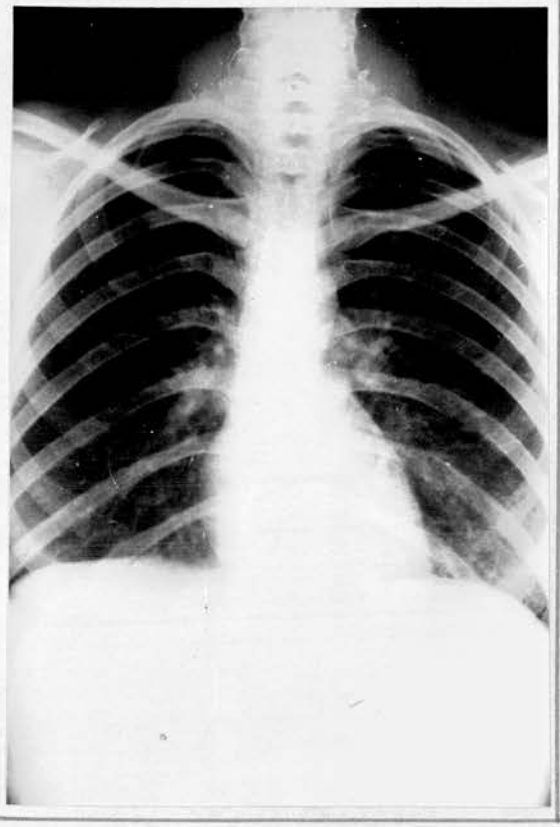


Fig. 2: Chest X-ray 12/10/62.

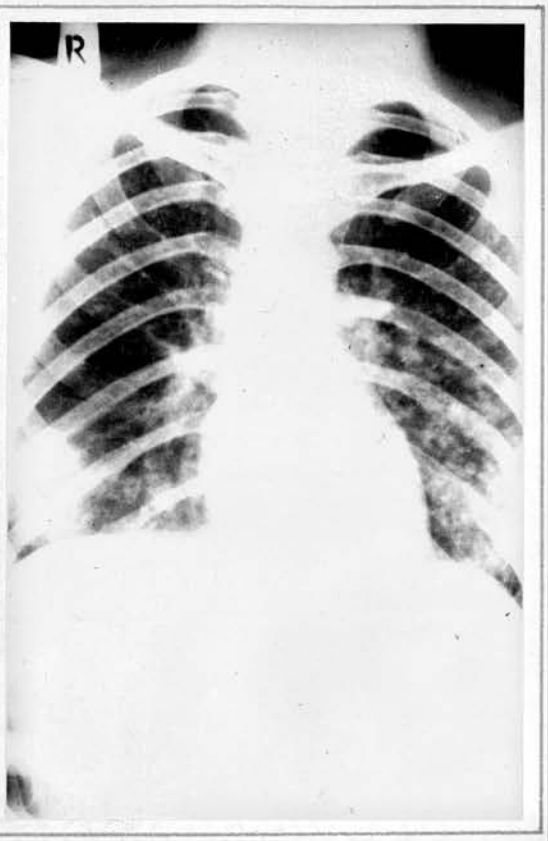
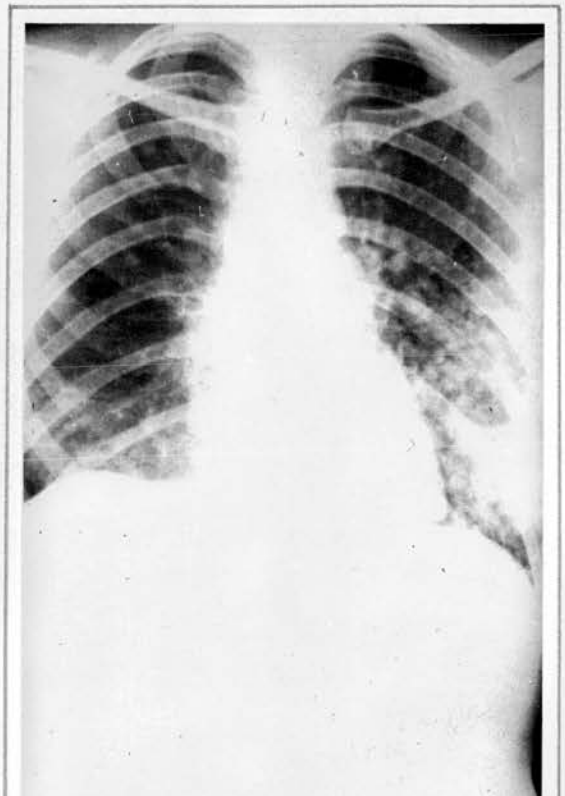


Fig. 3: Chest X-ray 28/5/63.



GROUP M : CARCINOMA OF OESOPHAGUS

Table 13a

Case: 73	A.A.C. 4/11/62 Age: 45 Sex: M
Diagnosis:	Carcinoma of oesophagus - middle third. Lymph node, lung and liver metastases. Anaplastic squamous cell carcinoma.
History:	First admitted to another hospital 24/10/62 with a 1-month history of increasing dysphagia. Able to swallow fluids only. Anorexia, general malaise and listlessness for same period. Occasional vomiting of recently taken food. Loss of 1 stone in weight over 3 months. Congenitally absent (R) kidney diagnosed July 1962; otherwise no previous or family history of note.
Previous or concurrent treatment:	(1) Oesophagoscopy: obstruction at 22 cm. - could not be passed. ? extrinsic lesion. 30/10/62 (2) Biopsy gland (L) axilla: 9/11/63 (3) Oesophagoscopy: malignant lesion of oesophagus just above aortic arch - biopsy 29/11/62 (4) Laparotomy and insertion of Mousseau-Barbin tube - inoperable carcinoma of oesophagus 6/12/62 All above carried out at another hospital. (5) Antibiotics: penicillin 250 mg. 6-hourly by mouth from 28/12/62 (6) Diuretics: Hydrosaluric K - from 28/12/62 (7) Analgesics: Pethidine, omnopon. 25/12/62-28/12/62
Cytotoxic treatment:	(1) Cyclophosphamide: 1,000 mg. by continuous infusion 27/12/62-30/12/62 4,000 mg. by mouth (200 mg./day) 31/12/62-20/1/63
Clinical course and comments:	Advanced carcinoma of oesophagus when first presented. At time of operation was already complaining of severe pain in (R) hip and leg. Numbness and weakness (R) buttock - thought to have metastases in pelvis and sacrum. Dehisced wound on 5th post-operative day. Thereafter developed urinary retention and required an indwelling catheter. Developed anaesthesia of perineum 14/12/62 and although X-ray evidence was lacking, was considered to have a cauda equina lesion. Also bilateral chest signs. Allowed home for Christmas but re-admitted on 27/12/62 with continuous, severe pain in (R) buttock and perineum since previous day - unrelieved by repeated analgesics. Now showing evidence of weight loss with swelling of feet and ankles. Bedsore. Started cyclophosphamide 27/12/62 and by next day was pain free. Remained virtually pain free thereafter, but general condition gradually deteriorated with increasing chest infection and ? congestive cardiac failure. Died 27/1/62.
Autopsy/	

Table 13a (continued)

Autopsy report:	Wasted. Large bedsore over sacrum. Bilateral pleural effusions. Few metastatic deposits in lungs. Middle third of oesophagus replaced by carcinoma with invasion of regional lymph nodes and also those of abdomen. Few small deposits in liver. Deposits in sacrum. Death from bronchopneumonia due to carcinomatosis from carcinoma of oesophagus.
Result:	Dramatic and sustained relief of pain with cyclophosphamide but no effect on course of disease. 0-1 for 3 months.

Case No. 73: Carcinoma of Oesophagus

Fig. 1: Barium swallow:
Carcinoma of oesophagus
26/10/62.

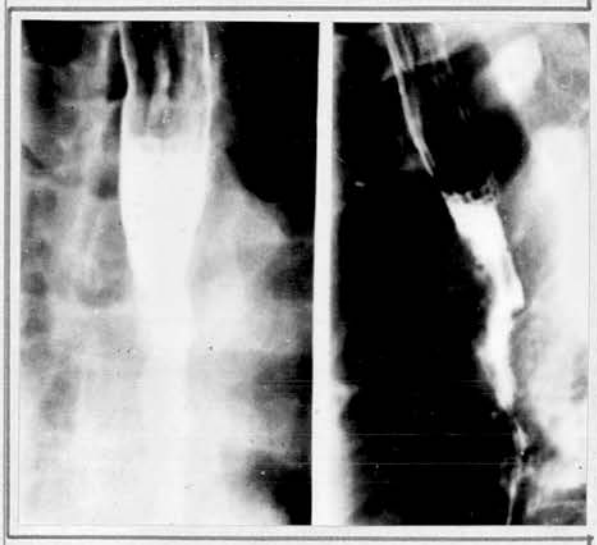


Fig. 2: Chest X-ray 26/10/62.

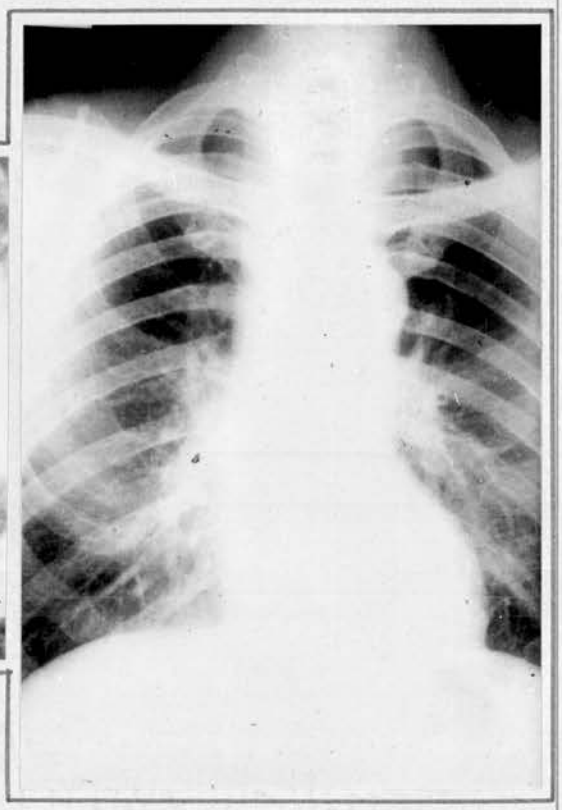


Fig. 3: Chest X-ray 5/11/62.

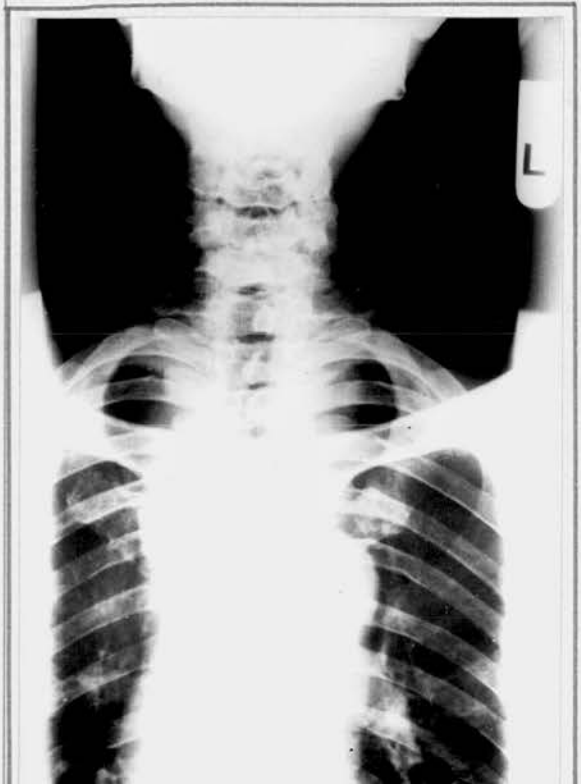


Fig. 4: Chest X-ray 1/1/63.

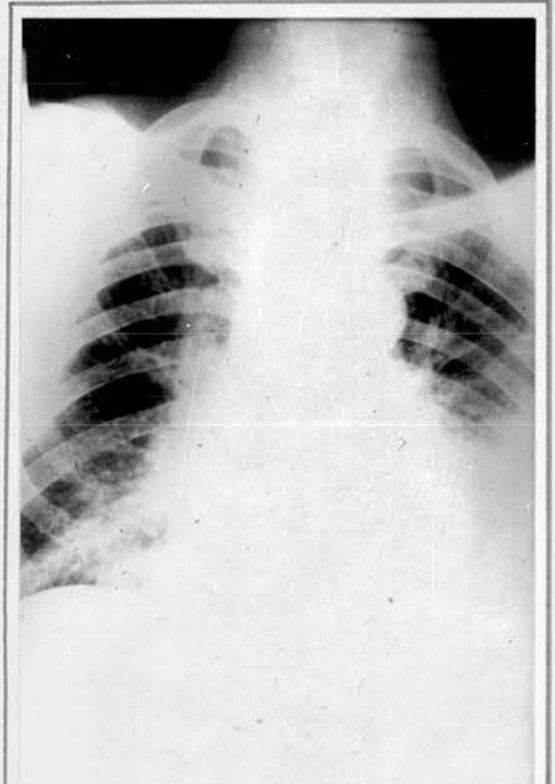


Table 13b

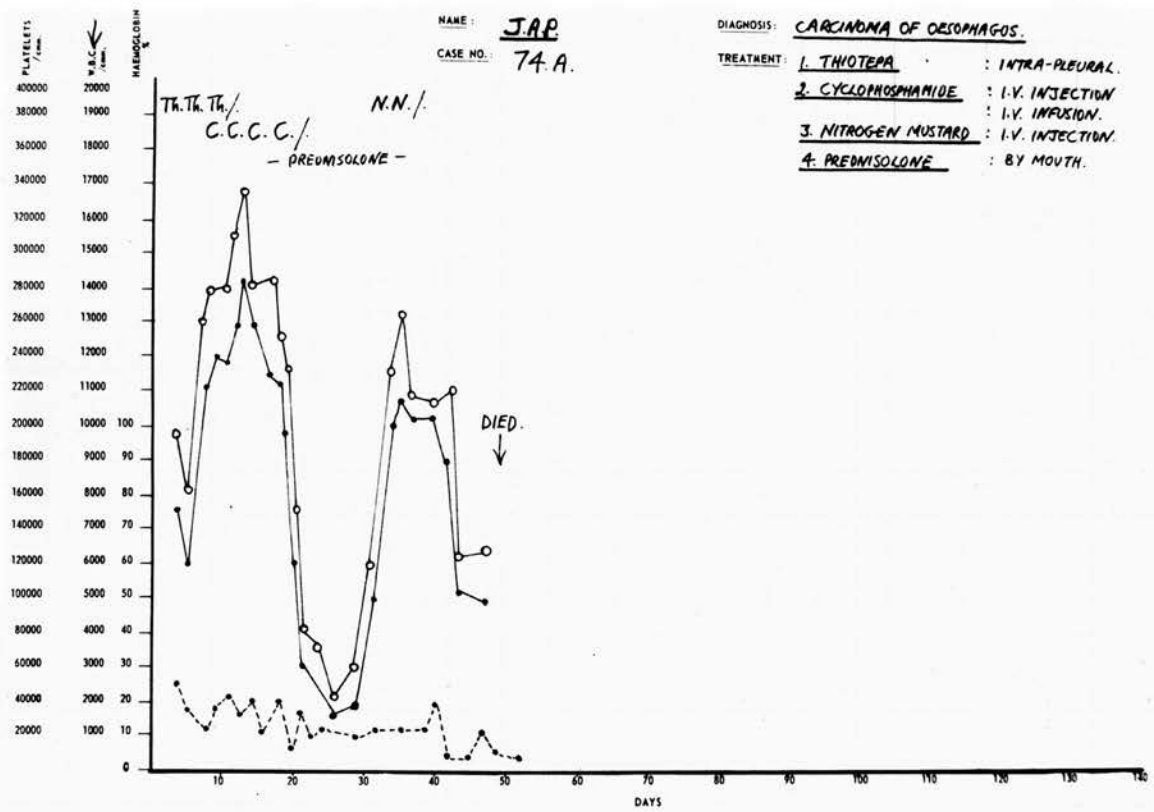
Case: 74	J.A.P. 17/7/63 Age: 33 Sex: M
Diagnosis:	Carcinoma of oesophagus - middle third - with metastases in lymph glands and brain; extensive local invasion. Anaplastic squamous cell carcinoma.
History:	7-month history of increasing hoarseness, heartburn and dysphagia. Subsequently developed exertional dyspnoea, cough and tightness around lower chest. Laryngoscopy on 5 occasions between January and June 1963 revealed oedema of larynx only and bronchoscopy was negative also. Diagnosis missed until 15/7/63 when oesophagoscopy revealed lesion at 27 cm. At this stage breathlessness was marked; could only swallow fluids, appetite poor and weight decreasing. Transferred for further management. No previous or family history of note.
Previous or concurrent treatment:	(1) Symptomatic treatment: for hoarseness and heartburn — January to June 1963 (2) Repeated laryngoscopy and bronchoscopy: between January and June 1963 (3) Oesophagoscopy: carcinoma of the oesophagus at 27 cm. — 15/7/63 (4) Tracheostomy: Under local anaesthesia — 3/8/63 (5) Radiotherapy: 1,470r to primary tumour area — 13/8/63-22/8/63 (6) Prednisone: 20 mg./day by mouth — 29/7/63-3/8/63 (7) Antibiotics: (a) Erythromycin — 23/7/63-3/8/63 (b) Crystamycin — 3/8/63-15/8/63 (c) Chloramphenicol — 15/8/63-21/8/63 (8) Pleural aspiration: 250 ml. — 18/7/63 250 ml. — 19/7/63
Cytotoxic treatment:	(1) Thiotepa: 60 mg. intrapleural (1 x 15 mg., 2 x 30 mg.) — 19/7/63-25/7/63 (2) Cyclophosphamide: 1,000 mg. by continuous I.V. infusion over 24 hours — 23/7/63 1,500 mg. by I.V.I. (3 x 500 mg.) — 26/7/63-31/7/63 (3) Nitrogen mustard: 18 mg. by I.V.I. (3 x 6 mg.) — 10/8/63-12/8/63
Clinical/	

Table 13b (continued)

Clinical course and comments:	Diagnosis repeatedly missed over a period of 6 months and disease already advanced when finally diagnosed. On admission, was ill-looking, cyanosed, grossly dyspnoeic with inspiratory stridor. Severe respiratory distress was only partly relieved by tracheostomy. Small (L) pleural effusion. Tube feeding throughout. Slight improvement following intrapleural thiotepa and intravenous cyclophosphamide but developed weakness of (R) hand and transient jaundice between 27/7/63 and 5/8/63. Started radiotherapy 13/8/63 but no effect after 10 day course and finally unfit to attend. Thereafter developed periods of extreme distress and agitation culminating in sudden extreme dyspnoea, agitation, coma and death on 28/8/63.
Autopsy report:	Marked finger clubbing. (L) pleural effusion. (L) lung collapsed. Invasion of (L) bronchus by tumour arising from middle third of oesophagus. Tumour invading mediastinum and (L) hilum lymph nodes with massive haemorrhage into secondary in (L) parietal region of brain. Death due to respiratory embarrassment and cerebral metastases from carcinoma of oesophagus.
Result:	Although a large amount of cytotoxic drugs where administered over a short period no significant benefit was obtained and the disease pursued a relentless downhill course. 0 for $1\frac{1}{2}$ months.

CASE NO. 74 PERIPHERAL BLOOD COUNTS

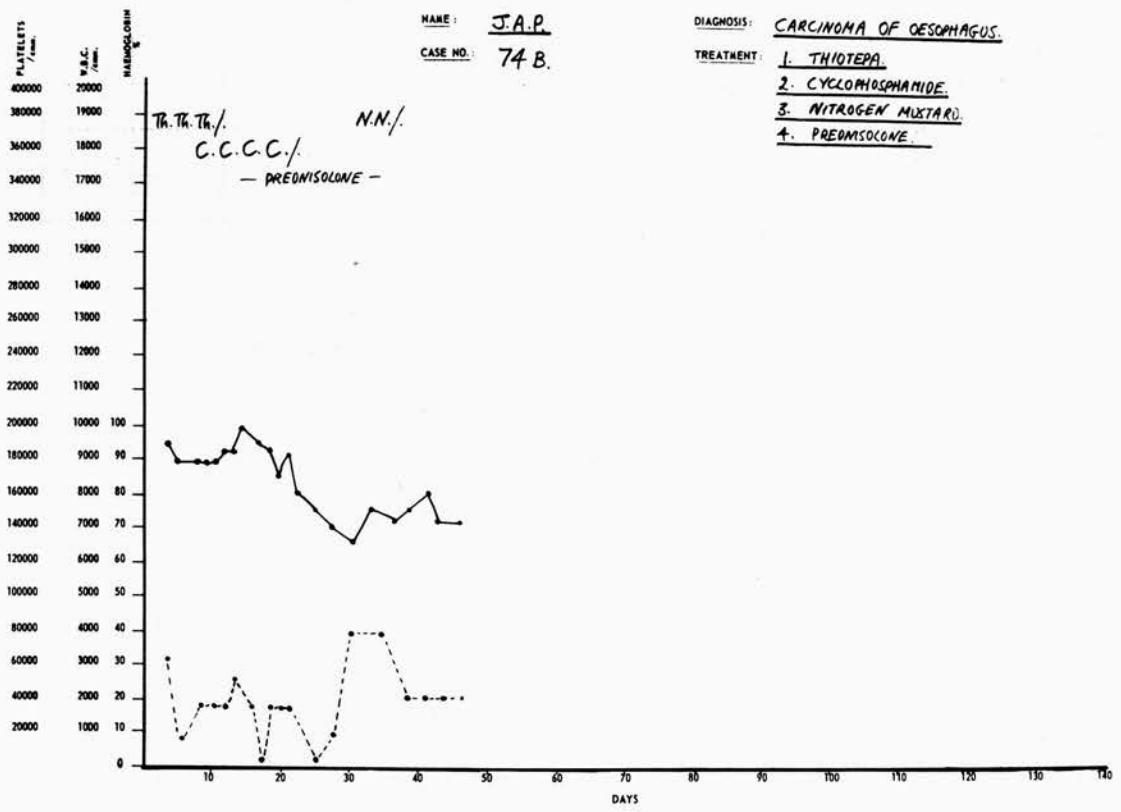
GRAPH A



CASE NO. 74

PERIPHERAL BLOOD COUNTS

GRAPH B



Case No. 74: Carcinoma of Oesophagus

Fig. 1: Chest X-ray 5/3/63.

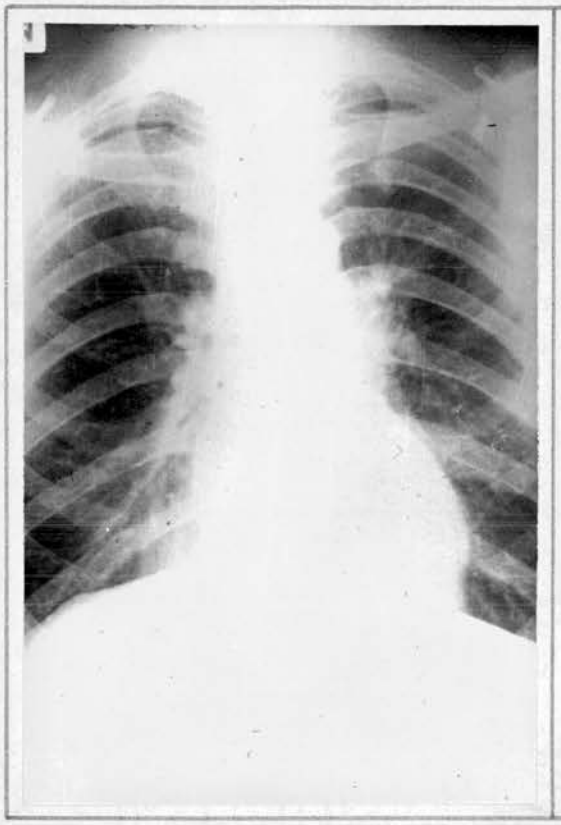


Fig. 2: Chest X-ray 10/7/63.

Fig. 3: Chest X-ray 9/8/63.

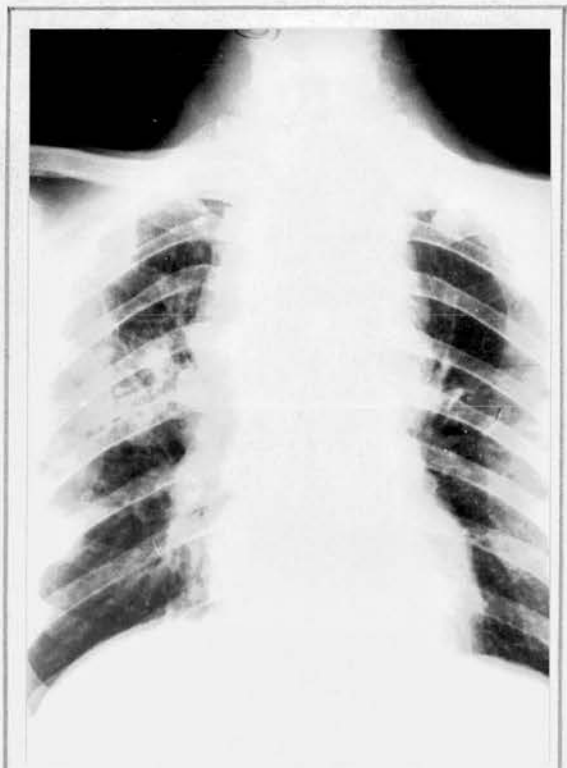
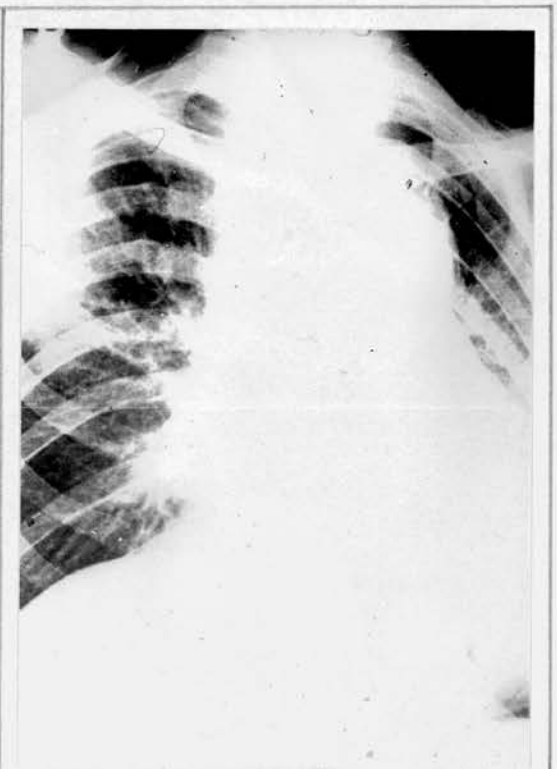


Fig. 4: Chest X-ray 12/8/63.



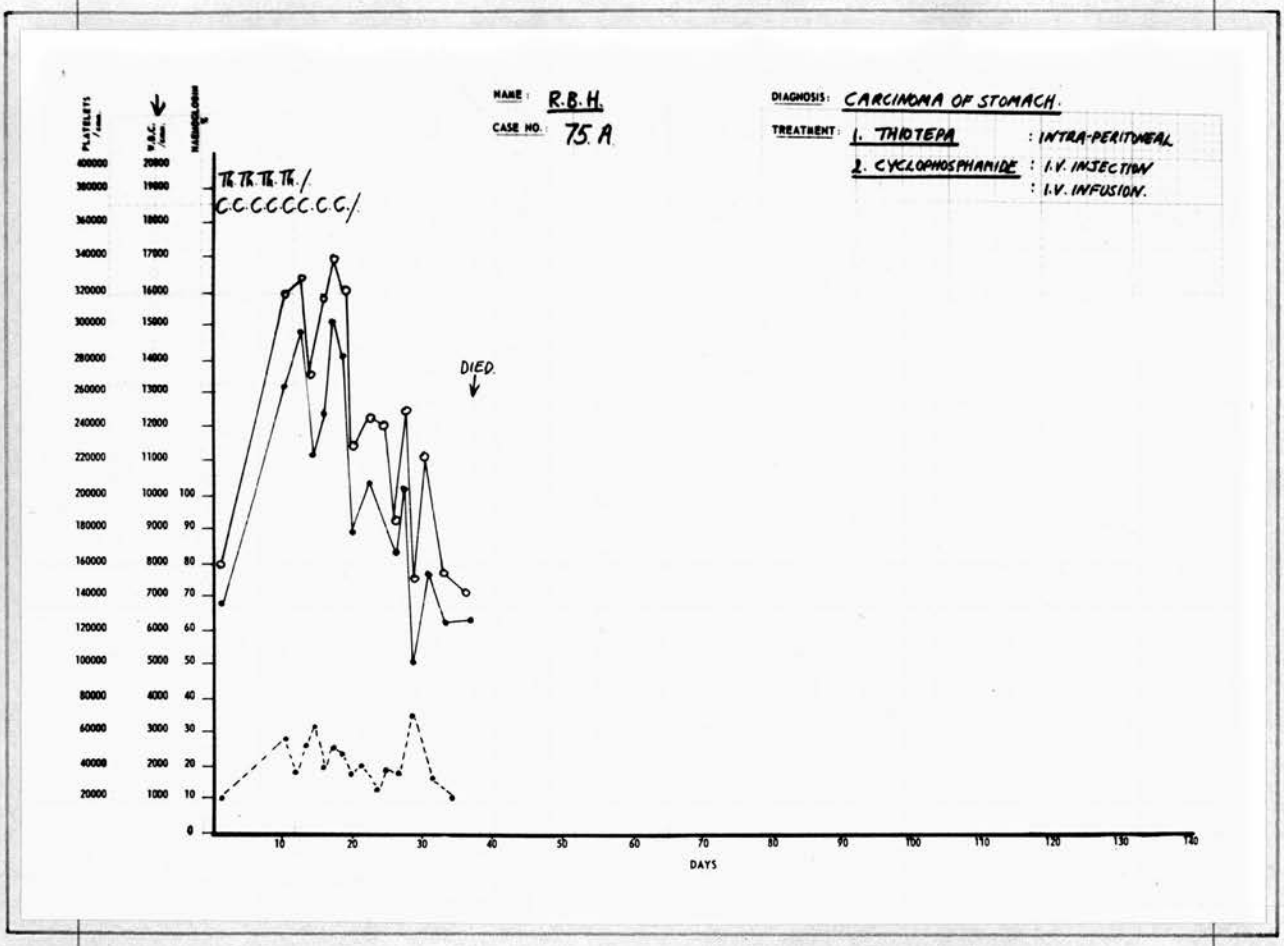
GROUP N : CARCINOMA OF STOMACH

Table 14a

Case: 75	R.B.H. 21/10/63 Age: 42 Sex: M
Diagnosis:	Carcinoma of stomach with hepatic metastases and local recurrence. Anaplastic carcinoma of stomach.
History:	Partial gastrectomy for 20-year history of chronic duodenal ulcer 7/5/63 - in another hospital. Examination of stomach remnant revealed a small pyloric carcinoma. Post-operative recovery was slow and convalescence interrupted by a subphrenic abscess. Thereafter remained fit and well and at work until 21st October 1963 when he was re-admitted with a 3 week history of severe (R) upper abdominal pain, abdominal distension, nausea, heartburn and anorexia. Weight steady. Found to have ascites and massive hepatomegaly from metastases. Transferred for further management. No previous or family history of note, but was Battle of Britain pilot.
Previous or concurrent treatment:	(1) Partial gastrectomy: presence of gastric carcinoma not suspected at operation - in another hospital 7/5/63 (2) Abdominal paracentesis: Amounts of $2\frac{1}{2}$-$3\frac{1}{2}$ litres aspirated on each of 6 occasions between 21/10/63 and 12/11/63 (3) Diuretics and low-salt diet from 21/10/63
Cytotoxic treatment:	(1) Thiotepa: 60 mg. intraperitoneally (4 x 15 mg.) 21/10/63-29/10/63 (2) Cyclophosphamide: 2,600 mg. by I.V.I. and I.V. infusion 21/10/63-12/11/63
Clinical course and comments:	Presented with massive hepatic deposits and ascites from gastric carcinoma $5\frac{1}{2}$ months after partial gastrectomy for chronic duodenal ulcer, at which operation carcinoma was not suspected. Despite use of cytotoxins, diuretics and low-salt diet continued to experience severe upper abdominal pain, recurrent ascites, nausea and vomiting. Increasing naevi over upper trunk, progressive hepatic enlargement and venous dilatation over anterior abdominal wall. Progressing to liver failure and death in coma 14/11/63.
Autopsy report:	$1\frac{1}{2}$ litres of ascitic fluid. Many small peritoneal deposits scattered throughout abdomen; omental masses. Large mass of tumour in stomach remnant, adherent to pancreas and transverse colon. Liver widely infiltrated by large metastases. Abdominal lymph glands invaded but no metastases elsewhere.
Result:	No benefit from cytotoxins either in controlling recurrent ascites or in affecting disease progress. Nausea and vomiting severe after thiotepa instillations but no other side effects. 0 for 1 month.

CASE NO. 75 PERIPHERAL BLOOD COUNTS

GRAPH A



CASE NO. 75 PERIPHERAL BLOOD COUNTS

GRAPH B

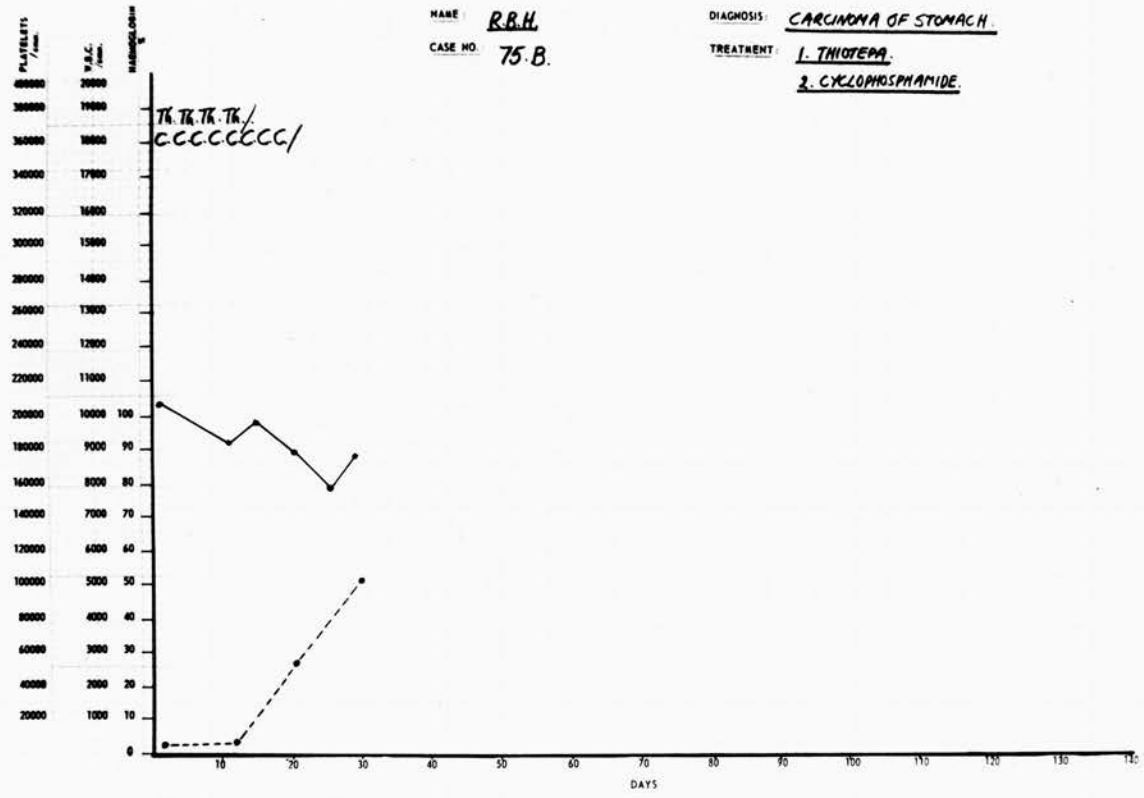


Table 14b

Case: 76	T.H. 11/10/64 Age: 58 Sex: M
Diagnosis:	Carcinoma of stomach with local invasion of liver and lymph glands. Histology of associated glands - replaced by adenocarcinoma consistent with gastric primary.
History:	Admitted as a transfer from a medical ward with a 3 months history of anorexia, lassitude and loss of 3 st. in weight. No vomiting; bowels normal. Haemoglobin 50% on admission to medical ward. No previous history of note, but father believed to have died of cancer of bowel. Confident clinical and radiological diagnosis of carcinoma of stomach.
Previous or concurrent treatment:	(1) Laparotomy: Extensive, inoperable carcinoma of stomach invading (L) lobe of liver with numerous involved glands around coeliac axis and in omentum. Biopsy of gland only. 12/10/64 (2) Blood transfusion: 6 litres of whole blood between 25/9/65 and 11/12/64
Cytotoxic treatment:	(1) Thiocolciran: 350 mg. by I.V.I. 18/10/64-4/1/65 (2) Methotrexate: 390 mg. by mouth 18/10/64-7/1/65
Clinical course and comments:	Patient presented with a typical history and tumour inoperable at laparotomy. Commenced cytotoxins 18/10/64 with the hope of being able to carry out a "second-look" procedure. General condition remained poor throughout and persistently anaemic. No benefit from cytotoxins, but side-effects not severe. Progressive deterioration to death at home 15/1/65, 3 months from first diagnosis.
Autopsy report:	Died at home. Post-mortem not obtained.
Result:	No benefit from cytotoxins over a period of 2½ months. Mild to moderate side-effects only. 1-2 for 3 months.

Table 14c

Case: 77	W.M. 14/10/64 Age: 64 Sex: M
Diagnosis:	Carcinoma of the stomach with invasion of liver and regional lymph glands.
History:	3 months history of dysphagia, epigastric pain, anorexia and diarrhoea. Had eaten no solid foods for 6 weeks. Loss of 1 stone in weight over 2 months. No symptoms referable to other systems. No previous history of note but father probably died of carcinoma. Confident clinical and radiological diagnosis of carcinoma of stomach.
Previous or concurrent treatment:	(1) Laparotomy: Large carcinoma posterior wall fixed to (L) lobe of liver. Numerous large, fleshy glands. No other deposits. 19/10/64
Cytotoxic treatment:	(1) Thiocolciran: 60 mg. by I.V.I. (2 x 30 mg.) 23/10/64-25/10/64 (2) Methotrexate: 25 mg. by mouth (5 mg. daily) 23/10/64-26/10/64
Clinical course and comments:	Patient presenting with typical history of gastric carcinoma confirmed by barium meal. Large posterior wall lesion in stomach, just possibly reactable but considered suitable for chemotherapy and second-look operation. Virtual collapse after first 2 injections of thiocolciran (epigastric pain on each occasion) and died 27/10/64 in peripheral circulatory failure.
Autopsy report:	No post-mortem obtained.
Result:	Death almost certainly accelerated by cytotoxins although no obvious side effects produced. Note severe pain in epigastrium after each injection of thiocolciran.

Table 14d

Case: 78	I.M. 3/1/65 Age: 69 Sex: F
Diagnosis:	Carcinoma of stomach with involvement of regional lymph nodes. Undifferentiated carcinoma of stomach.
History:	Anorexia, nausea and vomiting for 6 months with loss of 2-3 stones in weight over 1 year. One episode of diarrhoea lasting 2 weeks 6 months previously. Diabetic for 1 year. No other significant previous or family history. Confident clinical and radiological diagnosis of carcinoma of stomach.
Previous or concurrent treatment:	(1) Laparotomy: extensive, inoperable carcinoma of stomach with extensive lymph gland involvement. Biopsy of tumour only. 11/1/65 (2) Steroids: Cortisone acetate - 100 mg. 6-hourly by mouth 22/1/65-24/1/65
Cytotoxic treatment:	(1) Thiocolciran: 40 mg. by I.V.I. (2 x 20 mg.) 16/1/65-19/1/65 (2) Methotrexate: 35 mg. by mouth (5 mg. daily) 16/1/65-22/1/65
Clinical course and comments:	Carcinoma of stomach presenting with long history. Beyond any form of surgery when first seen. Immediate post-operative condition fair, but when chemotherapy was started on 5th post-operative day, patient developed severe watery diarrhoea, buccal ulceration and agranulocytosis. Deteriorated to death on 25/1/65 despite cortisone and other supportive measures.
Autopsy report:	Carcinoma of stomach with extensive spread to regional lymph glands. Chronic pyelonephritis and myocardial fibrosis. Pulmonary infarction. Marrow: sparsity of cellular tissue consistent with marked depression.
Result:	Death almost certainly accelerated by cytotoxins to which severe side effects rapidly developed with minimal dosage. 0 for 2 weeks.

Table 14e

Case: 79	R.C. 24/3/65 Age: 66 Sex: M
Diagnosis:	Carcinoma of stomach. Moderately differentiated adenocarcinoma with marked stomal reaction.
History:	First admitted to a medical ward in February 1965 with a 20-year history of intermittent episodes of epigastric pain and nausea. Over previous 6 months these episodes had increased in frequency and severity and were now associated with vomiting. During this period appetite decreased and lost 2 stones in weight. Investigations in medical ward did not establish a diagnosis and patient transferred for diagnostic laparotomy. No previous or family history of note.
Previous or concurrent treatment:	(1) Laparotomy: Inoperable carcinoma of proximal stomach invading glands, pancreas and omentum. Biopsy only. 26/3/65 (2) Oesophagoscopy: with view to inserting Souttar's tube, but not feasible 22/6/65 (3) Analgesics and anti-emetics: intermittently throughout treatment period and frequently in last month
Cytotoxic treatment:	(1) Thiocolciran: 390 mg. by I.V.I. 31/3/65-1/7/65 (2) Methotrexate: 220 mg. by mouth 31/3/65-10/6/65
Clinical course and comments:	Diagnosis of carcinoma of stomach not established until diagnostic laparotomy 26/3/65. Tumour inoperable due to local invasion and fixation. Cytotoxic treatment started on 5th post-operative day. Although thiocolciran injections produced epigastric pain, nausea and vomiting on almost every occasion, there was a short period of 1 month between 20/4/65 and 20/5/65 when patient felt greatly improved. Thereafter general condition deteriorated, despite continued treatment, with increasing epigastric pain and vomiting. Died of pulmonary embolism 4/7/65.
Autopsy report:	Carcinoma of stomach invading the (L) lobe of liver and lesser omentum associated with metastatic deposits in coeliac and para-aortic lymph nodes and in liver. Pulmonary embolism from thrombosed leg veins.
Result:	Short period of subjective benefit from cytotoxins, but over-all result was unsatisfactory. Marked pain in tumour from thiocolciran. Terminal evidence of impending bone marrow depression. 1-2 for 3 months.

Table 14f

Case: 80	E.C. 16/2/65 Age: 71 Sex: M
Diagnosis:	Carcinoma of stomach.
History:	Admitted as an emergency with a 2-week history of constant dull, dragging pain in (L) iliac fossa associated with excessive flatulence, constipation and anorexia for 5 days. No relevant past history. Clinical examination, barium enema and sigmoidoscopy failed to establish a diagnosis, but at diagnostic laparotomy on 1/3/65 an extensive, inoperable carcinoma of stomach was found.
Previous or concurrent treatment:	(1) Laparotomy: Large carcinoma of pyloric region of stomach. Numerous small metastases throughout peritoneal cavity; lymph glands involved but liver clear. Palliative gastro-enterostomy.
Cytotoxic treatment:	(1) Thiocolciran: 140 mg. by I.V.I. 7/3/65-15/4/65 (2) Methotrexate: 215 mg. by mouth 7/3/65-29/4/65
Clinical course and comments:	Advanced carcinoma of stomach found at laparotomy for unexplained abdominal pain. Commenced cytotoxic therapy on 6th post-operative day. No untoward effects, but felt slightly nauseated after initial injection. No increase in pain in tumour area following injections. After 3 weeks' treatment was feeling well; weight steady. Remained well, apart from a few days of an influenzal illness, until 29/4/65 when his general condition began to deteriorate, began to experience back pain and died at home 7/5/65 - 2 months from diagnosis.
Autopsy report:	Died at home and no post-mortem obtained.
Result:	Initially cytotoxins well tolerated and possibly of some benefit. But over-all effect on disease course was minimal. 1-2 for 2 months

Table 14g

Case: 81	P.D. 21/3/65 Age: 63 Sex: M
Diagnosis:	Carcinoma of stomach, involving lower end of oesophagus - hepatic metastases. Adenocarcinoma of stomach.
History:	Admitted as an emergency on 21/3/65 with a history of severe dysphagia for one week and several small haematemeses on the night of admission. Patient had previously been investigated in same unit in 1963 for dysphagia, dyspepsia and weight loss and was regarded as peptic oesophagitis. His symptoms had been increasing in severity over recent months and he was on the waiting list for operation. Investigations now confirmed the presence of a carcinoma of proximal stomach involving distal oesophagus. No family history of note.
Previous or concurrent treatment:	(1) Thoraco-laparotomy: Inoperable carcinoma of cardiac region of stomach involving lower oesophagus; hepatic metastases. 7/4/65 (2) Insertion of Souttar's tube: 30/5/65 (3) Blood transfusion: 2 litres of whole blood 21/3/65-23/3/65
Cytotoxic treatment:	(1) Thiocolciran: 150 mg. by I.V.I. 16/4/65 - 10/5/65 (2) Methotrexate: 110 mg. by mouth 16/4/65 - 19/5/65
Clinical course and comments:	Inoperable tumours of proximal stomach with hepatic metastases at thoraco-laparotomy 7/4/65. Commenced chemotherapy on the 8th post-operative day without disturbance. One month later was eating a normal diet without pain or discomfort and general condition was good. Occasional dysphagia only, but feeling of nausea and weakness for 2-3 days after thiocolciran injections. After a further two weeks dysphagia was again marked, but pain free and general condition good. Thereafter dysphagia rapidly became complete, patient refused further injections (attributing the dysphagia to their effects). Souttars' tube inserted 30/5/66 with relief of acute symptoms. Patient remained reasonably well despite progressive anaemia until 26/8/66, then deteriorated rapidly and died at home 20/9/66.
Autopsy Report:	Died at home - no post-mortem obtained.
Result:	Short, but definite response to cytotoxins. Return of dysphagia after five weeks and thereafter patient refused further injections. 1-2 for 5 months.

Table 14h

Case: 82	A.W. 25/4/65 Age: 58 Sex: F
Diagnosis:	(1) Carcinoma of stomach with advanced local spread. (2) Carcinoma of (R) breast. 1960. Pulmonary metastases ? from breast lesion. Biopsy of abdominal gland: metastatic anaplastic carcinoma consistent with operative findings of carcinoma of stomach.
History:	Admitted to the ward 25/4/65 with a history of anorexia and weight loss of 2 stones over previous 6 months; dysphagia and gnawing epigastric pain for 2 months. Barium meal revealed a carcinoma of body of stomach. In 1942 had been diagnosed as having pernicious anaemia with regular follow-up thereafter. Above symptoms noted at review 26/3/65. In addition, a Stage I carcinoma of (R) breast was treated by simple mastectomy and radiotherapy in 1960. In 1962 recurrent glands excised from (R) axilla but thereafter remained well until onset of abdominal symptoms in October 1964. When admitted in April 1965, metastases already present in lungs.
Previous or concurrent treatment:	(1) Laparotomy: Infiltrating carcinoma of lesser curve of stomach. Extensive local fixation. Biopsy of gland only. 28/4/65 (2) (R) simple mastectomy: 26/4/60 (3) Radiotherapy: (R) breast and shoulder regions - details not known. 11/5/60-9/6/60 (4) Excision of metastatic glands (R) axilla: 8/2/62 (5) "Cytamin" Vitamin B_{12} for P.A.
Cytotoxic treatment:	(1) Thiocolciran: 210 mg. by I.V.I. 27/5/65-23/9/65 (2) Methotrexate: 287.5 mg. by mouth 27/5/65-23/9/65
Clinical course and comments:	At laparotomy, lesion in stomach considered primary but uncertain if deposits in lung were from stomach or breast. Cytotoxins started 27/5/65 in hope of controlling abdominal symptoms. Treatment continued for 4 months with 2-week interval between 15/7/65 and 2/8/65. During this period general condition remained fair, but appetite poor with occasional vomiting. Pain and nausea experienced after initial injections. Gained 6 lb. in weight between 27/5/65 and 19/8/65, but thereafter developed a persistent head cold, memory impairment and increasing pulmonary metastases. Treatment continued 23/9/65; gradual decline to death at home on 21/10/65.
Autopsy report:	Died at home. Post-mortem not obtained.
Result:	Tumour activity possibly checked for 2 months but little over-all benefit. 1-2 for 4 months. Mild to moderate side effects - nausea, pain and vomiting after injections; persistent coryza.

GROUP 0 : CARCINOMA OF COLON AND RECTUM

Table 15a

Case: 83	J.N.S. 24/5/61 Age: 32 Sex: M
Diagnosis:	Inoperable carcinoma of rectum. Biopsy of tumour.
History:	First discovered to have a carcinoma of the rectum in May 1961 when he gave a 6 months history of increasing constipation, a feeling of incomplete defaecation and blood and mucus in the stools. Had lost over 1 stone in weight and recently experienced occasional abdominal distension and (L) sided sciatic pain. At laparotomy on 5/6/61 a large, almost completely obstructing and irremovable carcinoma of the rectum was found. N.B. At age of 9 had had sclerosing oil injections for mild rectal prolapse. No other previous or family history.
Previous or concurrent treatment:	(1) Laparotomy: inoperable cancer of rectum. Permanent (L) iliac colostomy. 5/6/61 (2) Radiotherapy: 6,800r to pelvis 29/6/61-17/8/61 (3) Radiotherapy: 5,000r to pelvis 9/4/63-16/5/63 (4) Analgesics: Principally codeine for sciatic pain
Cytotoxic treatment:	(1) Thiocolciran: 210 mg. by I.V.I. 14/6/61-12/7/61 (2) Vinblastine sulphate: 60 mg. by I.V.I. 4/4/63-15/5/63 (3) Thiotepa: 60 mg. by intra-rectal infusion 20/9/63 60 mg. by intra-rectal infusion (15 mg. in 100 ml. saline x 4 on each occasion) 5/12/63 (4) Cyclophosphamide: 2,000 mg. by I.V. drip 9/1/64-10/1/64 1,000 mg. by I.V.I. (200 mg. x 5) 14/1/64-18/1/64 4,800 mg. orally 23/1/64-12/3/64 continuing
Clinical course and comments:	Inoperable carcinoma of rectum when first seen. Treated initially with combination of cytotoxins and radiotherapy June 1961. Result of therapy was good with sustained relief of symptoms and good general health until January 1963 when clinical examination suggested recrudescence of the tumour. Repeat rectal biopsy was carried out on 5/2/63 and confirmed active carcinoma. In view of patient's general well-being, however, and freedom from symptoms, no active treatment was undertaken at this stage. By 28/3/63, however, increasing (L) sided abdominal pain and (L) sided sciatica led to a further course of radiotherapy and resumption of cytotoxins. Treatment resulted in some improvement but was associated with listlessness, weight loss and mild anorexia. 2 courses of intra-rectal thiotepa produced much foul-smelling discharge from rectum and although temporary relief was obtained general tendency was for increasing (L) low abdominal pain and sciatica requiring analgesics. Commenced cyclophosphamide in January 1964 and this produced considerable relief which was maintained for 2 months to last review.
Autopsy/	

Table 15a (continued)

Autopsy report:	-
Result:	2-3 for 2 years 10 months. Cytotoxins initially used in conjunction with radiotherapy and combined result produced sustained objective and subjective improvement for 18 months. Further symptomatic relief was obtained by second course of combined radiotherapy and cytotoxins. Cyclophosphamide alone producing good response.

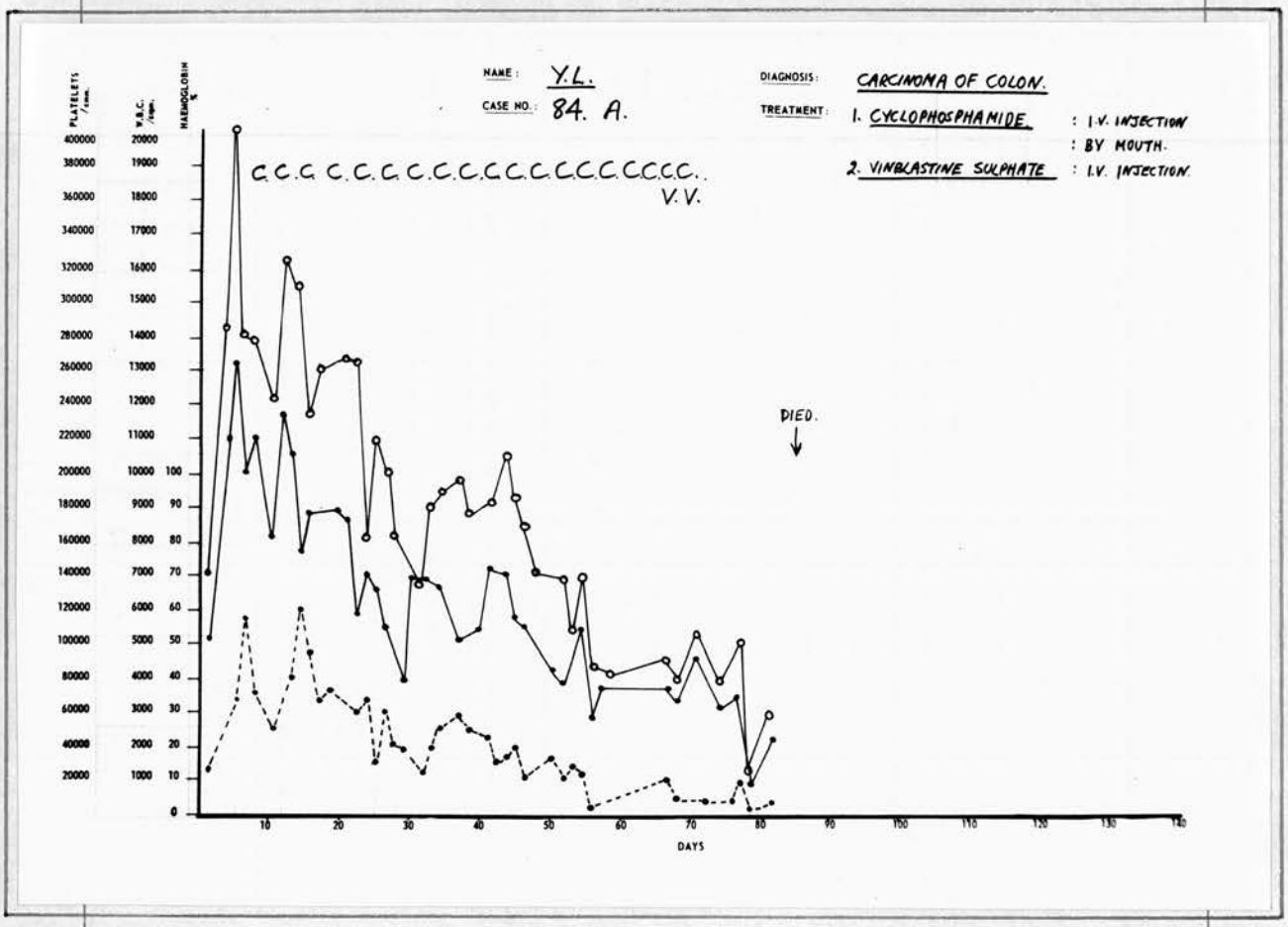
Table 15b

Case: 84	I.L. 9/11/62 Age: 22 Sex: F
Diagnosis:	Carcinoma of sigmoid colon. Carcinomatosis peritonei. Mucus-secreting adenocarcinoma.
History:	Laparotomy 3 years previously at another hospital for persistent rectal bleeding. Laparotomy negative but polyp found on sigmoidoscopy and removed. Well until June 1962 when she began to experience colicky lower abdominal pain with the passage of fresh blood and mucus in the stools. Subsequently developed diarrhoea with 3-4 loose motions per day and lost 1 stone in weight. Investigations, including sigmoidoscopy and barium enema were inconclusive. Laparotomy on 3/10/62 in another hospital revealed carcinomatosis peritonei with the primary tumour apparently arising in the sigmoid colon. Transferred for further management. No other previous history of note, but mother died of carcinoma of colon.
Previous or concurrent treatment:	(1) Laparotomy: in another hospital. Carcinomatosis peritonei. No operative procedure. 3/10/62 (2) Radiotherapy: 1,000r to whole abdomen 10/12/62-17/12/62 (3) Blood transfusion: 3 pints whole blood 26/10/62 (4) Prednisone: 20 mg. daily by mouth 16/11/62-29/12/62
Cytotoxic treatment:	(1) Cyclophosphamide: 5,200 mg. by mouth 16/11/62-29/12/62 700 mg. by I.V.I. 3/1/63-6/1/63 (2) Vinblastine sulphate: 6 mg. by I.V.I. 3/1/63-5/1/63
Clinical course and comments:	Investigated for 3 months for symptoms of colicky abdominal pain, diarrhoea with blood and mucus in stools, before diagnosis established by laparotomy. In view of widespread nature of lesion treatment was commenced with cytotoxins and prednisone. This resulted in lessening of pain, diarrhoea and rectal discharge and radiotherapy in the form of an "abdominal bath" was commenced on 10/12/62. This resulted in nausea, vomiting and general distress and was abandoned. Treatment with cytotoxins was resumed and the patient was out of hospital for 2 weeks. Thereafter developed increasing abdominal distension, nausea and vomiting culminating in complete obstruction on 30/12/62. Large tumour masses palpable in abdomen. Perforated bowel and died on 7/1/63.
Autopsy report:	Gross peripheral oedema. Widespread gas gangrene (positive cultures from peritoneal fluid and subcutaneous tissues) from perforated colon following chronic obstruction from carcinoma with carcinomatosis peritonei.
Result:	Initial response to cytotoxins was fair - some subjective relief of symptoms. Subsequently cytotoxins of little effect but no definite evidence of toxic effects. 0-1 for 6 weeks.

CASE NO. 84

PERIPHERAL BLOOD COUNTS

GRAPH A



CASE NO. 84 PERIPHERAL BLOOD COUNTS

GRAPH B

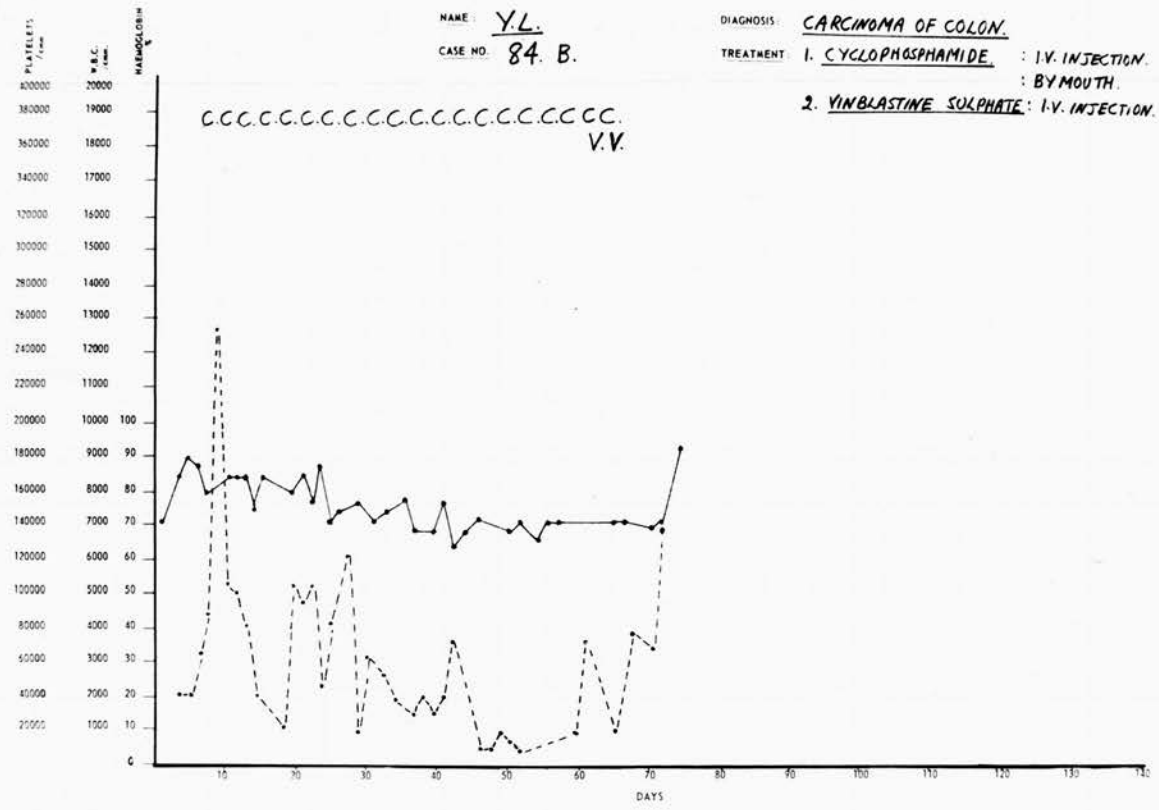


Table 15c

Case: 85	A.M.T. 4/3/63 Age: 52 Sex: M
Diagnosis:	Carcinoma of rectum. Moderately well differentiated adenocarcinoma.
History:	First reported to own doctor in April 1962 with a 5 week history of intermittent diarrhoea. Treated symptomatically and remained relatively free of trouble until July 1962 when a further severe bout of diarrhoea was experienced. Again symptoms relieved by treatment with sulphonamides and patient continued until November 1962 when patient again reported with recurrence of diarrhoea, blood and mucus in stools and rectal pain. Examination at another hospital in December 1962 revealed the presence of an ulcerating, encircling carcinoma of rectum at 10 cm. Defunctioning colostomy carried out on 4/1/63 to empty colon but at laparotomy on 5/2/62 the tumour proved inoperable.
Previous or concurrent treatment:	(1) Defunctioning colostomy: 4/1/63 (2) Laparotomy: inoperable carcinoma of rectum because of local invasion 5/2/63 (3) Resuture of burst wound - on two occasions 6/2/63 and 14/2/63 - all above carried out at another hospital. (4) Radiotherapy: 6,500r to pelvis 11/3/63-26/4/63 (5) Abdomino-perineal excision of rectum: no glandular, hepatic or omental metastases 12/6/63 (6) Blood transfusion: total of 13 pints of whole blood between 7/2/63 and 26/10/63 (7) Entero-caecostomy for small bowel obstruction 29/10/63
Cytotoxic treatment:	(1) Mannitol mustard: 500 mg. by I.V.I. 2/1/63-5/1/63 (3 x 100 mg, 1 x 200 mg. as operation "cover") (2) Cyclophosphamide: 1,400 mg. by I.V.I. 2/2/63-13/2/63 (200 mg. x 7) as operation "cover" (3) Mannitol mustard: 500 mg. by I.V.I. 11/6/63-15/6/63 (100 mg. x 5) as operation "cover" (4) Cyclophosphamide: 1,250 mg. by I.V. infusion 31/10/63-2/11/63 3,800 mg. by I.V.I. 6/11/63-19/1/64 2,700 mg. orally 9/12/63-25/1/64 (5) Thiotepa: 60 mg. intraperitoneally 13/11/63-16/1/64
Clinical/	

Table 15c (continued)

Clinical course and comments:	One year delay before diagnosis of carcinoma of rectum made. At this stage tumour was locally inoperable and a full therapeutic course of radiotherapy was carried out. Recovery from exploratory laparotomy had been complicated and a further 1 month's delay occurred before radiotherapy commenced. Completed course of radiotherapy without incident. General condition improved and local symptoms subsided. Two months later abdomino-perineal excision of the rectum was successfully carried out under cytotoxic "cover". Good recovery from this operation and home for 4 months. During this time, however, there was a persistent discharge from a perineal sinus and recurrent tumour nodules were present in the abdominal scar. Readmitted 25/10/63 with small bowel obstruction. At laparotomy 29/10/63 loops of small bowel were inextricably bound together by recurrent tumour masses and there was a large mass of recurrent tumour in the pelvis. Ileo-caecostomy carried out and fair recovery. Home for a further 1month but readmitted 2/2/64 with rigors, abdominal pain and vomiting and marked weight loss. Temporarily improved by symptomatic treatment but then deteriorated to death on 8/3/63.
Autopsy report:	Peritoneal cavity obliterated by adhesions and large quantities of tumour tissue. Loculated intra-abdominal abscesses. Two small surface metastases in liver only. Pancreas and abdominal lymph glands invaded by tumour. Large tumour mass in wound and in pelvis. No pulmonary metastases.
Result:	Cytotoxins initially employed as operation "cover" and it is of interest to note that at time of second operation (6 months after transverse colostomy) there were no deposits in liver or glands. Subsequently cytotoxins employed to control recurrent tumour but no real evidence of benefit. 1-2 for 14 months.

Table 15d

Case: 86	E.R.W. 6/7/63 Age: 50 Sex: M
Diagnosis:	Carcinoma of pelvi-rectal junction. Moderately well differentiated adenocarcinoma.
History:	First admitted to another hospital on 12/6/63 with a 3 week history of constipation, generalised abdominal pains, mild anorexia and vomiting. Treated by colonic lavage at that time but readmitted 2/7/63 with severe diarrhoea for 2 weeks (7-8 motions/day) and the loss of $1\frac{1}{2}$ stones in weight. Had noted a little fresh blood and mucus in stools. Now complained of listlessness and anorexia. Barium enema now revealed a carcinoma of pelvi-rectal junction with a fistula to small bowel. Transferred for further management.
Previous or concurrent treatment:	(1) Laparotomy and defunctioning colostomy: 15/7/63 Large tumour of pelvi-rectal junction with fistula to jejunum. No other metastases. Faecal laden colon. (2) Abdomino-perineal excision of rectum: Tumour and fistulous loop excised but tumour tissue known to be left in pelvis. 14/9/63 (3) Blood transfusion: 12 pints of whole blood between 9/7/63 and 14/9/63 (4) Antibiotics: (a) Crystamycin 13/7/63-28/7/63 and 15/9/63-24/9/63 (b) Penbritin 25/9/63-9/10/63
Cytotoxic treatment:	(1) Cyclophosphamide: 1,500 mg. by I.V.I. (3 x 500 mg.) 12/8/63-14/8/63 2,700 mg. by mouth (300 mg. x 3/week for 3 weeks) 16/8/63-12/9/63 900 mg. by I.V.I. (3 x 300 mg.) 13/9/63-15/9/63
Clinical course and comments:	Patient's general state on admission was poor. By attention to diet, blood replacement and by establishing a defunctioning colostomy, general condition rapidly improved. By 25/7/63 (3 weeks after admission) was well, eating normally and gaining weight. Discharged home 16/8/63 for period of convalescence. Readmitted 7/9/63 for elective abdomino-perineal excision of tumour and fistula. Had remained well in the interval with further gain in weight. Operation carried out 14/9/63 and recovery complicated only by an infected haematoma in perineal wound, discharging spontaneously. Discharged home 25/10/63. At last review in February 1964 was remaining well in all respects and free of evidence of metastases. Had regained normal weight and colostomy function good.
Autopsy/	

Table 15d (continued)

Autopsy report:	-
Result:	Cytotoxins initially used in the hope of diminishing tumour activity and spread during the necessarily long wait between the first and the definitive surgical procedures. After an initial course of I.V. cyclophosphamide the drug was continued until the second operation by mouth. Additional dose given intravenously over operation. No toxic effects from drugs and at 5 months from operation was remaining free of metastases. 2-3 for 6 months to date.

Table 15e

Case: 87	A.W.S. 12/8/63 Age: 53 Sex: M
Diagnosis:	Carcinoma of caecum with extensive local spread.
History:	Appendicectomy and drainage of appendix abscess on 16/3/62 at another hospital for a 10 day history of colicky lower abdominal pain and anorexia. Following this operation patient continued to experience intermittent (R) sided abdominal pain which was twice investigated with negative findings. Symptoms persisted and in January 1963 barium enema revealed an irregular filling defect in caecum. ?inflammatory ?neoplastic. Laparotomy was carried out in another hospital on 11/2/63 when a carcinoma of caecum with advanced local spread found. Palliative (R) hemicolectomy carried out and patient transferred for further management when recurrent symptoms developed in July 1963.
Previous or concurrent treatment:	(1) Appendicectomy and drainage of appendix abscess: in another hospital 16/3/62 (2) Laparotomy and palliative (R) hemicolectomy: for large carcinoma of caecum with extensive local spread - also in another hospital 11/2/63 (3) Radiotherapy: 5,300r to tumour area (R) lower abdomen 17/10/63-22/11/63
Cytotoxic treatment:	(1) Cyclophosphamide: 3,000 mg. by I.V.I. (9 x 200 mg., 3 x 400 mg.) 16/12/63-7/1/64 3,600 mg. by mouth (300 mg. x 2 weekly for 6 weeks) 8/1/64-26/2/64
Clinical course and comments:	Carcinoma of caecum presenting as obstructive, acute appendicitis and overlooked at operation. Continued symptoms finally led to laparotomy in another hospital and to the diagnosis of locally extensive tumour February 1963. When admitted here in August 1963 was complaining of pain in R.I.F., constipation and backache. Known to have residual tumour in abdomen and a full course of radiotherapy was therefore given in October 1963. This course was completed without incident but abdominal pain and backache persisted and, if anything, were more severe. Bowels remained constipated. Liver first palpable on 26/10/63 and noted to be jaundiced on 19/11/63. By 28/11/63 was experiencing considerable backache, was listless and anorexic and jaundice was marked. In view of pain, increasing jaundice and good general state cytotoxins were commenced on 16/12/63 in hope of obtaining some symptomatic relief. By 23/12/63 backache was minimal and despite increasing jaundice he remained reasonably well until 4/2/64 then deteriorated rapidly and died at home 27/2/64.
Autopsy/	

Table 15e (continued)

Autopsy report:	Died at home and post-mortem not obtained.
Result:	Cytotoxins employed when patient already jaundiced in hope of relieving severe abdominal and back pain. Despite increasing jaundice and increasing hepatomegaly marked symptomatic relief was obtained for $2\frac{1}{2}$ months. No toxic effects from drugs.

Table 15f

Case: 88	E.M.H. 17/10/63 Age: 39 Sex: F
Diagnosis:	Carcinoma of transverse colon with extensive hepatic metastases.
History:	First admitted to another hospital on 12/9/63 with a 4 month history of (R) subcostal pain, vomiting, weight loss and amenorrhoea. Bowels regular but blood in motions. Examination at that time revealed a greatly enlarged irregular liver and at laparotomy on 26/9/63 a carcinoma of transverse colon with extensive hepatic metastases was found. No operative procedure was undertaken and the patient transferred for further management. No previous or family history of note.
Previous or concurrent treatment:	(1) Laparotomy: in another hospital. Carcinoma of transverse colon with massive hepatic involvement. No operative procedure and no biopsy. 26/9/63 (2) Blood transfusion: 3 pints of whole blood 19/10/63 (3) Antibiotics: (a) Sulphathalazole 17/10/63-28/10/63; (b) Crystamycin 17/10/63-28/10/63 (4) Abdominal paracentesis: 1,000 ml. 25/10/63; 2,200 ml. 4/11/63; 1,000 ml. 14/11/63
Cytotoxic treatment:	(1) Cyclophosphamide: 200 mg. intraperitoneally 25/10/63; 2,000 mg. by I.V.I. (200 mg. x 10) 26/10/63-4/11/63; 3,000 mg. by mouth 13/11/63-4/12/63
Clinical course and comments:	Disease already advanced by time of diagnosis. Patient ill, pyrexial and with obvious weight loss. Examination revealed a moderate degree of ascites and marked hepatomegaly. Anaemic. General condition improved a little by 22/10/63 following blood transfusion and antibiotics. Commenced chemotherapy 25/10/63 and although there was a little improvement initially, progress was generally downhill with recurrent ascites, weakness, anorexia, dyspnoea and finally death in coma on 19/12/63 - 2 months after admission without leaving hospital.
Autopsy report:	Confirmed extensive metastatic disease of liver from carcinoma of colon. Ascites. No other metastases.
Result:	No benefit from cytotoxins, but despite extensive hepatic involvement toxic effects did not occur. 0-1 for 2 months.

Table 15g

Case: 89	E.D. 12/12/63 Age: 35 Sex: F
Diagnosis:	Recurrent carcinoma of rectum. Pulmonary metastases.
History:	Abdomino-perineal excision of rectum at another hospital 2 years previously for histologically proven carcinoma of rectum. Extremely well until two months ago when she began to experience increasing pain in perineum, particularly marked when sitting or walking and not relieved by simple analgesics. When seen in October 1963 in another hospital symptoms thought due to coccyx, but excision produced no relief. Subsequently nodules developed in posterior wall of vagina. These were biopsied on 17/12/63 and found to be recurrent adenocarcinoma. No other previous or family history.
Previous or concurrent treatment:	(1) Abdomino-perineal excision of rectum: in another hospital, 1961 (2) Biopsy of recurrent tumour nodules: 17/3/63 (3) Radiotherapy: 6,500r to pelvis 30/12/63-6/2/64
Cytotoxic treatment:	(1) Vinblastine sulphate: 29 mg. by I.V.I. 21/12/63-7/2/64 (2) Cyclophosphamide: 50 mg. by mouth on alternate days from 27/2/64 continuing
Clinical course and comments:	Patient experiencing considerable pain in perineum at time of admission; unable to sit or to walk comfortably and sleep greatly disturbed. General health good; no respiratory symptoms. Commenced radiotherapy combined with cytotoxic therapy on 30/12/63 and within a few days pain decreased and sleeping improved. By 3/2/64 was entirely free of pain, posterior vaginal wall was less indurated and nodular and general health was good. Started cyclophosphamide by mouth on 27/2/64 in hope of controlling pulmonary metastases since these were apparently enlarging. Remained well and under continued treatment at last review June 1964.
Autopsy report:	-
Result:	Vinblastine used as an adjunct to radiotherapy for control of local recurrence. Subsequently small oral dose of cyclophosphamide given to control pulmonary metastases. Result difficult to assess but patient remaining well and metastases not advancing rapidly after 6 months. 2-3 for 6 months to date.

Table 15h

Case: 90	P.W.N. Age: 44 Sex: M
Diagnosis:	Carcinoma of rectum. Moderately well differentiated adenocarcinoma of rectum with invasion of related lymph nodes.
History:	4 month history of rectal pain, diarrhoea and urgent desire to defaecate. Occasional abdominal discomfort. No blood or mucus in stools. General health good but steady loss of $1\frac{1}{2}$ stones in weight over 1 year. Patient had reported symptoms 3 weeks and again 5 weeks after onset but was not examined and treated symptomatically. Extensive carcinoma of rectum at 10 cm., confirmed by sigmoidoscopy and biopsy.
Previous or concurrent treatment:	(1) Laparotomy and defunctioning colostomy: 18/12/63 extensive tumour completely occupying pelvis with hard, fixed glands in root of mesentery; colon distended with faeces. (2) Abdomino-perineal excision of rectum: 9/1/64 malignant tissue known to be left in pelvis and in abdominal glands. (3) Radiotherapy: 500r to abdomen 30/1/64-13/3/64 (4) Blood transfusion: 6 pints whole blood 18/12/63-9/1/64 (5) Antibiotics: (a) Sulphonamide and neomycin - bowel prep. (b) Crystamycin
Cytotoxic treatment:	(1) Cyclophosphamide: 2,800 mg. by I.V.I. (14 x 200 mg.) 18/12/63-12/1/63 (2) Thiotepa: 15 mg. - local instillation in pelvis during operation 9/1/64
Clinical course and comments:	Advanced carcinoma of rectum when first diagnosed. Two stage abdomino-perineal excision of tumour but palliative only. Because of delay between stages of operation cyclophosphamide was given intravenously before and for a few days after the second stage in the hope of reducing tumour activity and spread. Course of post-operative radiotherapy given to abdominal residual tumour. Course completed without incident. Discharged home 13/3/64 well, with good appetite, increasing weight and satisfactory colostomy action. Remaining well with no evidence of further spread of disease at review May 1964.
Autopsy report:	-
Result:	Cyclophosphamide given because of delay between stages of operation in hope of reducing tumour activity and spread. Thiotepa given as "prophylactic" measure at time of second stage operation. Result of cytotoxic therapy cannot be assessed, but no side effects accrued and patient well 4 months post-operatively

Table 15i

Case: 91	R.G. 9/3/65 Age: 59 Sex: M
Diagnosis:	Carcinoma of colon with local invasion of abdominal wall and omentum. Moderately well-differentiated adenocarcinoma.
History:	First admitted to ward 9/3/65 with 3-month history of abdominal pain, anorexia and intermittent diarrhoea. No weight loss. Extensive, locally invasive carcinoma of transverse colon at laparotomy on 17/3/65. No previous or family history of note.
Previous or concurrent treatment:	(1) (R) hemicolectomy: Extensive tumour invading abdominal wall, ileum and omentum with spread in transverse meso-colon towards pancreas. Excision of tumour judged at operation to be incomplete. 17/3/65 (2) Blood transfusion: 1 litre whole blood 17/3/65 1½ litres whole blood 20/9/65
Cytotoxic treatment:	(1) Thiocolciran: 530 mg. by I.V.I. 26/3/65-2/9/65 (2) Methotrexate: 775 mg. by mouth 26/3/65-2/9/65
Clinical course and comments:	In view of extensive nature of tumour and its incomplete removal, cytotoxins were commenced in hope of obtaining additional palliation. It is to be noted that the early injections of thiocolciran resulted in moderately severe epigastric pain within half an hour of the injection. Pain usually subsided within 2-3 hours. No other effects. Remained well and on continued treatment 2/9/65 when his haemoglobin fell to 50% and transfusion was necessary. Low haemoglobin had been associated with vomiting and nose bleeds for 1 week. This was accepted as a suitable point to stop treatment. Slow return to good health and at last review on 27/4/66 was well in all respects, had gained 1 stone in weight and normal blood picture.
Autopsy report:	-
Result:	Treatment commenced in hopes of delaying spread of tumour. Prolonged period of treatment before significant bone marrow depression developed. Treatment stopped after 6 months and patient remained in good general health. 2-3 for 1 year to date.

GROUP P : CARCINOMA OF PANCREAS

Table 16a

Case: 92	F.H.R. 13/2/63 Age: 62 Sex: F
Diagnosis:	Carcinoma of pancreas with peritoneal and omental deposits and ascites. Mucin-secreting adenocarcinoma of pancreas.
History:	History of pain between shoulder blades, particularly after meals, for 3 months. Anorexia for 2 months and loss of 5 lb. in weight. Pain in (L) shoulder with radiation to (L) ear and (L) elbow for 1 month. Epigastric pain for 2 weeks. Nausea but no vomiting. No significant previous or family history. Examination on admission revealed a hard fixed gland in (L) side of neck, a (L) Horner's syndrome and a palpable mass in (R) upper abdomen. Chest X-ray and barium meal negative. Gland biopsy of neck - adenocarcinoma. Diagnostic laparotomy.
Previous or concurrent treatment:	(1) Laparotomy: $2\frac{1}{2}$ litres of bile-stained fluid. Extensive carcinoma of pancreas, covering (R) posterior abdominal wall, almost burying gallbladder and infiltrating the omenta widely. Numerous peritoneal nodules. Cholecyst-gastrostomy and biopsy only. 19/3/63 (2) Blood transfusion: 1 litre of whole blood 19/3/63 (3) Steroids: Hydrocortisone and cortisone acetate 23/3/63-25/3/63
Cytotoxic treatment:	(1) Mannitol mustard: 300 mg. by I.V.I. (3 x 100 mg.) 22/2/63-24/2/63 (2) Cyclophosphamide: 600 mg. by I.V.I. (6 x 100 mg.) 28/2/63-4/3/63 1,000 mg. by mouth 7/3/63-21/3/63 (3) Vinblastine sulphate: 16 mg. by I.V.I. 29/2/63-10/3/63 (4) Thiotepa: 15 mg. intraperitoneally at time of operation 19/3/63
Clinical course and comments:	Patient presenting with vague history and diagnosis of advanced carcinoma of pancreas only finally established at laparotomy 1 month after admission. Clinically the diagnosis of malignant disease was not, however, in doubt and with a positive gland biopsy cytotoxic therapy was commenced on 22/2/63. At this stage patient was nauseated with continued back-pain. Within 2 weeks of starting treatment neck glands had considerably reduced in size and pressure symptoms less marked. A few days later became jaundiced, abdomen distended and general condition deteriorated. Laparotomy to relieve jaundice. Immediate post-operative condition fair, but by 3rd post-operative day condition deteriorating and despite use of steroids, progressed to death on 25/3/63.
Autopsy/	

Table 16a (continued)

Autopsy report:	Post-mortem not requested.
Result:	Disease too advanced when patient first seen to allow of much benefit from therapy. Temporary relief of pressure symptoms from glands in neck but no overall effect on course of disease. 0-1 for 6 weeks only.

GROUP P : CARCINOMA OF PANCREAS

Table 16b (continued)

Case: 93	E.L. 1/12/64 Age: 48 Sex: F
Diagnosis:	Carcinoma of pancreas with extensive local invasion and peritoneal metastases.
History:	Admitted to a medical ward in November 1964 with a 6-month history of anorexia, listlessness, lethargy, intermittent vomiting, and loss of 1 stone in weight. Had also experienced epigastric pain, unrelated to meals, for 3 weeks, breathlessness and angina of effort. Found on investigation to be severely anaemic and thought to have a carcinoma of stomach. Hysterectomy 2 years previously for menorrhagia; no other significant past or family history. Transferred for diagnostic laparotomy.
Previous or concurrent treatment:	(1) Blood transfusion: packed cells of 2 litres 20/11/64 (2) Laparotomy: large, inoperable tumour of pancreas infiltrating stomach and liver. Gastroenterostomy and biopsy. 2/12/64 (3) Blood transfusion: 500 ml. whole blood 2/12/64
Cytotoxic treatment:	(1) Cyclophosphamide: 1,000 mg. by I.V.I. 7/12/64-14/12/64 12,250 mg. by mouth (150 mg. daily) 15/12/64-15/4/65
Clinical course and comments:	Presented with severe anaemia and large tumour mass producing incomplete obstruction to stomach. Commenced chemotherapy on 5th postoperative day. No untoward effects and discharged home 17/12/64. Remained on out-patient treatment and reasonably well for 3½ months despite steady increase in size of abdominal mass and moderate loss of hair. By 1/4/64, however, general condition was deteriorating; she experienced intermittent vomiting and appetite decreased. Died at home 31/5/64, but remained alert and active until 24 hours before.
Autopsy report:	Died at home - no post-mortem obtained.
Result:	Gastroenterostomy was probably responsible for most of postoperative improvement, but it is significant that the patient remained reasonably well, active and entirely pain-free despite a large intra-abdominal neoplasm. Moderate alopecia from cyclophosphamide starting after 1 month of treatment, reaching a peak after 7 weeks and then regrowing a little while on continued treatment. 1 - 2 for 5 months.

Table 16c

Case: 94	J.K. 5/3/62 Age: 65 Sex: M
Diagnosis:	Carcinoma of pancreas
History:	First presented in February 1962 with an 8 month history of increasing epigastric pain, anorexia and weight loss. Thought to have a duodenal ulcer but at laparotomy 6/3/62 an inoperable carcinoma of head of pancreas was discovered. Palliative gastro-enterostomy. Remained well until May 1964 when returned, again with increasing epigastric pain, anorexia, weight loss and steatorrhoea. Obvious malignant mass in epigastrium. Assessed for cytotoxic therapy Nov. 1964. Previous prostatectomy 1961. No other significant past or family history.
Previous or concurrent treatment:	(1) Palliative gastro-enterostomy: for inoperable carcinoma head of pancreas 6/3/62 (2) Analgesics and anti-emetics: from May 1964 (3) Blood transfusion: 1 litre whole blood 31/12/64 (4) Dianabol: orally 1/5/64-25/11/64
Cytotoxic treatment:	(1) Cyclophosphamide: 4,650 mg. by mouth 26/11/64-24/12/64 1,000 mg. by I.V. infusion 25/12/64
Clinical course and comments:	2 years of good palliation from gastro-enterostomy for carcinoma of head of pancreas diagnosed at laparotomy 6/3/62. Returned in May 1964 with increasing epigastric pain, anorexia and weight loss. Temporary benefit from oral pethidine and dianabol (anabolic steroid), but symptoms severe and general condition poor by November 1964. Then commenced treatment with cyclophosphamide but pain remained severe, continued to have steatorrhoea and to lose weight. Condition deteriorated to death at home on 8/1/65.
Autopsy report:	Died at home - post-mortem not obtained.
Result:	No benefit from cytotoxins either on pain or course of disease. Evidence of increasing bone marrow depression terminally. 0-1 for 6 weeks only.

Table 16d

Case: 95	J.T. 1/12/64 Age: 59 Sex: M
Diagnosis:	Carcinoma of head of pancreas with extensive hepatic metastases. Moderately differentiated adenocarcinoma.
History:	2 year history of increasing central and lower abdominal pain, particularly persistent and severe over 2 months prior to admission. Occasional nausea and vomiting with anorexia and loss of 3 stones in weight over 3 months. Discovered to have diabetes 6 months prior to admission but no other findings at that time - treated with oral agents. No other previous or family history of significance.
Previous or concurrent treatment:	(1) Laparotomy: Inoperable carcinoma head of pancreas with extensive hepatic metastases. No procedure. 2/12/64 (2) Cholecysto-jejunostomy: for obstructive jaundice due to tumour 8/2/65 (3) Ferrous sulphate: 200 mg. t.i.d. from 17/2/65 (4) Aspiration of peritoneal effusion: 1,125 ml. 8/3/65 5 litres 18/3/65 2 litres 1/4/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1,200 mg. by I.V.I. 14/12/64-22/1/65 7,200 mg. orally 14/12/64-5/3/65 1,000 mg. intraperitoneally 18/3/65-1/4/65
Clinical course and comments:	Good recovery from initial laparotomy for advanced carcinoma of pancreas. Started chemotherapy 2 weeks after operation. 2 weeks after starting therapy patient's pain decreased and appetite improved. Thereafter remained well and pain-free for 1 month during which time he returned to work. Then became progressively jaundiced (although remaining pain-free) and palliative cholecysto-jejunostomy was carried out on 8/2/65. Again a good recovery, but gradually developed ascites requiring repeated aspiration. Steady deterioration to death at home on 18/4/65, 4 months after starting cytotoxins.
Autopsy report:	Died at home - post-mortem not obtained.
Result:	Good initial response to cyclophosphamide with relief of pain and improvement in appetite. Improvement maintained for 1 month and thereafter, although pain-free, gradually deteriorated. 1-2 for 4 months.

GROUP 9 : MALIGNANT MELANOMA

Table 17a

Case: 96	R.G.C. 15/12/62 Age: 52 Sex: M
Diagnosis:	Malignant melanoma of (R) thigh with lymph gland metastases. Histology of primary and lymph glands (R) groin confirmed.
History:	First admitted to another hospital 30/11/62 with a 4 month history of increase in size and bleeding from a mole on medial aspect of (R) thigh. He was noted to have enlarged glands in (R) groin at this time but there was no other evidence of spread and he was entirely free of other symptoms. No previous or family history of note, but for past 3 years had lived in Aden. Transferred for further management after excision of primary lesion.
Previous or concurrent treatment:	(1) Wide excision biopsy of lesion (R) thigh - primary suture - in another hospital 5/12/62 (2) (a) Wide re-excision and skin grafting primary site (b) Block dissection (R) groin 22/12/62 (3) Antibiotics: (a) Crystamycin - for infected wound
Cytotoxic treatment:	(1) Melphelan: 175 mg. by mouth 19/12/62-18/1/63 (2) Cyclophosphamide: 500 mg. by I.V. infusion during second operation 22/12/62
Clinical course and comments:	Presented with obvious malignant melanoma (R) thigh with metastases in glands (R) groin. Initial excision of primary inadequate and wide excision with skin grafting carried out at same time as block dissection (R) groin. These last operations were carried out under cytotoxic cover and, in the hopes of preventing further spread or delaying recurrence, cytotoxins were continued for 1 month post-operatively. There was gross infection and wide breakdown of groin wound requiring a prolonged period for healing. Subsequently developed swelling of (R) leg subsiding with elastic bandaging. Blood count depressed by cytotoxins and finally discharged home 19/2/63. At this stage was fit and well. Remained well for 2 weeks only and then developed a febrile illness with nausea, vomiting, neck stiffness, personality change, epileptiform fits, collapse and death on 16/3/63.
Autopsy report:	Obese. Wound and graft intact and free of deposits. Large blood clot in posterior cranial fossa pushing cerebellar hemispheres up off mid brain. Clot semi-walled off and apparently arising from small aneurysm of (R) cerebellar artery. No evidence of metastases in brain or elsewhere in body.
Result:	Cytotoxins given as operation "cover" and in hope of preventing or delaying the appearance of recurrence. Moderate degree of bone marrow depression produced and considerable delay in wound healing. Although there is no direct proof the occurrence of a fatal cerebral haemorrhage might in part be due to cytotoxins.

Table 17b

Case: 97	M.S. 18/5/65 **Age:** 50 **Sex:** F
Diagnosis:	Recurrent malignant melanoma of (L) leg. Histologically a typical naevocarcinoma.
History:	First seen with a view to cytotoxic therapy on 18/5/66 for recurrent malignant melanoma of (L) leg. Patient had first noticed a growing black mark on (L) leg one year previously. Biopsy at that time, at another hospital, confirmed malignant melanoma and wide excision with block dissection of inguinal glands was carried out. Good recovery from operation, but was re-admitted to same hospital 6 months later with cellulitis of (L) leg. Resolved with antibiotic therapy, but limb became lymphoedematous and was subject to repeated mild episodes of cellulitis. Remained free of recurrence of disease until end of April 1965 and then rapidly developed nodules in area of extension and in (L) groin. No other family history of note.
Previous or concurrent treatment:	(1) Wide local excision of primary tumour and block dissection of inguinal glands: 19/5/64 - in another hospital. (2) Antibiotics: (a) 5-day course of orbenin for cellulitis (L) leg 3-7/9/65 (b) Tetracycline 50 mg. 6-hourly 25/1/66-3/2/66 (3) Blood transfusion: 3 litres of whole blood 22/12/65 - 2/2/66 (4) Analgesics: Various, but in small doses over last 3 months
Cytotoxic treatment:	(1) Methotrexate: 277-5 mg. by mouth 4/6/65-13/12/65 (2) Melphalan: 720 mg. by mouth 4/6/65 - 13/12/65 (3) 2-ethyl-hydrazine: 2 G. by intra-arterial injection 14/1/66 - 24/1/66
Clinical course and comments:	When first seen on 18/5/65 there was extensive recurrent tumour in (L) groin, in the fragted area (L) calf and a few small nodules elsewhere on (L) leg. No other known metastases. Commenced cytotoxic therapy 4/6/65 and after 10 days in-patient treatment there was a moderate fall in platelet and white cell counts. Treatment was suspended for 2 weeks and then resumed as an out-patient. Remained reasonably well and active for 3 months, but then general condition began to slowly deteriorate and tumour masses to increase in size and extent. Large gland masses now palpable above inguinal ligament. Re-admitted to ward 21/12/65 for blood transfusion; general condition poor and disease slowly spreading. Home for two weeks and then re-admitted with large masses in (L) groin, extensive bleeding nodules in grafted area, swelling and cellulitis of entire leg. There was some improvement in condition of leg after arterial injection of 2-ethyl-hydrazine (S.P.T.) general condition fair.

Table 17b (continued)

Autopsy report:	Died at home - no post-mortem obtained.
Result:	Although on cytotoxic therapy for six months local disease slowly extended to a final ugly fungating, bleeding state. It is doubtful whether therapy was of any benefit, apart from the first few weeks. 0-2 for 7 months. Mild alopecia.

Table 17c

Case: 98	J.S. 13/7/65 **Age:** 65 **Sex:** F
Diagnosis:	Malignant melanoma of (L) foot; skin and gland metastases. Ulcerated malignant melanoma.
History:	First seen in mid-July 1965 with a history of painful swelling over instep of (L) foot present for three to four weeks. Swelling had been preceded by a blue discolouration of skin of (L) instep. No other significant history or findings at this stage, but it is to be noted that the (L) foot had been the site of a triple arthrodesis forty years previously. Admitted to ward 25/7/65, excision and grafting of swelling (L) foot carried out 26/7/65. Histologically lesion shown to be a malignant melanoma.
Previous or concurrent treatment:	(1) **Excision and grafting lesion instep (L) foot:** 26/7/65 (2) **Radiotherapy:** palliative to (L) groin 18/11/65 - 15/12/65 (3) **Analgesics:** Various at intervals throughout treatment period. (4) **Antibiotics:** **Tetracycline** - 250 mg. 6-hourly by mouth 24/1/66 - 4/2/66
Cytotoxic treatment:	(1) **Melphelan:** 25 mg. by intra-arterial infusion 7/1/66 (2) **2-ethyl-hydrazine:** 1G by intra-arterial infusion 24/1/66 1G by intra arterial infusion 22/3/66 1.8G by I.V.I. 26/3/66 - 12/5/66 3 x 400 mg. 1 x 600 mg. **Total** = 3.8G
Clinical course and treatment:	Glands were first noted in (L) groin one month after excision and grafting of primary lesion on 26/7/65. By mid-October 1965 glands in (L) groin were painful and numerous. A palliative course of radiotherapy was given between 18/11/65 and 15/12/65 with shrinkage of groin glands and moist desquamation of skin in area treated. Before this course was completed, however, local recurrence was noted in grafted area (L) foot. Recurrence growing rapidly painful and associated with skin metastases (L) foot and thigh. Good response to intra-arterial melphelan given on 7/1/66 into (L) femoral artery. Pain much reduced and lesion less florid Further arterial infusion with 2-ethyl-hydrazine on 24/1/66 produced little further benefit . Further nodules developed and recurrent lesion (L) foot increasing in size - considerable local pain. Transient relief only from further intravenous cytotoxin and re-admitted for terminal care 18/5/66. Died 24/5/66 from progress of disease.
Autopsy/	

Table 17c (continued)

Autopsy report:	No post-mortem obtained.
Result:	Initial good response to intra-arterial cytotoxins, but short lived. No significant side-effects from treatment. 1-2 for 4 months.

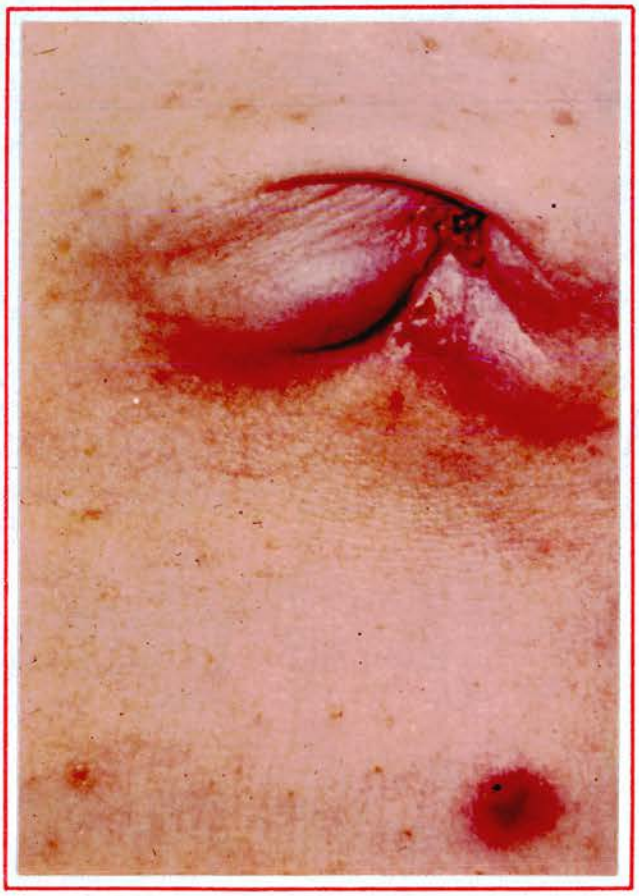
GROUP R : CARCINOMA OF UNKNOWN PRIMARY

Table 18a

Case: 99	C.J.B. 22/3/63 Age: 46 Sex: M
Diagnosis:	Carcinoma of unknown primary. Biopsy of umbilical mass - squamous cell carcinoma.
History:	First admitted to another hospital on 1/3/63 with a 3-month history of increasing indigestion and abdominal discomfort. Appetite good but progressive weight loss since onset of symptoms. Claimed to be in reasonably good general health. No bowel or urinary symptoms. Apart from one brief episode of abdominal pain and diarrhoea 7 months previously there was no significant past or family history. Smoked 20/day. Biopsy of mass at umbilicus revealed a squamous cell carcinoma and patient transferred for further management.
Previous or concurrent treatment:	(1) Biopsy of umbilical mass - at another hospital 3/3/63 (2) Radiotherapy: 6,000r to abdominal tumour mass 2/4/63-8/5/63 (3) Blood transfusion: 2 litres of whole blood 22/4/63
Cytotoxic treatment:	(1) Cyclophosphamide: 1,200 mg. by I.V.I. 25/3/63-27/3/63 4,300 mg. by mouth 1/4/63-20/5/63 2,400 mg. by mouth 27/6/63-27/7/63
Clinical course and comments:	Although symptoms were indefinite and patient claimed to feel reasonably well, he presented the picture of advanced intra-abdominal malignant disease with ascites. Large masses of tumour were palpable in the abdomen with a very large mass in lower central and (R) abdomen. Liver also palpable. Histology - squamous-celled carcinoma, primary unknown. Attempt to aspirate ascites produced 10 ml. of pseudo-mucinous material only. Commenced cyclophosphamide 25/3/63 and in view of his good general state radiotherapy was started on 2/4/63. By 10/4/63 patient claimed to feel well with no complaints of any kind. Completed radiotherapy on 8/5/63 with only mild diarrhoea and cystitis - no appreciable shrinkage of abdominal mass. Losing a little more weight. Discharged 9/5/63 continuing cyclophosphamide as out-patient but stopped for 1 month from 20/5/63. By 4/6/63 was remarkably well with good appetite, weight improving and mass in abdomen reduced in size. Moderate depression of bone marrow requiring cessation of treatment 27/7/63. At last review 9/3/64 remission was maintained.
Autopsy report:	-
Result:	Cytotoxins used in conjunction with radiotherapy for control of advance intra-abdominal malignancy of unknown origin. Despite almost cachetic state on admission patient was alive, active and well 1 year later. 2-3 for 1 year to date.

Case No. 99: Carcinoma of Unknown Primary

Fig. 1: Metastatic tumour at umbilicus.



GROUP N : CARCINOMA OF UNKNOWN PRIMARY

Table 18b (continued)

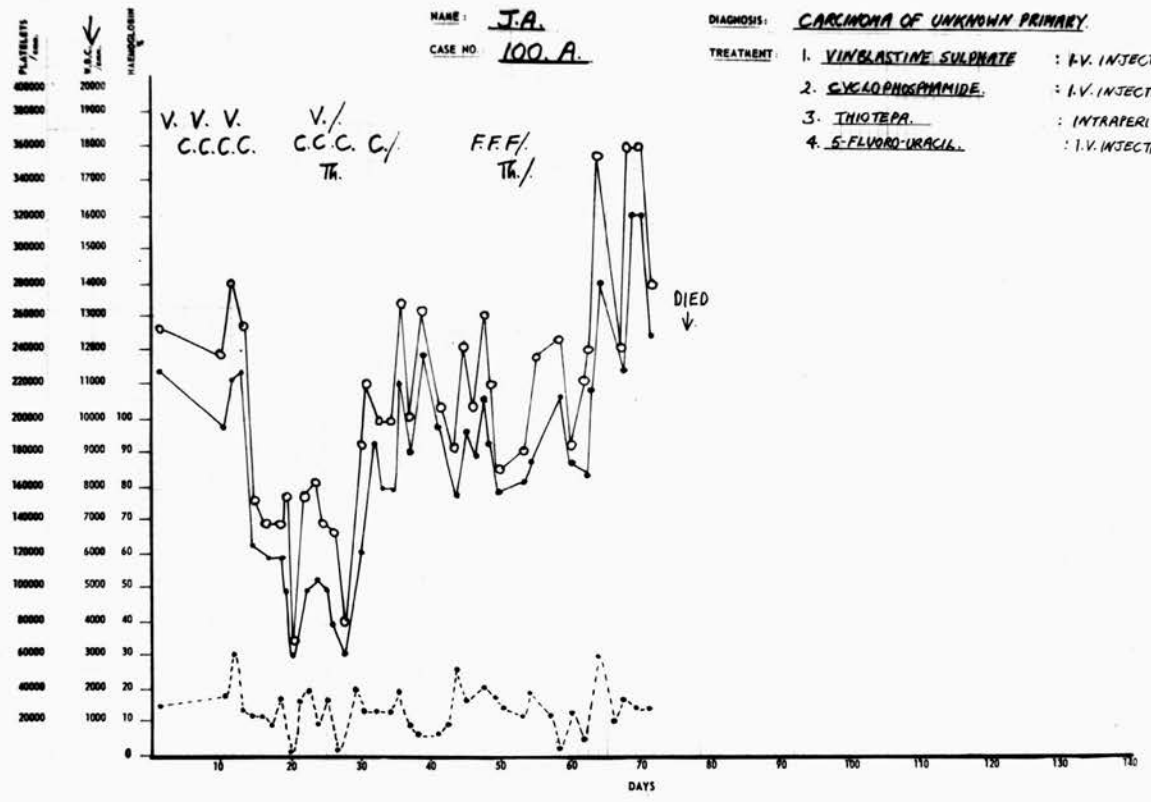
Case: 100	J.A. 29/8/63 Age: 24 Sex: M
Diagnosis:	Carcinoma of unknown origin with skin and glandular metastases. Neck gland biopsy - papillary carcinoma consistent with origin in ? thyroid or bowel. Primary site remained uncertain despite post-mortem examination.
History:	First reported 26/8/63 with a 4-day history of painless swelling in (L) side of neck. Appetite, weight and general health normal. No symptoms referable to other systems. Smoked 20/day. Investigated for ? thyrotoxicosis aged 15, but negative findings. No other previous or family history of note.
Previous or concurrent treatment:	(1) Gland biopsy (L) side of neck: 31/8/63 (2) Radiotherapy: to (L) side of neck and (L) axilla - dose not known 6/9/63-8/11/63 3,100r to dorsal spine and (L) posterior chest wall 18/12/63-15/1/64 2,070r to (L) upper neck 31/12/63-15/1/64 (3) L-thyroxine: 0.1 mg. t.i.d. 16/9/63-8/11/63 0.1 mg. b.i.d. 17/12/63-3/1/64 (4) Meprobamate: (tranquilliser) 400 mg. 6-hourly by mouth 29/12/63-13/2/64 (5) Pleural aspiration: 1,500 ml. 14/1/64
Cytotoxic treatment:	(1) Vinblastine sulphate: 15 mg. by I.V.I. (3 x 5 mg.) 1/1/64-20/1/64 (2) Cyclophosphamide: 3,100 mg. by I.V.I. 3/1/64-25/1/64 (3) Thiotepa: 30 mg. intrapleurally 14/1/64-15/2/64 (4) 5-fluorouracil: 2,750 mg. by I.V.I. (1 x 250 mg., 5 x 500 mg.) 10/2/64-13/2/64
Clinical course and comments:	Rapid increase in size of masses (L) side of neck and (L) axilla even in the short time between onset of symptoms 24/8/63 and commencement of treatment with radiotherapy 6/9/63. Radiotherapy produced a rapid shrinkage of gland masses and at end of course patient claimed to feel fit and well despite a loss of 10 lb. in weight. Discharged home 9/11/63 but readmitted 3 days later with severe epigastric pain and vomiting. Symptoms settled rapidly and there were no new clinical findings. By 18/11/63 was again complaining of low back and abdominal pain. Had now lost a total of 16 lb. On 13/12/63 developed severe pain between shoulder blades and nodules in (L) side of neck and (L) axilla were enlarging. X-rays suggested a lesion about D 6/7. Backache increased and further radiotherapy given and L-thyroxine resumed. Further gland (L) side of neck also irradiated. Patient now extremely/

Table 18b (continued)

	extremely anxious and agitated and required regular sedation. By 1/1/64 general state was deteriorating, weight and appetite decreasing. Developed a (L) pleural effusion and cytotoxins were commenced at this time. Despite using a variety of cytotoxins general condition deteriorated, disease fungated through skin of chest wall and axilla, hair loss was marked and patient died with extensive disease 21/2/64.
Autopsy report:	Died 21/2/64. Widespread tumour infiltration of skin of (L) side of chest wall, (L) shoulder and (L) axilla with extensive superficial ulceration. Large necrotic tumour mass 6 cm. in diameter at (L) hilum invading pericardium. Numerous metastases (R) lung, pancreas and liver. Mass of infiltrated glands around abdominal aorta and in porta hepatis. No tumour in thyroid or bowel.
Result:	Marked but short-lived response to radiotherapy but no obvious benefit from even large doses of cytotoxins used alone and in combination. Marked alopecia from cyclophosphamide. 0-1 for 6 weeks only.

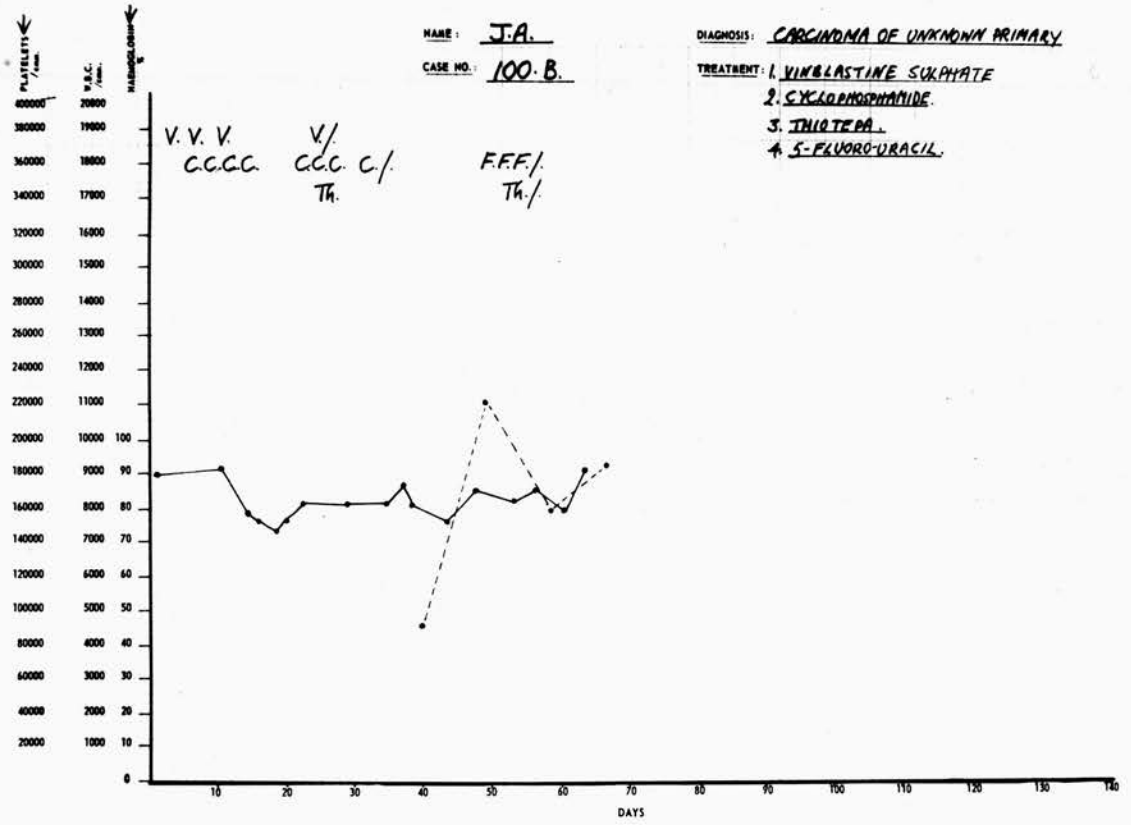
CASE NO. 100 PERIPHERAL BLOOD COUNT

GRAPH A



CASE NO. 100 PERIPHERAL BLOOD COUNTS

GRAPH B



Case No. 100: Carcinoma of Unknown Primary

Fig. 1: Chest X-ray 27/8/63.

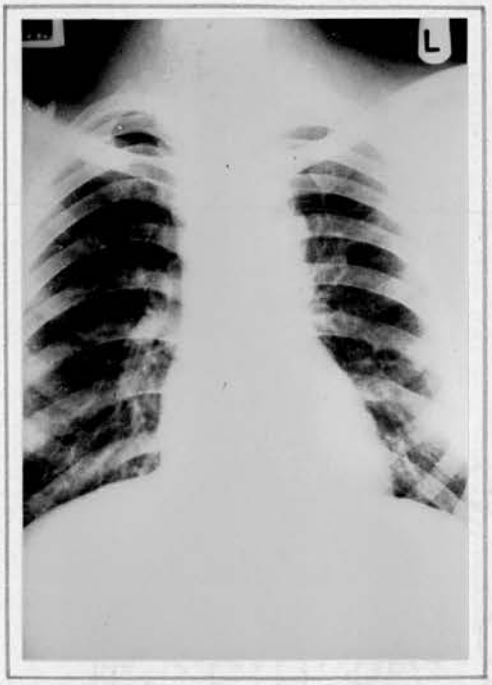


Fig. 2: Chest X-ray 22/10/63.

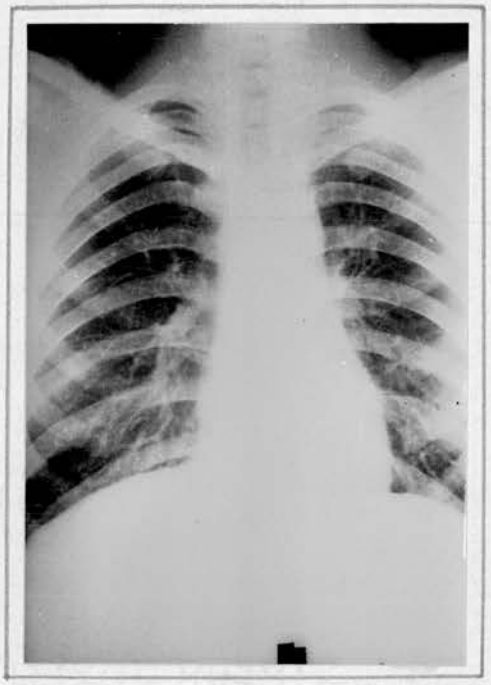


Fig. 3: Chest X-ray 30/12/63.

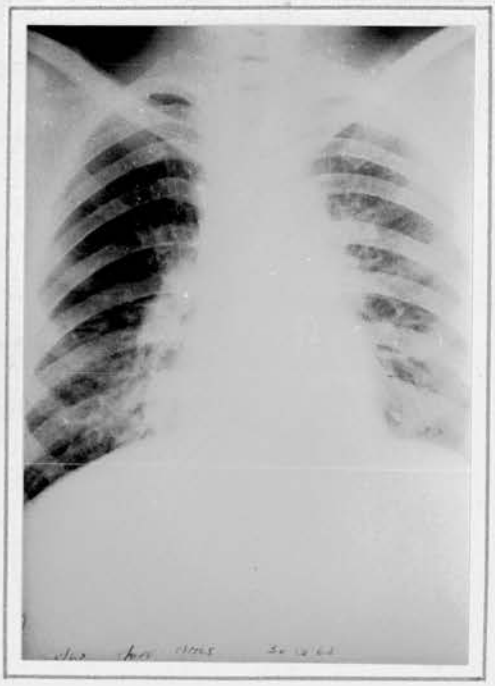
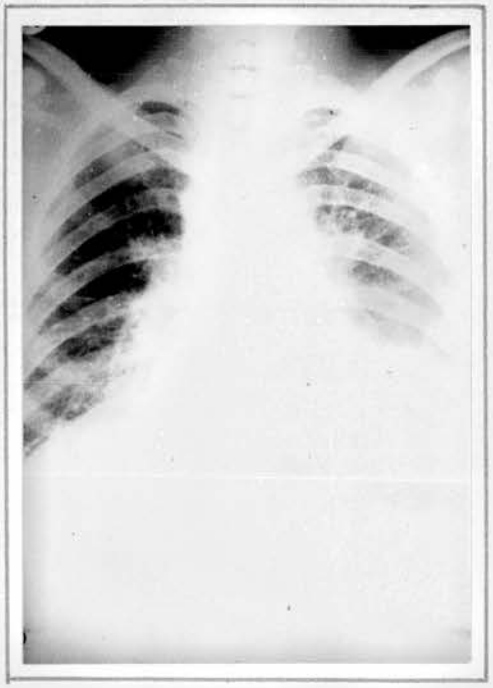


Fig. 4: Chest X-ray 7/1/64.



Case No. 100.

Fig. 5: Chest X-ray 21/1/64.

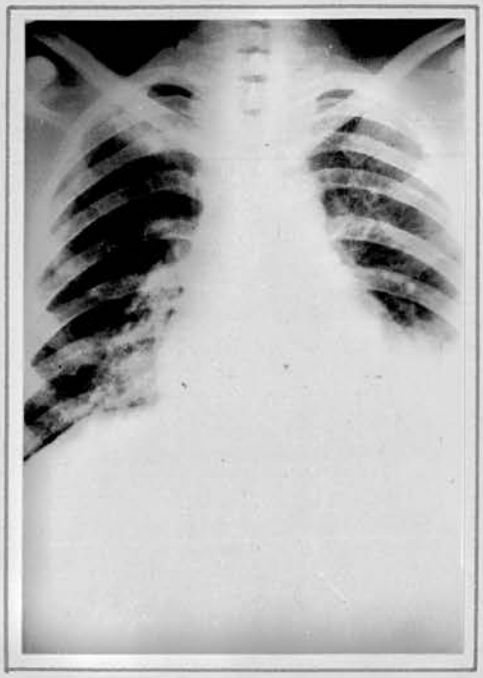


Fig. 6: Chest X-ray 11/2/64.

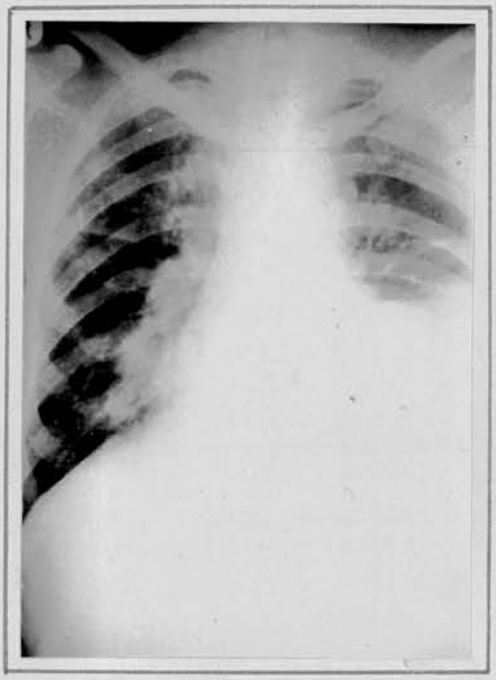


Fig. 7: Tumour infiltration of skin of chest wall: 11/2/64 and L. axilla.

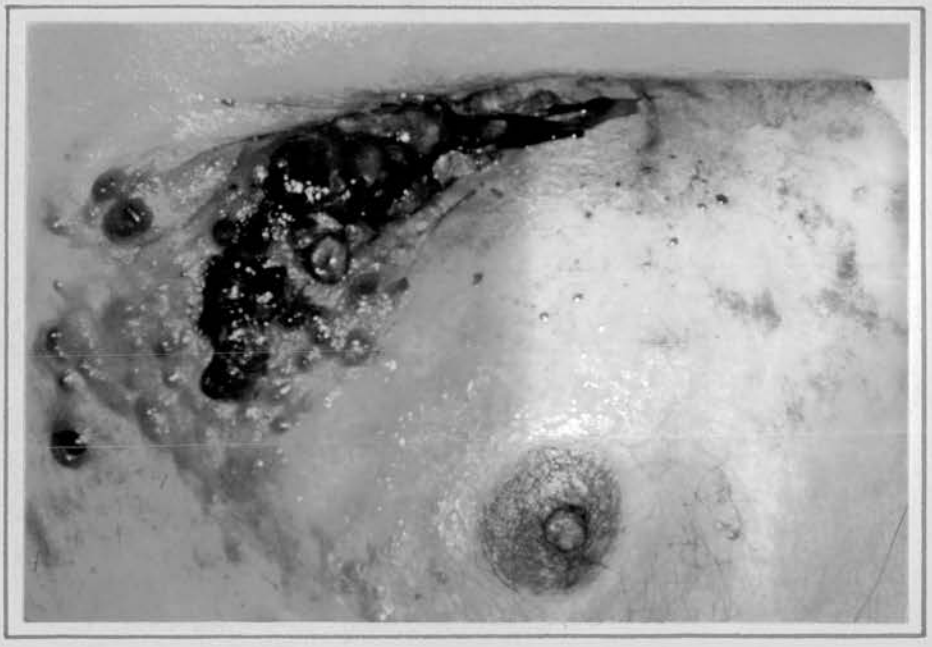


Table 18c

Case: 101	J.McI. 29/12/64 Age: 54 Sex: F
Diagnosis:	Carcinoma of unknown origin with skeletal and glandular metastases. Undifferentiated carcinoma.
History:	First seen in December 1964 with enlarged glands in (R) groin. No obvious cause found on out-patient investigation and admitted overnight for gland biopsy 10/2/65. At this stage glands were painless and patient had no other complaints. Histology of gland showed undifferentiated carcinoma. Readmitted 17/2/65 for further investigation. No primary lesion could be detected, however, but metastases present in dorsal spine and mandible. Now complained of back pain and aching pain in (R) groin when standing. No relevant previous or family history.
Previous or concurrent treatment:	(1) Radiotherapy: single palliative dose to mid-dorsal spine and (R) groin glands 3/3/65 (2) Gland biopsy: (R) groin - undifferentiated carcinoma. 10/2/65
Cytotoxic treatment:	(1) Cyclophosphamide: 1,000 mg. by I.V. infusion over 24 hours 14/3/65-15/3/65 800 mg. by I.V.I. 17/3/65-18/3/65 Total = 1,800 mg. I.V.
Clinical course and comments:	Primary lesion not detected despite prolonged, but not exhaustive investigation. Because of pain in dorsal spine and commencing deterioration, single dose of X-rays given to dorsal spine and (R) groin with some relief. Cytotoxins started 14/3/65 without disturbance. No significant improvement in condition by discharge on 6/4/65 and subsequently patient unable to attend as an out-patient. Rapid deterioration and died at home from bronchopneumonia on 18/4/65.
Autopsy report:	Died at home. Post-mortem not obtained.
Result:	Little or no benefit obtained from relatively small dose of cyclophosphamide. No side effects. 0 for 6 weeks only.

Table 18d

Case: 102	J.W. 11/1/65	Age: 35 Sex: M
Diagnosis:	Carcinoma of unknown primary with peritoneal, lymph gland and cutaneous deposits. Undifferentiated adenocarcinoma with certain features consistent with origin in bowel.	
History:	Admitted as a transfer from a medical ward where he had been admitted on 3/12/65 with a 5-month history of increasing (R)-sided abdominal pain, nausea, weight loss, anorexia and constipation. Cause for symptoms not discovered in medical ward despite extensive investigations. Malignant disease was, however, suspected and patient transferred for diagnostic laparotomy. No previous or family history of note.	
Previous or concurrent treatment:	(1) Biopsy of gland (R) axilla:	12/1/65
	(2) Laparotomy: widespread peritoneal and omental deposits from undiscovered primary. Biopsy of wall of transverse colon.	18/1/65
	(3) Analgesics and anti-emetics: intermittently throughout treatment	
	(4) Aspiration of pleural effusion: 2 litres 1½ litres	2/3/65 12/3/65
Cytotoxic treatment:	(1) Nitrogen mustard: 30 mg. by I.V.I.	22/1/65-29/1/65
	(2) Cyclophosphamide: 2,450 mg. by mouth	15/2/65-9/3/65
Clinical course and comments:	Patient presenting with widespread malignant disease from primary which remained undiscovered despite extensive investigations and laparotomy. Commenced cytotoxins 22/1/65 and by 15/2/65 condition was sufficiently improved to allow discharge home. Previous severe abdominal pain less marked, glands in neck and skin nodules smaller. 9 lb. gain in weight. Readmitted 2/3/65 with severe dyspnoea and large (R) pleural effusion - aspirated. Benefit short lived and bilateral effusions required aspiration. Thereafter general condition deteriorated and died in severe respiratory distress at home 22/3/65 - 7 months from onset of symptoms.	
Autopsy report:	Died at home - post-mortem not obtained.	
Result:	Objective and subjective benefit from cytotoxins lasting 6 weeks only. Nausea, vomiting and increased abdominal pain after initial injections of nitrogen mustard, but no other side effects. 0-1 for 2 months.	

"OTHERS"

GROUP S : RETROPERITONEAL LEIOMYOSARCOMA

Table 19a

Case: 103	S.L.P. 24/4/62 Age: 37 Sex: M
Diagnosis:	Retroperitoneal leiomyosarcoma
History:	First reported 28/3/62 with a 3 month history of frequency of micturition, a feeling of incomplete emptying of bladder, constipation and intermittent abdominal distension. Had been aware of a "lump" in abdomen for 2 months with anorexia and loss of weight over same period. Laparotomy 10/4/62 in another hospital revealed extensive, highly vascular and friable tissue masses occupying pelvis and (R) lower abdomen, but no obvious primary. Biopsy - leiomyosarcoma. Transferred for further management with main complaint of constipation. No previous or family history of note.
Previous or concurrent treatment:	(1) Laparotomy: large highly vascular tumour masses in pelvis and (R) abdomen. Biopsy only. No metastases. Carried out in another hospital. 10/4/62 (2) Bone marrow extraction and storage: 30/4/62 (3) Radiotherapy: 6,500r to abdominal tumour masses 3/5/62-26/6/62 (4) Blood transfusion: 1 litre of whole blood 12/4/62 (5) Laparotomy: findings as before but tumour even more extensive. No metastases. Biopsy only. 12/2/63 (6) Sulphonamides: for urinary infection. 10/10/63-17/10/63
Cytotoxic treatment:	(1) Mannitol mustard: 300 mg. by I.V.I. 11/2/63-13/2/63 (3 x 100 mg. over second operation) (2) Thiotepa: 10 mg. intraperitoneal at operation 12/2/63 (3) Mannitol mustard: 500 mg. by I.V. infusion 1/3/63-3/3/63 (50 mg./500 ml./5-hourly) 2,900 mg. by mouth 8/3/63-11/9/63 (4) Cyclophosphamide: 1,200 mg. by I.V. infusion 11/9/63 3,000 mg. by I.V.I. 13/9/63-10/10/63 (5) Vinblastine sulphate: 10 mg. by I.V.I. 1/10/63-4/10/63
Clinical/	

Table 19a (continued)

Clinical course and comments:	Diagnosis of retroperitoneal leiomyosarcoma established following laparotomy and biopsy when other investigations had been largely unhelpful. Tumour irremovable and a radical course of radiotherapy was completed without incident between 3/5/62 and 26/6/62. This resulted in only slight shrinkage of tumour mass, but urinary and bowel symptoms were partly relieved. Remained well and at work for 6 months despite slow increase in size of tumour. Readmitted 31/1/63 with recurrent urinary and bowel symptoms and second look operation carried out 12/2/63 in hope of doing something further. Tumour even more extensive and friable than before and even biopsy resulted in prolonged oozing from wound postoperatively. Further radiotherapy deemed unfeasible and since cytotoxin "cover" had been used at second operation this treatment was continued. Definite tumour shrinkage had occurred by the end of 1 month. Remained reasonably well and at work for a further 7 months but was then (9/9/63) readmitted with increasing backache, constipation, difficulty with micturition and weight loss. Further cytotoxic therapy produced only temporary relief and condition slowly deteriorated with urinary retention and uraemia. Died 15/10/63.
Autopsy report:	Emaciated. Obvious protuberant mass in (R) lower abdomen. Scattered throughout parenchyma of both lungs were small tumour nodules approx. 5 mm. in diameter. Arising from pelvis was a large necrotic encephaloid tumour infiltrating bladder, rectum and colon. Large dilated veins over tumour. Peritoneal deposits. Liver clear of deposits.
Result:	Initial good response to radical radiotherapy alone and remission maintained for 6 months. Further 7 months remission with mannitol mustard but only slight benefit from addition of cyclophosphamide and vinblastine in later stages. 2-3 for 15 months.

GROUP S$_2$: SALIVARY GLAND TUMOURS

Table 19.b

Case: 104	D.L.O. 7/1/63 Age: 42 Sex: M
Diagnosis:	Mixed salivary tumour (R) parotid gland with pulmonary metastases. Histology - typical "mixed" salivary tumour.
History:	Small swelling (R) sub-mandibular region excised locally 1956 in another hospital. Specimen not sent for histology. Swelling recurred in 1960 and was re-excised in February of that year. Histology showed a typical mixed salivary tumour and operation on this occasion was followed by a course of conventional voltage radiotherapy. Remained well and free of recurrence until 21/12/62 when he reported with swelling in the irradiated area (R) sub-mandibular region. Examination confirmed local recurrence in an area of marked radiotherapy scarring, and a solitary metastasis in upper zone of (L) lung. General health otherwise excellent, weight steady. No previous or family history of note.
Previous or concurrent treatment:	(1) Excision of (R) sub-mandibular swelling: as detailed under History - both operations carried out elsewhere. 1956 & 1960 (2) Radiotherapy: to (R) sub-mandibular area. Details not known. (3) Radiotherapy: 5,500r to anterior (R) neck, anterior and posterior (L) chest 28/8/63-14/10/63
Cytotoxic treatment:	(1) Cyclophosphamide: 15,000 mg. by mouth 12/1/63-20/8/63 (2) Vinblastine sulphate: 172 mg. by I.V.I. 15/1/63-20/8/63 (3) Cyclophosphamide: 2,000 mg. by I.V. infusion over 40 hours (10 x 200 mg. 4-hourly) 7/2/64-9/2/64 2,400 mg. by mouth - continuing 16/2/64-18/3/64
Clinical course and comments:	Malignant "mixed" salivary tumour appearing with local recurrence and a solitary pulmonary metastasis 6 years after initial local excision and 2 years after excision of recurrence and radiotherapy. In view of previous radiotherapy and lung deposit, cytotoxic therapy was started on 12/1/63 using a combination of oral cyclophosphamide and intravenous vinblastine. Remained on this treatment for 8 months during which time he remained fit and well and at work. During this period also the local recurrence and pulmonary metastasis remained almost static. By 16/8/63 was experiencing neuralgic pains in (R) side of face and it was decided to try further irradiation to local recurrence and also to lung lesion. Completed radiotherapy 14/10/63 with relief of symptoms and virtual disappearance of lung lesion. By 30/1/64, however, was again experiencing neuralgic pains in (R) side of face and chest X-ray revealed multiple metastases throughout both lung fields. Further course of intravenous cyclophosphamide with complete relief of facial pain within 5 days. Patient fit and well at last review 18/3/64, continuing treatment.
Autopsy/	

Table 19b (continued)

Autopsy report:	-
Result:	Local recurrence and solitary lung metastasis remained static during 8 months of cytotoxic therapy. Subsequent flare-up of disease after radiotherapy. Further relief of symptoms from intravenous cyclophosphamide given by continuous effusion. Remaining well but with slowly advancing disease at end of period of review. 2-3 for 1 year 3 months.

Case No. 104: Salivary Gland Tumour

Fig. 1: Recurrent tumour 7/1/63.

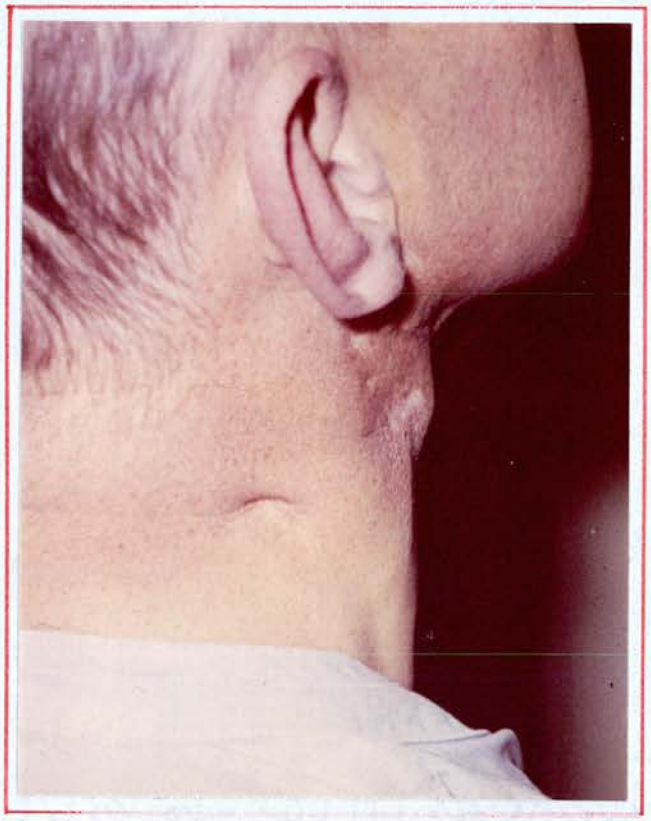
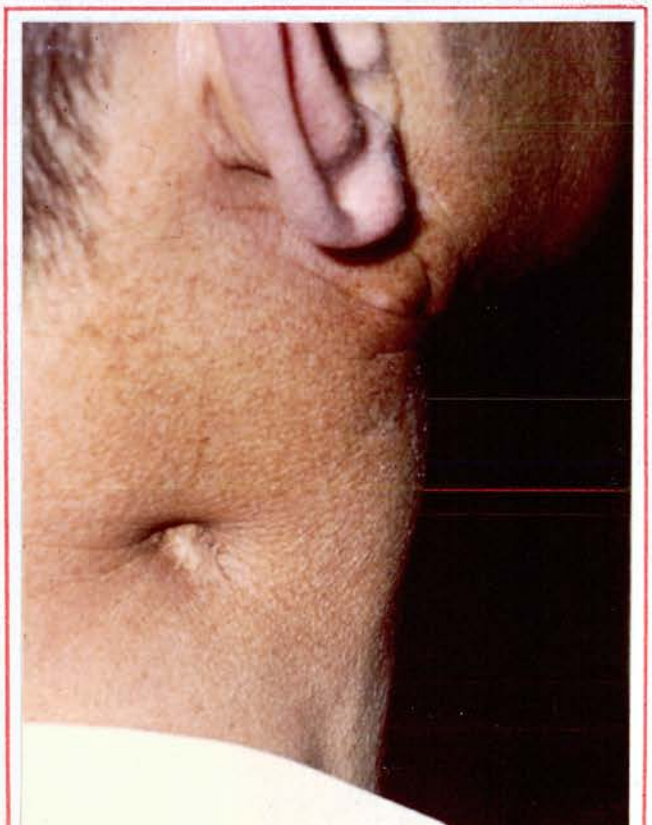


Fig. 2: After cytotoxic therapy 8/8/63.



"OTHERS"

GROUP S : RHABDOMYOSARCOMA

Table 19c

Case: 105	J.S.W. 28/3/63 and 31/8/63 Age: 53 Sex: M
Diagnosis:	Rhabdomyosarcoma of (L) upper arm. Histology - typical appearances of rhabdomyosarcoma.
History:	First noted a small, painless swelling anterior aspect of (R) upper arm in January 1963. First seen in another hospital 18/3/63 when swelling was 1" in diameter. Excised under G.A. and on histology found to be a rhabdomyosarcoma. No symptoms referable to other systems and no significant past or family history.
Previous or concurrent treatment:	(1) Excision biopsy of swelling (R) upper arm: in another hospital 22/3/63 (2) Wide excision of primary site and skin-grafting: under cytotoxic cover 30/3/63 (3) Further wide excision of primary area and sacrifice of anterior muscles: 18/8/63 (4) Radiotherapy: 5,000r to primary area (R) upper arm 6/9/63-11/10/63 (5) Blood transfusion: 2 litres packed cells 21/8/63-4/12/63 (6) Cardiac stimulants: Digoxin and quinine from 23/3/63 (7) Antibiotics: Cristamycin 25/11/63-29/11/63
Cytotoxic treatment:	(1) Mannitol mustard: 1,000 mg. by I.V.I. 29/3/63-16/4/63 (2) Cyclophosphamide: 3,000 mg. by I.V. infusion between 25/11/63 and 27/11/63
Clinical course and comments:	Presented with small lesion on (R) upper arm which unexpectedly proved to be a rhabdomyosarcoma. Primary area widely excised on 30/3/63 under cytotoxic "cover" but skin grafts repeatedly failed to take, local recurrence occurred and further wide excision was required 18/8/63 leaving a large granulating surface. At this stage a course of megavoltage radiotherapy was completed without incident. Marked pigmentation of arm, slow healing. By 1/11/63, however, (R) forearm swollen and there was evidence of recurrent tumour. Doubtful metastases on X-ray of chest. Course of cyclophosphamide infused intravenously (R) arm produced some improvement and forequarter amputation was considered. Cardiac state, which had been poor since first anaesthetic, was now worse and required further treatment. Forequarter amputation finally carried out on 4/12/63 but operation unfortunately coincided with severe fall in WBC to 700. Immediate postoperative state critical with severe respiratory distress from tension pneumothorax, developed congestive cardiac failure and died, possibly with terminal septicaemia, on 7/12/63.
Autopsy/	

Table 19c (continued)

Autopsy report:	Respiratory failure secondary to collapse of (R) lung and myocardial infarct. Possibly an example of septicaemic shock. Two small metastases posterior surface (R) lung but none elsewhere.
Result:	Rapidly progressing sarcoma not influenced by any form of treatment. Cytotoxins of no benefit, produced severe bone marrow depression and probably resulted in graft failure and terminal septicaemia. 0-1 for 9 months.

Case No. 105

Fig. 1: Chest X-ray 18/3/63.

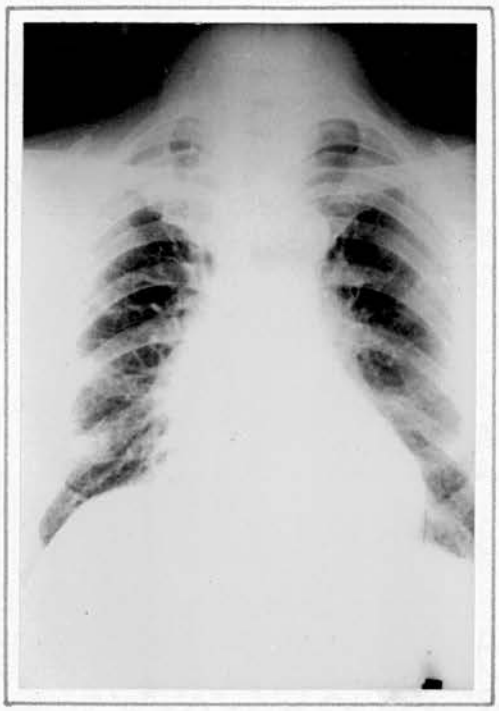


Fig. 2: R. Upper arm 22/3/63.

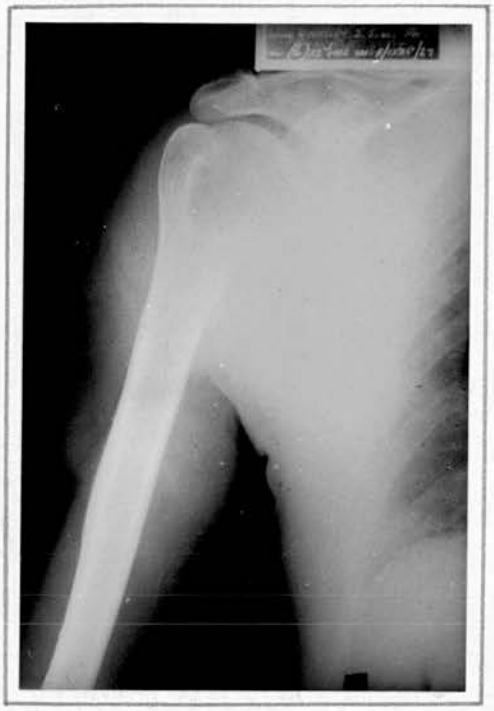


Fig. 3: Chest X-ray 29/11/63.

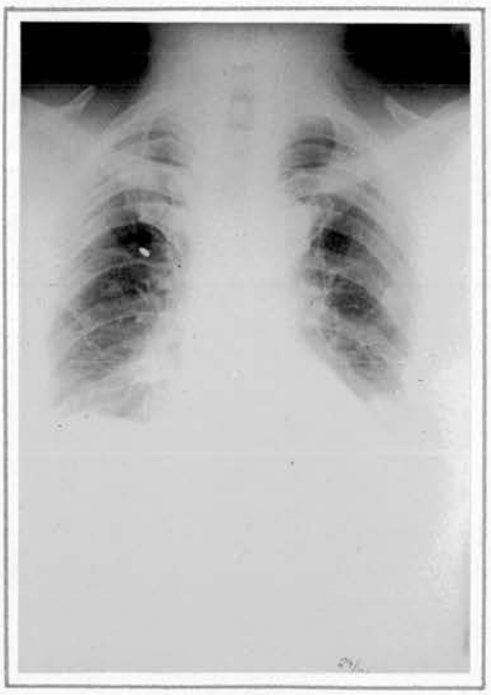
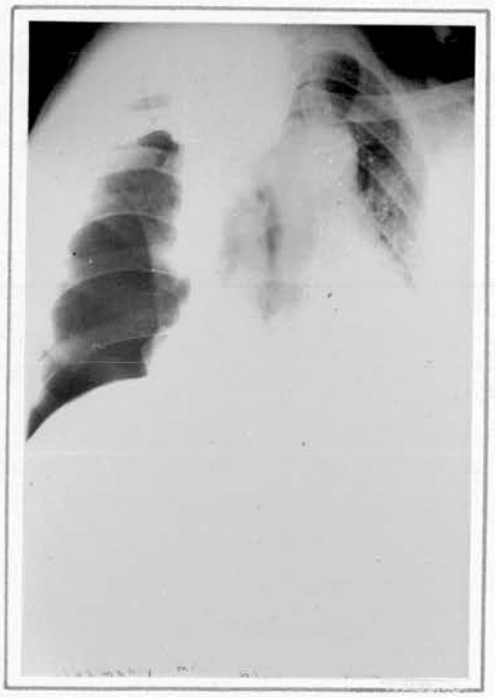


Fig. 4: Chest X-ray 6/12/63.
6 hours post-operation



Case No. 105

Fig. 5: Chest X-ray 6/12/63. 12 hours post-operation

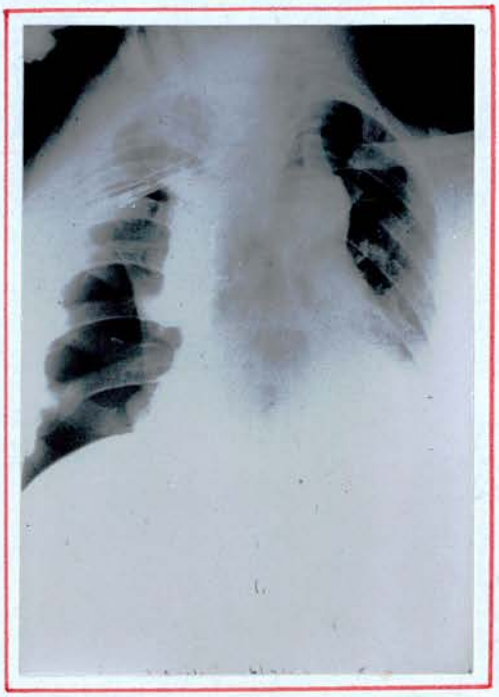


Fig. 6: View of rhabdomyosarcoma R. arm before operation

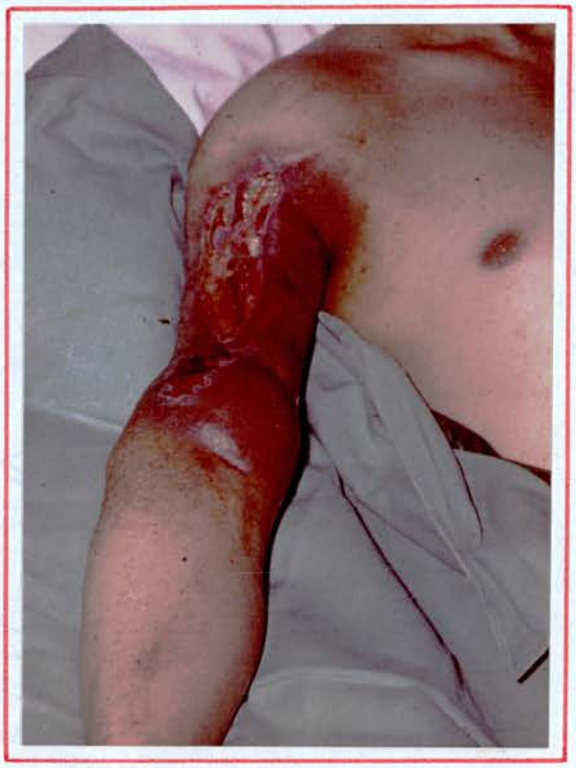


Fig. 7: View of rhabdomyosarcoma R. arm before operation

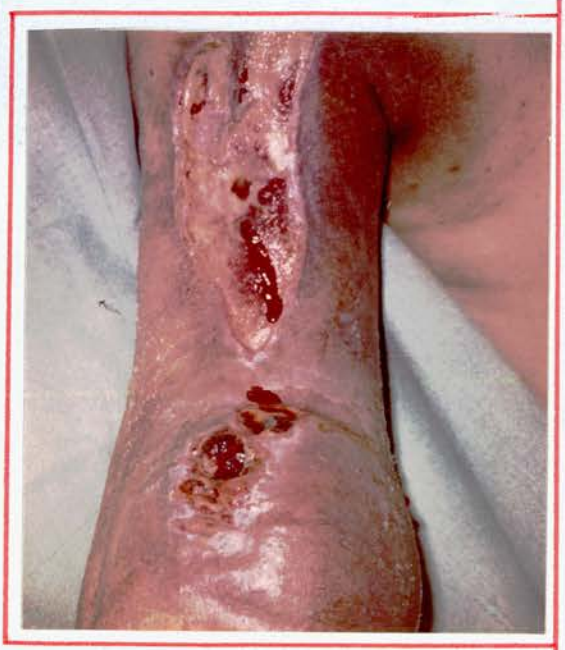
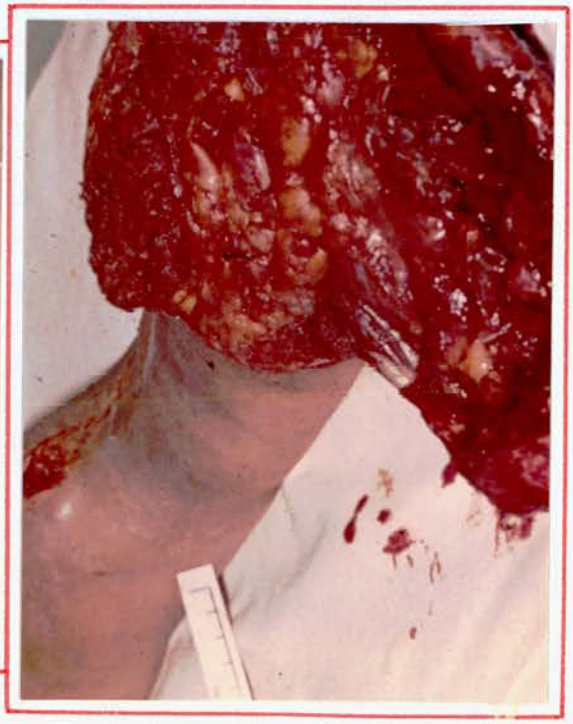


Fig. 8: View of rhabdomyosarcoma R. arm after operation



"OTHERS"

GROUP S : TUMOURS OF BONE

Table 19d

Case: 106	M.M.H. 5/9/63 Age: 45 Sex: F	
Diagnosis:	Chondro-fibrosarcoma of left tibia.	
History:	15 month history of progressive swelling over upper end of (L) tibia. Initially pain free but increasing ache amounting, on occasion, to gnawing pain over swelling for 6 months. Walking with a limp. General health otherwise excellent and no other symptoms. No relevant past or family history.	
Previous or concurrent treatment:	(1) Drill biopsy of tumour:	12/9/63
	(2) Radiotherapy: 6,200r to tumour (L) upper tibia	9/9/63-21/10/63
	(3) (L) mid thigh amputation:	4/12/63
	(4) Physiotherapy:	
	(5) Blood transfusion: 3 pints whole blood	4/12/63
Cytotoxic treatment:	(1) Mannitol mustard: 500 mg. by I.V.I. (operation cover) (5 x 100 mg.)	10/9/63-14/9/63
Clinical course and comments:	Clinically and radiologically, slowly growing malignant tumour of (L) tibia. No other lesions. After initial 1,050r to tumour, drill biopsy was carried out and confirmed diagnosis of chondro-fibrosarcoma. Course of radiotherapy completed without incident. After interval of 3 months, without appearance of metastases, a (L) mid thigh amputation was carried out. Uncomplicated postoperative recovery, but stump slow to heal. Remaining well and free of evidence of recurrence of disease at review March 1963.	
Autopsy report:	-	
Result:	Cytotoxin given as "cover" for drill biopsy and not possible to assess result. No adverse effects other than area of induration at site of cytotoxic injection (R) arm - no actual ulceration.	

Case No. 106: Osteogenic Sarcoma of Tibia

Fig. 1: X-ray of Tumour.

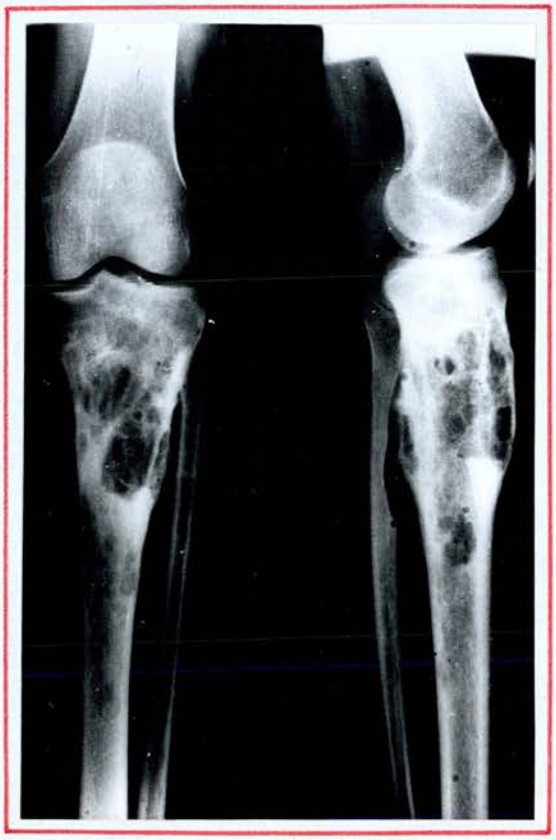


Fig. 2: Appearance of Affected Limb.

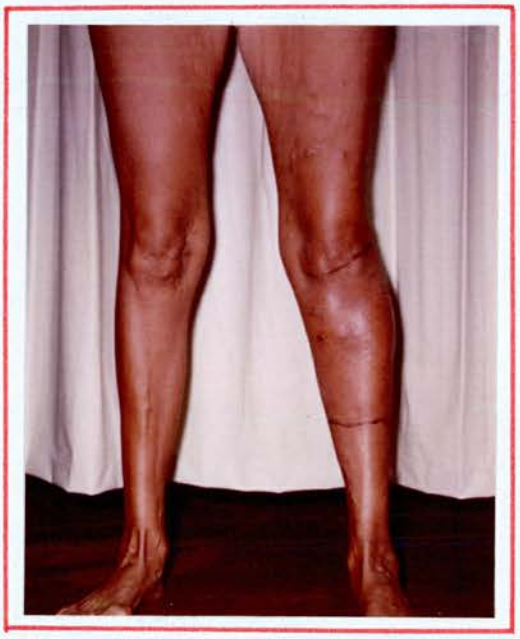
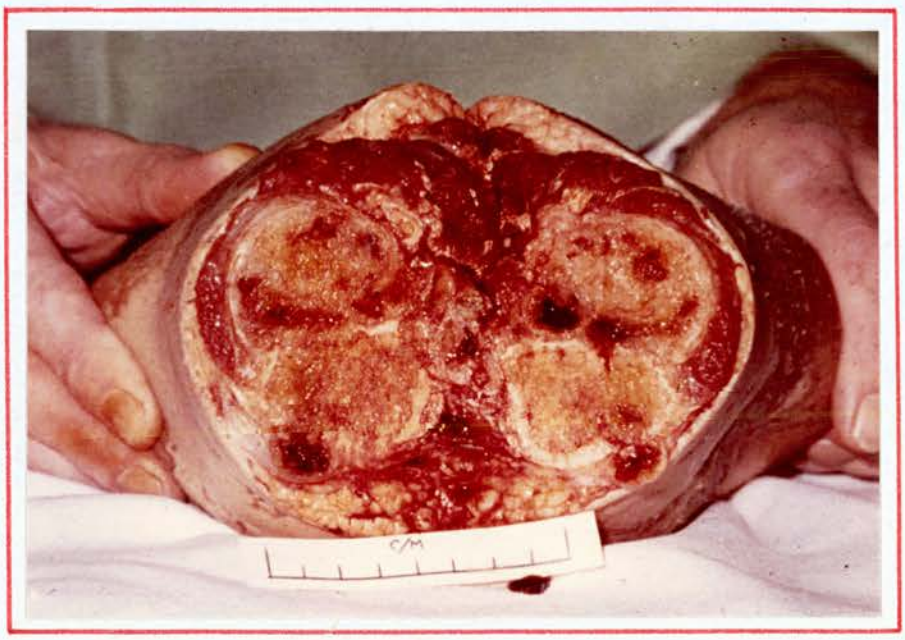


Fig. 3: Cut Surface of Tumour After Limb Amputation.



"OTHERS"

GROUP S : CEREBRAL TUMOURS

Table 19e

Case: 107	W.J.P. 9/4/62 and 11/10/63 Age: 39 Sex: M
Diagnosis:	Frontal astrocytoma, Grade III.
History:	First admitted to another hospital on 26/3/62 with a 15-month history of headaches, minimal paraesthesiae in (R) arm and recent vomiting. Investigations confirmed presence of a space-occupying lesion (L) anterior temporo-frontal region. (L) frontal-lobectomy 29/3/62 established the lesion as a Grade III astrocytoma. Uninterrupted postoperative recovery and transferred for further management on 9/4/62. No previous or family history of significance.
Previous or concurrent treatment:	(1) (L) frontal lobectomy: for Grade III astrocytoma - at another hospital 29/3/62 (2) Radiotherapy: to (L) fronto-temporal region - dose not known 17/4/62-5/6/62
Cytotoxic treatment:	(1) Cyclophosphamide: 800 mg. by I.V.I. (4 x 200 mg.) 28/10/63-3/11/63
Clinical course and comments:	Following initial surgery and course of postoperative radiotherapy patient remained remarkably well and at successive reviews between 10/7/62 and 11/10/63 was judged free of recrudescence of disease. Appetite, weight and general health excellent. Returned to work and to driving a car. No detectable neurological defect or personality change. Readmitted 11/10/63 with 6-day history of recurrent headaches and occasional vomiting. Within a few days he was experiencing frequent, severe frontal headaches, vomiting and demonstrating episodes of bizarre behaviour. General state remained good but general deterioration in mental state with occasional lucid periods. Cyclophosphamide was started 28/10/63, but insufficient given and increasing vegetation to death on 27/11/63.
Autopsy report:	No post-mortem obtained.
Result:	Complete and prolonged remission from surgery and radiotherapy for advanced cerebral tumour. Cytotoxins exhibited late in terminal illness and produced no obvious benefit. 0 for 1 month following cytotoxins.

TABLE 20

CHEMOTHERAPY OF CANCER

DURATION OF SURVIVAL - RESULTS BY SEX

	SEX	DURATION OF SURVIVAL							TOTALS	
		Less than 6 Months	6-12 Months	13-18 Months	19-24 Months	Over 24 Months	5 Years	Alive at Last Review		
1. Survival From Commencement of Cytotoxic Therapy	M	39	7	2	1	-	-	13	62	107
	F	18	7	3	1	-	-	16	45	
2. Survival from Diagnosis of Disease	M	27	16	3	1	2	-	13	62	107
	F	13	8	4	1	1	2	16	45	

Total Cases : 107

Deaths : 78

Alive at last Review : 29

CHEMOTHERAPY OF CANCER

AGENTS USED - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS : 107 CASES

TABLE 21

CYTOTOXIC AGENTS	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Alkylating Agents	M	6*	2*	1	-	-	-	1	-	2	11	11
(a) Nitrogen Mustard	F	-	-	-	-	-	-	-	-	-	-	
(b) Cyclophosphamide	M	4	13	2	3	-	8	8	1	11	50	83
	F	-	2	-	-	16	8	3	-	4	33	
(c) Thiotepa	M	-	1	1	-	-	-	5	-	2	9	18
	F	-	-	-	-	3	4	-	-	2	9	
(d) Mannitol Mustard	M	5*	2*	-	-	-	4	1	-	2	13	28
	F	-	1	-	-	11	-	-	-	3	15	
(e) Uracil Mustard	M	1	-	-	-	-	-	-	-	-	1	1
	F	-	-	-	-	-	-	-	-	-	-	
(f) Melphelan	M	-	-	-	-	-	-	-	1	-	1	3
	F	-	-	-	-	-	-	-	2	-	2	
2. Antimetabolites	M	-	-	-	-	-	3	6	-	-	9	14
(a) Methotrexate	F	-	1	-	-	1	-	1	1	1	5	
(b) Chlorambucil	M	1	1	1	-	-	-	-	-	-	3	4
	F	1	-	-	-	-	-	-	-	-	1	
(c) Fluouracil	M	-	-	-	-	-	1	-	-	1	2	2
	F	-	-	-	-	-	-	-	-	-	-	
(d) 6 Mercaptopurine	M	-	-	-	1	-	-	-	-	-	1	1
	F	-	-	-	-	-	-	-	-	-	-	

TABLE 21 (continued)

CYTOTOXIC AGENTS	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
3. Antibiotics and Plants	M	-	-	-	-	-	-	7	-	-	7	12
(a) Thiocolciran	F	-	1	-	-	2	-	2	-	-	5	
(b) Vinblastine Sulphate	M	4	4	1	-	-	5	1	-	4	19	29
	F	1	-	-	-	2	4	2	-	1	10	
(c) 2-Ethyl-hydrazine	M	-	-	-	-	-	-	-	-	-	-	2
	F	-	-	-	-	-	-	-	2	-	2	
(d) Imuran	M	1	-	-	-	-	-	-	-	-	1	1
	F	-	-	-	-	-	-	-	-	-	-	

40 patients (19 female, 21 male) were treated with one agent only

45 patients (17 female, 28 male) were treated with two agents in combination

7 patients (4 female, 3 male) were treated with three agents in combination

15 patients (5 female, 10 male) were treated with four or more in combination

CHEMOTHERAPY OF CANCER

USE OF HORMONES - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS

TABLE 22

NATURE OF HORMONES	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Corticosteroids	M	3	2	1	4	-	2	1	-	3	16	26*
	F	1	-	-	-	6	-	1	-	2	10	
2. Sex Hormones	M	-	-	-	-	-	2	-	-	1	3	9+
	F	-	1	-	-	5	-	-	-	-	6	

* In 13 patients (4 female, 9 male) corticosteroids were used for their anti-mitotic effects.

In 13 patients (6 female, 7 male) corticosteroids were used as supportive therapy.

\+ In 8 patients (6 female, 2 male) sex hormones were used for their anti-mitotic effects.

In 1 male patient sex hormones were used as supportive therapy.

METHODS OF APPLICATION - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS

TABLE 23

METHOD OF APPLICATION	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Prophylactic	M	1*	2*	-	-	-	3	4	1	2	12	34+
	F	-	1	-	-	15	4	-	-	2	22	
2. As adjunct to: (a) Radiotherapy	M	4*	7*	3	-	-	4	5	-	6	29	58✓
	F	1	1	-	-	17	4	2	1	3	29	
(b) Surgery	M	-	4	1	-	-	7	6	1	2	21	36✓
	F	-	-	-	-	11	2	-	-	2	15	
3. Used alone	M	2	5	-	4	-	2	6	-	3	22	34
	F	-	1	-	-	2	4	2	1	2	12	

* 1 case with Hodgkin's disease and carcinoma of lung

\+ 22 patients (11 female, 11 male) subsequently received cytotoxins as adjuvant therapy in addition to prophylactically and are included in both groups

✓ 23 patients (11 female, 12 male) were treated by surgery and radiotherapy and are included in both groups

ROUTES OF ADMINISTRATION - RESULTS BY SEX AND AGENT USED : 107 CASES

TABLE 24

Agents	Topical		By Mouth		Intravenous				Intra-arterial						Intracavitary			
					Injection		Infusion		Injection		Infusion		Perfusion		Peritoneal		Pleural	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1. N	-	-	-	-	11	-	-	-	-	-	-	-	-	-	-	-	-	-
2. C	1	-	27	20	38	23	17	5	1	2	2	8	-	-	1	2	1	5
3. P	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-
4. D	-	-	2	1	9	15	4	-	-	-	-	-	-	-	-	-	-	-
5. U	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6. CL	-	-	3	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7. Th	1	-	-	-	-	2	-	-	-	-	-	-	-	-	3	7	4	3
8. M	-	-	9	4	1	-	2	1	-	-	-	-	-	-	-	-	-	-
9. MP	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10. F	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-
11. V	-	-	-	-	20	10	-	-	-	-	-	-	-	-	-	-	-	-
12. EH	-	-	-	-	-	-	-	1	-	2	-	1	-	-	-	-	-	-
13. TC	-	-	-	-	7	4	-	-	-	-	-	-	-	-	-	1	-	-
14. I	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTALS	2	-	44	26	88	54	23	7	1	4	2	10	-	-	4	10	5	8

35 Patients were given cytotoxic agents by one route only

55 Patients were given cytotoxic agents by two routes

17 Patients were given cytotoxic agents by three or more routes

RESULTS OF LIVER FUNCTION TESTS, SERUM PROTEINS, ELECTROPHORESIS AND URIC ACID

TABLE 25

GROUP A : HODGKINS DISEASE

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
1 (J.G.)	11/1/62	0.5	4.5	1	3	9	-	+	7.4	4.9	2.4	1.7:1	+	+	N	N	-	(1) Vinblastine Sulphate: 15/1/62
	20/2/62	0.7	5.0	1	3	11	-	-	6.8	4.3	2.5	1.6:1	+	+	N	N	3.0	(2) Prednisone: 14/9/61 (Chlorambucil: 22/8/60)
	27/6/62	0.5	6.5	2	1	-	-	+	6.0	4.1	1.9	2.1:1	N	+	N	N	3.5	
	11/1/64	0.6	5.0	2	1	8	-	-	6.3	4.1	2.2	1.9:1	N	+	N	N	-	
2 (P.O.)	5/3/62	0.4	32	-	7	6	-	+	7.8	4.7	3.1	1.3:1	+++	+++	N	N	3.0	(1) Mannitol Mustard: 9/3/62
	26/3/62	0.3	23.1	1	2	-	-	-	-	-	-	-	-	-	-	-	-	(2) Vinblastine Sulphate: 16/3/63
	17/9/62	0.2	20.4	-	2	7	-	-	5.7	4.1	1.6	2.6:1	+++	++	+	D	4.1	(3) Nitrogen Mustard: 2/4/63
	12/12/62	0.6	18	1	4	-	-	N	-	-	-	-	-	-	-	-	-	(4) Cyclophosphamide: 1/6/63
	8/3/63	0.4	14	1	5	-	-	-	5.9	3.8	2.1	1.8:1	+	++	+	N	3.8	(5) Uracil Mustard: 2/7/63
	28/5/63	0.4	16.1	5	8	6	-	-	5.4	-	-	-	-	-	-	-	2.7	
	7/6/63	-	-	-	-	-	-	-	7.0	4.3	2.7	1.8:1	+	++	N	N	2.9	
3 (G.R.)	10/7/62	0.6	6.7	2	6	10	-	N	6.5	3.9	2.6	1.8:1	0.23	1.02	0.62	0.44	-	(1) Nitrogen Mustard: 18/7/62
	27/8/62	0.4	4.0	3	4	8	-	-	6.3	4.0	2.3	1.8:1	N	++	N	N	4.3	(2) Mannitol Mustard: 25/7/62
	28/5/63	0.4	9.8	4	8	-	-	-	6.4	4.0	2.4	1.7:1	N	+	N	N	5.0	(3) Vinblastine Sulphate: 21/5/63
	5/9/63	0.5	10.6	5	10	7	-	-	5.3	3.7	1.6	2.3:1	N	++	N	N	6.0	(4) Cyclophosphamide: 4/9/63

GROUP A : HODGKINS DISEASE (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
4 (J.B.)	24/7/62	0.4	12.7	1	4	6.0	-	N	6.0	4.0	2.0	2:1	+	++	N	N	-	(1) Vinblastine Sulphate: 4/10/62
	5/11/62	0.6	12.0	2	3	-	-	-	5.0	3.2	1.8	1.8:1	++	+	N	N	-	(2) Nitrogen Mustard: 4/1/63
	10/1/63	-	-	-	-	-	-	-	5.8	3.9	1.9	2.0:1	+++	N	N	N	6.4	(3) Mannitol Mustard: 11/4/63
	4/3/63	0.7	15.3	1	5	10	-	+	4.9	3.5	1.4	2.5:1	-	-	-	-	-	(4) Imuran: 19/3/63
	27/3/63	2	20.6	3	4	12	-	-	5.2	3.5	1.7	2.0:1	++	N	N	N	5.0	
5 (W.McG)	15/8/62	0.5	11.7	3	5	22	-	+	6.6	4.5	2.1	2.0:1	N	+	N	N	-	(1) Nitrogen Mustard: 22/10/62
	17/11/62	0.4	32.0	1	3	53	-	+	6.4	4.1	2.3	1.8:1	N	+	N	N	6.0	(2) Mannitol Mustard: 31/10/62
	12/12/62	-	-	-	-	-	-	-	7.4	4.8	2.6	1.8:1	N	+	N	N	4.8	
	10/1/63	0.5	15.0	1	3	24	-	-	-	-	-	-	-	-	-	-	-	
	8/3/63	0.25	11.3	1	7[illegible]	20	-	N.[illegible]	6.6	4.5	2.1	2.1:1	N	N	N	N	4.3	
	19/4/63	-	-	-	-	-	-	-	6.0	4.0	2.0	2.0:1	N	+	N	N	3.8	
6 (G.C.)	9/4/62	0.5	9.6	5	9	3	-	-	-	-	-	-	-	-	-	-	-	(1) Nitrogen Mustard: 7/5/62
	13/4/62	0.4	8.0	4	8	3	7.0	-	7.5	4.7	2.8	1.7:1	0.36	1.27	0.27	1.06	6.4	(2) Mannitol Mustard: 14/5/62
	1/5/62	0.1	12.2	2	4	66	-	N	6.0	4.0	2.0	2.0:1	+	++	N	N	6.0	(3) Chlorambucil: 14/12/62
	17/10/62	0.4	10	2	6	8	-	-	6.3	4.1	2.2	1.8:1	+	++	N	N	-	(4) Vinblastine Sulphate: 19/12/63
	10/1/64	0.6	11	3	6	10	-	-	6.5	4.1	2.4	1.7:1	+	+	N	N	3.8	(5) Cyclophosphamide: 11/1/64
7 (R.P)	8/1/64	0.1	10.1	3	11	-	-	-	5.8	3.0	2.8	1.2:1	0.32	1.0	0.6	0.9	4.2	(1) Nitrogen Mustard: 9/1/64
	28/1/64	0.2	13	3	12	-	-	-	4.9	3.2	1.7	2.0:1	0.20	0.9	0.1	0.5	5.2	(2) Cyclophosphamide: 16/1/64
	8/2/64	0.4	15	4	15	18	-	-	4.8	2.0	2.8	1:1.2	0.4	1.2	0.4	0.9	5.4	

TABLE 25

GROUP B : CARCINOMA OF LUNG

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
8 (A.W.)	10/1/63	0.6	20	6	4	30	-	+	7.0	4.0	3.0	1.3:1	0.30	1.0	0.6	1.1	-	(1) Cyclophosphamide: 11/1/63
	21/1/63	0.4	13.6	5	4	9	-	+	7.6	3.4	4.2	1:1.2	0.49	0.9	1.1	1.7	8.0	(2) Vinblastine Sulphate: 30/5/63
	24/5/63	0.8	21.6	8	4	34	-	+	7.1	4.0	3.1	1.3:1	-	-	-	-	-	
	25/5/63	-	-	-	-	-	-	+	6.6	3.0	3.6	1:1.1	0.43	1.0	0.87	1.34	6.2	
	17/6/63	3.0	34	8	3	-	-	-	6.2	3.4	2.8	1.2:1	-	-	-	-	-	
9 (J.G.)	8/10/63	0.25	9.8	8	11	-	-	-	7.3	4.9	2.4	2.0:1	N	++	N	N	-	(1) Cyclophosphamide: 28/10/63
	28/10/63	0.6	8.2	9	10	-	-	-	6.6	4.3	2.3	1.9:1	+++	++	N	N	4.9	(2) Vinblastine Sulphate: 30/10/63
	6/11/63	0.4	8	8	10	-	-	-	6.5	4.3	2.2	1.9:1	++	++	N	N	4.8	
10 (T.W.)	21/11/62	2.3	99.3	2	6	33	-	+	6.6	4.5	2.1	2.2:1	-	-	-	-	-	(1) Chlorambucil: 29/11/63
	23/11/62	-	-	-	-	-	-	-	6.7	3.3	3.4	1:1	0.28	1.3	0.8	1.0	-	(2) Cyclophosphamide: 20/12/63
	7/12/62	1.9	9.0	3	8	30	-	+	6.4	3.3	3.1	1.1:1	0.20	1.2	0.6	1.0	4.0	
	30/1/63	0.3	7	2	10	-	-	-	6.8	4.0	2.8	1.5:1	0.22	1.0	0.5	1.1	3.8	
11 (L.T.)	22/11/63	0.7	31.0	1	1	36	20	-	5.1	3.0	2.1	1.4:1	+	++	N	N	-	(1) Cyclophosphamide: 2/12/63
	28/11/63	0.5	28.5	3	1	42	-	-	5.2	4.3	1.9	2.1:1	-	-	-	-	-	
	2/12/63	0.3	35.4	4	10	-	-	-	5.8	2.3	3.5	1:1.4	0.68	1.27	0.93	0.68	2.4	
	12/12/63	0.4	40	4	12	48	-	-	5.5	2.8	2.7	1:1	0.60	1.10	0.60	0.51	4.0	

TABLE 25

GROUP B : CARCINOMA OF LUNG (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
12 (H.S.)	23/1/63	1.3	14.3	2	2	17	-	-	7.0	4.2	2.8	1.5:1	+	++	N	N	-	(1) Thiotepa: 1/3/63
	26/2/63	0.3	16	1	7	-	-	+	6.4	3.7	2.7	1.4:1	+	++	N	N	6.8	(2) Cyclophosphamide:
	11/3/63	0.4	15	2	8	20	-	-	-	-	-	-	-	-	-	-	6.2	1/3/63
	26/4/63	0.5	12	2	6	22	-	N	6.2	3.2	3.0	1.1:1	N	+	N	N	5.0	
	17/3/64	0.4	8	4	6	10	-	-	6.7	3.6	3.1	1.2:1	N	+	N	N	5.2	
13 (J.P.)	2/3/63	0.4	11	4	10	30	-	+	5.8	3.6	2.2	1.5:1	+	+	N	N	4.0	(1) Nitrogen Mustard:
	12/3/63	0.5	10	3	10	28	-	-	6.0	4.2	1.8	2.2:1	+	+	N	N	-	4/3/63
	14/4/63	0.5	12	4	8	-	-	N	5.7	3.6	2.1	1.6:1	-	-	-	-	4.4	(2) Cyclophosphamide:
	20/8/63	0.3	14	9	12	40	-	-	5.7	4.4	1.3	3:1	++	+	N	N	4.2	20/8/63
14 (A.M.)	28/2/63	0.2	18.0	2	8	28	-	++	5.8	4.0	1.8	2.1:1	N	+	N	N	4.2	(1) Cyclophosphamide:
	28/3/63	0.3	22.0	1	7	42	-	+	5.9	3.8	2.1	1.8:1	-	-	-	-	6.0	1/4/63
	30/3/63	-	-	-	-	-	-	-	6.5	3.1	3.4	1:1.1	0.23	1.03	0.86	1.18	-	
	10/4/63	0.25	24.8	7	6	-	-	+	6.2	4.0	2.2	2:1	0.16	1.0	0.23	0.91	5.8	
15 (A.P.)	8/4/63	0.2	10.0	5	3	20	-	N	3.0	5.1	2.9	1.8:1	N	N	N	N	3.0	(1) Mannitol Mustard:
	19/4/63	0.4	12.0	6	4	-	-	-	6.4	4.7	1.7	2.8:1	N	N	N	N	3.2	11/4/63
	29/4/63	0.6	15.0	7	4	22	-	-	6.7	4.6	2.1	2.1:1	N	N	N	N	2.6	(2) Cyclophosphamide:
																		2/5/63
16 (E.W.)	29/4/63	0.5	11.3	8	6	28	-	-	7.7	5.2	2.5	2:1	+	++	N	N	-	(1) Cyclophosphamide:
	10/5/63	0.8	14.0	7	10	48	-	-	6.0	3.6	2.4	1.5:1	+	++	N	N	5.0	2/5/63
	3/9/63	1.8	10.0	19	9	55	-	-	5.3	3.4	1.9	1.8:1	N	+	N	N	4.8	(2) Vinblastine
																		Sulphate: 30/5/63
17 (J.W.)	15/8/63	0.2	5	8	10	28	-	-	7.4	4.6	2.8	1.8:1	N	N	N	N	3.8	(1) Cyclophosphamide:
	22/8/63	0.1	6	8	12	-	-	N	6.2	3.2	3.0	1:1	0.14	0.69	0.87	1.28	4.1	14/8/63
	20/10/63	0.3	6	7	11	40	-	-	6.4	3.8	2.6	1.4:1	0.20	0.80	0.60	1.08	3.7	

TABLE 25

GROUP B : CARCINOMA OF LUNG (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
18 (A.McL)	10/6/63	0.5	11.0	4	3	48	-	+	6.0	3.2	2.8	1.2:1	+	++	N	N	4.0	(1) Mannitol Mustard: 13/6/63
	20/6/63	0.5	10.5	4	4	50	-	-	6.1	3.7	2.4	1.5:1	0.25	1.0	0.35	0.80	6.3	(2) Cyclophosphamide: 23/6/63
	28/6/63	0.4	15.0	5	7	-	-	+	7.0	2.9	4.1	1:1.3	0.26	1.20	0.78	0.67	6.2	
	26/7/63	7.5	37.6	9	10	54	-	-	6.9	4.9	2.0	2.5:1	-	-	-	-	-	
	31/7/63	9.2	40.5	12	15	60	-	-	7.4	4.8	2.6	1.8:1	0.24	1.10	0.62	0.64	6.8	
19 (A.F.)	27/5/63	0.3	7.7	1	3	7	-	N	8.0	4.6	3.4	1.3:1	++	+++	N	N	-	(1) Cyclophosphamide: 29/6/63
	3/7/63	0.5	8	2	4	-	-	-	6.2	2.5	3.7	1:1.2	0.62	1.53	N	N	6.4	(2) Vinblastine Sulphate: 20/7/63
	28/7/63	0.5	21.6	4	6	45	20	+	6.4	3.0	3.4	1:1.1	0.52	1.40	0.61	0.90	5.2	
	25/8/63	0.4	23	4	8	50	22	-	-	-	-	-	-	-	-	-	-	
20 (R.C.)	9/10/63	0.25	17.2	5	9	5	10	N	5.9	3.0	2.90	1.0;1	0.50	1.0	0.94	1.2	7.1	(1) Cyclophosphamide: 16/10/63
	24/10/63	0.40	22	6	14	-	-	+	6.0	3.2	2.8	1.1:1	0.54	1.2	0.80	1.06	6.4	
	22/12/63	0.8	28	7	14	20	-	-	5.8	2.4	3.4	1:1.3	+++	++	N	N	5.1	
21 (M.W.)	4/9/65	0.4	6	3	-	-	-	-	7.7	3.5	3.2	1.1:1	0.30	0.80	1.10	1.90	3.9	(1) Cyclophosphamide: 26/8/65
	16/9/65	-	-	-	-	-	-	-	8.0	4.1	3.9	1:1	0.40	0.90	1.20	1.50	3.6	(2) Thiocolciran: 21/10/65
	23/9/65	-	-	-	-	-	-	-	6.5	3.6	2.9	1.2:1	0.30	0.80	0.70	1.10	-	(3) Methotrexate: 21/10/65
	28/9/65	-	-	-	-	-	-	-	6.7	3.1	3.6	1:1.2	0.30	0.80	1.10	1.40	3.5	(4) 2-ethyl-hydrazine: 19/1/66
	4/10/65	-	-	-	-	-	-	-	7.2	3.6	3.6	1:1	0.30	0.90	1.20	1.30	-	
	7/10/65	-	-	-	-	-	-	-	6.6	2.6	4.0	1:1.4	0.30	0.90	1.10	1.60	3.7	
	14/10/65	-	-	-	-	-	-	-	6.3	3.0	3.3	1:1.1	0.30	0.80	1.00	1.20	5.0	
	28/10/65	-	-	-	-	-	-	-	6.9	3.2	3.7	1:1.2	0.30	1.00	1.00	1.50	4.0	
	11/11/65	-	-	-	-	-	-	-	6.1	2.4	3.7	1:1.5	0.60	1.30	0.80	1.00	2.9	
	23/12/65	0.5	12	2	-	-	-	-	7.0	3.4	3.6	1:1	0.40	1.10	0.90	1.30	4.0	
	3/1/66	-	-	-	-	-	-	-	7.9	3.7	4.2	1:1.2	0.40	1.10	0.90	1.30	13.4	
	20/1/66	0.5	12	1	-	-	-	-	6.9	2.8	4.1	1:1.5	0.50	1.50	0.90	1.20	5.6	
22 (J.M.)	30/3/65	0.6	11	1	-	20	-	-	5.0	2.2	2.8	1:1.2	0.20	1.10	0.70	0.90	3.7	(1) Cyclophosphamide: 2/4/65
	3/4/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.8	
	5/4/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.0	
	7/4/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.7	
	9/4/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.3	
	13/4/65	0.6	10	2	-	20	-	-	4.1	1.2	2.9	2.1:1	0.22	1.18	0.60	1.00	4.2	
	15/4/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.9	

TABLE 25

GROUP C : LYMPHOSARCOMA

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
23 (T.W.)	22/4/63	0.2	9.3	5	2	20	-	N	6.9	4.4	2.5	1.9:1	0.16	0.96	0.50	0.80	6.4	(1) Thiotepa: 20/4/63
	7/5/63	0.3	8.7	4	4	24	-	-	6.7	3.8	2.9	1.2:1	0.25	1.15	0.88	0.57	6.8	(2) Nitrogen Mustard: 23/4/63
	28/5/63	0.25	11.1	4	4	-	-	N	5.4	3.4	2.0	1.6:1	0.10	0.91	0.50	0.54	7.0	(3) Vinblastine Sulphate: 21/5/63
	5/7/63	0.4	12	4	5	28	-	-	5.2	2.6	2.6	1:1	0.12	1.10	0.82	0.66	6.3	(4) Cyclophosphamide: 30/5/63
24 (T.H.W.)	10/9/63	0.6	8	3	4	8	-	N	5.8	3.2	2.6	1.2:1	N	+	N	N	5.1	(1) Chlorambucil: 12/9/63
	20/9/63	0.7	7	3	2	14	-	N	5.9	3.6	2.3	1.5:1	N	+	N	D	5.6	
	28/11/63	0.4	3	4	4	10	-	-	6.1	3.3	2.8	1.1:1	N	+	N	D	4.0	
	12/3/64	0.5	6	3	4	18	-	-	6.0	3.1	2.9	1:1	N	+	N	N	-	
25 (D.W.)	26/3/63	0.4	6	3	5	20	-	-	5.8	3.6	2.2	1.5:1	N	+	N	N	5.1	(1) Cyclophosphamide: 2/10/63
	2/8/63	0.5	8	2	6	-	-	-	6.0	3.7	2.3	1.3:1	N	+	N	N	-	
	15/8/63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	45	(2) Vinblastine Sulphate: 2/12/63
	16/8/63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	42.5	
	17/8/63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20.0	
	20/8/63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15.2	
	23/8/63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.1	
	26/8/63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.6	
	1/12/63	0.6	7	3	6	18	12	-	6.2	3.8	2.4	1.4:1	0.20	1.10	0.40	0.70	6.7	

TABLE 25

GROUP D : LEUKAEMIA

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
26 (B.W.)	26/6/62	0.3	5	2	3	78	-	+	5.4	3.2	2.2	1.4:1	+	+	N	D	-	(1) Cyclophosphamide: 13/6/63
	30/5/63	0.25	5.4	6	3	-	-	-	5.2	4.3	0.9	4.8:1	N	N	D	D	-	
	17/6/63	0.2	5.9	7	3	28	-	-	5.6	3.5	2.1	1.7:1	N	N	D	D	4.8	(2) Prednisone: 24/6/62
	30/6/63	0.4	6	7	4	32	-	-	5.1	3.0	2.1	1.5:1	N	N	N	D	5.2	
27 (T.P.)	23/5/63	0.8	6.3	3	4	24	-	-	6.7	3.2	3.5	1:1	0.78	0.87	0.83	1.30	-	(1) Cyclophosphamide: 4/6/63
	30/5/63	0.5	9.4	8	7	-	-	N	6.6	3.1	3.5	0.9:1	0.29	0.92	0.96	1.50	4.1	
	7/6/63	0.3	9.1	8	7	42	20	-	-	-	-	-	-	-	-	-	5.5	(2) Vinblastine Sulphate: 21/6/63
	13/6/63	0.3	9.1	8	7	-	-	-	6.3	3.4	2.9	1.1:1	0.30	1.01	0.78	0.82	4.1	
	14/7/63	0.4	9.2	7	7	40	28	-	6.4	3.1	3.3	1:1	0.27	1.12	0.83	1.16	4.8	
28 (M.C.C.)	7/6/63	0.6	8.0	5	6	20	14	-	6.2	4.0	2.2	2:1	N	+	N	N	5.7	(1) 6-Mercapto-purine: 24/11/62
	3/7/63	0.7	9.0	6	8	28	20	-	5.8	3.2	2.6	1.2:1	N	+	D	D	6.0	(2) Prednisone: 7/11/62
29 (L.C.)	14/8/63	0.2	7	5	4	-	-	-	7.0	5.3	1.7	3:1	N	N	D	D	6.2	(1) Cyclophosphamide: 30/8/63
	19/8/63	-	-	-	-	-	-	-	6.8	4.9	1.9	2.5:1	N	N	D	D	-	
	28/8/63	0.3	7	6	4	30	20	-	6.9	4.6	2.3	2.0:1	N	+	D	D	6.8	(2) Prednisone: 9/8/63

TABLE 25

GROUP E : MULTIPLE MYELOMA

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
30 (H.V.)	11/2/63	-	-	-	-	-	-	-	11.8	3.5	8.5	"Electrophoretic pattern typical of myeloma"						(1) Cyclophosphamide: 24/2/63
	12/2/63	0.5	5.2	1.0	24	9	-	+	-	-	-	-	-	-	-	-	6.4	
	8/3/63	0.4	4.7	1	40	8	-	+	9.8	2.0	7.8	1:3.8	0.52	1.34	0.57	5.35	7.0	(2) Prednisone: 25/3/63
	11/3/63	-	-	-	-	-	-	-	9.4	1.7	7.7	1:3.9	++	+++	D	+++	-	
	12/3/63	-	-	-	-	-	-	-	9.9	2.7	7.2	1:2.9	0.60	1.08	1.08	5.41	6.3	
	10/4/63	0.4	9.3	7	48	-	-	-	9.5	2.7	6.8	1:2.5	0.82	0.92	0.72	3.8	-	
	17/4/63	0.3	7.3	5	32	-	-	-	8.4	2.75	5.65	1:2.1	0.17	0.96	0.69	3.80	7.2	
	31/5/63	0.6	10	6	47	10	-	-	7.8	3.15	4.65	1:1.5	0.27	0.78	0.70	2.70	-	
	17/6/63	0.9	11.2	3	40	-	-	-	10.0	4.6	5.4	1:2.1	-	-	-	-	7.1	

TABLE 25

GROUP F : CARCINOMA OF BREAST

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
31 (E.B.)	4/1/62	0.6	7.5	4	5	21	8	N	7.0	3.8	3.2	1.1:1	N	+	N	N	-	(1) Cyclophosphamide: 15/1/62
	10/1/62	-	10	-	-	11	-	N	-	-	-	-	-	-	-	-	-	
	26/1/62	0.5	8	4	6	18	4	-	6.8	3.6	3.2	1.2:1	0.26	0.90	0.98	0.89	4.2	(2) Vinblastine Sulphate: 13/9/63
	6/2/62	0.6	7	3	6	-	-	-	6.8	3.8	3.0	1.3:1	0.30	1.0	0.80	0.90	4.8	
	23/8/62	1.8	4.5	1	3	20	8	-	6.3	5.3	1.0	5:1	D	N	D	D	6.0	
	12/3/63	0.2	4.7	1	3	-	-	-	6.5	3.6	2.9	1.2:1	0.50	0.72	0.87	0.72	4.8	
	20/8/63	0.1	6.6	7	5	24	10	N	5.8	3.7	2.1	1.5:1	0.19	0.50	0.89	0.50	6.2	
32 (M.C.)	5/11/62	0.5	4.3	2	5	-	-	-	6.9	4.3	2.6	1.6:1	D	N	N	D	-	(1) Mannitol Mustard: 5/11/62
	18/11/62	0.6	5	3	4	22	8	N	6.8	4.6	2.2	2:1	0.10	0.80	0.70	0.50	4.6	(2) Cyclophosphamide: 6/11/62
33 (D.B.)	15/12/62	0.3	5	1	2	12	-	N	6.4	4.8	1.6	3:1	N	N	N	N	-	(1) Mannitol Mustard: 16/12/62
	28/12/62	0.4	5	2	2	14	-	-	6.6	4.8	1.8	2.8:1	N	N	N	N	5.0	
34 (F.P.)	12/2/63	0.6	4	2	4	15	3	N	6.4	4.2	2.2	1.9:1	N	N	N	N	4.0	(1) Mannitol Mustard: 4/2/63

TABLE 25

GROUP F : CARCINOMA OF BREAST (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
35 (M.G.)	13/2/63	0.4	43	1	8	24	12	++	6.4	4.2	2.1	2:1	N	N	N	N	6.4	(1) Mannitol Mustard: 11/2/63 (2) Cyclophosphamide: 27/2/63
	20/2/63	0.7	24	1	5	20	-	++	7.0	3.7	3.3	1.1:1	0.23	0.92	0.75	1.38	6.7	
	25/2/63	0.7	37	2	8	-	-	-	-	-	-	-	-	-	-	-	-	
	6/3/63	0.5	42.7	1	6	22	8	-	6.6	4.5	2.1	2.1:1	0.21	0.87	0.52	0.52	4.8	
	28/5/63	0.4	20.1	3	3	-	-	++	7.8	5.3	2.5	2:1	-	-	-	-	-	
	3/7/63	0.4	22.8	7	7	24	10	-	7.0	4.1	2.9	1.4:1	0.18	0.74	1.02	1.00	6.0	
	15/8/63	0.4	21	6	5	28	6	-	7.4	5.7	1.7	2.4:1	0.12	0.62	0.40	0.61	6.6	
36 (D.N.)	1/3/63	0.4	8	3	2	-	-	-	6.4	4.2	2.2	1.9:1	N	N	N	N	3.0	(1) Mannitol Mustard: 3/3/63
	14/3/63	0.5	7	3	4	-	-	-	6.5	4.1	2.3	1.8:1	N	N	N	N	3.4	
37 (F.H.)	23/4/63	0.5	12	2	3	28	10	N	6.4	3.2	3.2	1:1	+	+	N	N	-	(1) Mannitol Mustard: 25/4/63 (2) Cyclophosphamide: 24/11/63 (3) Thiotepa: 28/11/63
	25/6/63	0.4	13	2	2	-	-	N	7.5	4.4	3.1	1.4:1	+	+	N	N	5.0	
	27/11/63	0.4	13.8	6	6	28	8	-	7.6	4.5	3.1	1.5:1	0.50	1.02	0.81	0.80	4.7	
	15/1/63	0.5	14	5	6	25	12	-	7.4	4.6	2.8	1.6:1	0.42	1.10	0.72	0.60	4.8	
38 (M.D.)	18/6/63	0.4	6	2	3	10	4	-	6.0	3.6	2.4	1.5:1	N	N	N	N	4.0	(1) Mannitol Mustard: 20/6/63
	27/63	0.5	6	4	3	12	-	-	5.8	3.4	2.4	1.4:1	N	N	N	N	3.2	
39 (M.P.)	20/8/63	1.0	7.3	6	6	20	-	N	6.6	3.9	2.5	1.4:1	0.27	0.60	0.87	0.98	4.0	(1) Mannitol Mustard: 26/8/63
	7/9/63	0.9	8	5	6	18	4	-	6.4	3.6	2.8	1.2:1	0.25	0.72	0.84	1.01	4.6	
	18/10/63	0.8	8	6	4	-	-	N	-	-	-	-	-	-	-	-	-	
40 (F.S.)	25/8/63	0.4	5	3	4	18	4	N	6.4	3.8	2.6	1.4:1	0.20	0.80	0.70	0.90	4.0	(1) Cyclophosphamide: 27/8/63 (2) Mannitol Mustard: 26/8/63
	7/9/63	0.3	4	4	5	21	-	-	6.6	4.0	2.6	1.6:1	0.18	0.81	0.68	1.02	4.2	

TABLE 25

GROUP F : CARCINOMA OF BREAST (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
41 (B.S.)	5/9/63 18/9/63	0.5 0.4	3.9 5	4 3	4 4	10 8	4 4	N N	6.6 6.4	4.1 4.2	2.5 2.2	1.7:1 1.9:1	0.22 0.12	0.75 0.72	0.70 0.83	1.10 1.10	4.0 3.6	(1) Mannitol Mustard: 5/9/63
42 (I.F.)	19/11/63 30/11/63	0.4 0.3	3.8 3.2	3 2	4 4	10 8	2 4	N N	6.9 6.6	4.7 4.3	2.2 2.3	2.1:1 1.9:1	N 0.20	N 0.72	N 0.70	N 0.70	3.2 2.8	(1) Cyclophosphamide: 22/11/63
43 (F.L.)	28/11/63 15/12/63	0.6 0.4	5.4 5.0	3 3	5 5	10 18	8 11	- N	6.3 6.4	4.3 4.6	2.0 2.6	2.1:1 1.8:1	N N	N N	N N	N N	N N	(1) Cyclophosphamide: 30/11/63
44 (M.McD)	25/11/63 1/1/64	0.3 0.3	10 12.7	5 5	5 5	28 24	10 12	- +	7.6 7.7	4.5 4.8	3.1 2.9	1.5:1 1.7:1	0.30 0.24	1.02 1.10	0.70 0.62	1.0 0.94	3.0 3.2	(1) Mannitol Mustard: 27/11/63 (2) Cyclophosphamide: 16/12/63
45 (L.B.)	26/3/63 8/4/63 15/5/63 18/11/63	0.8 0.9 0.92 1.20	14.0 14.2 16 18	5 6 7 7	14 15 15 18	38 42 44 46	10 12 8 12	+ - + -	6.4 6.2 5.8 5.9	4.3 4.6 3.2 3.6	2.1 1.6 2.6 2.3	2:1 2.9:1 1.1:1 1.5:1	+ + 0.40 0.42	++ + 1.20 1.22	N D 0.50 0.43	N D 0.50 0.30	8.0 7.6 6.2 7.4	(1) Cyclophosphamide: 31/3/63 6/4/62 (2) Vinblastine Sulphate: 2/10/63 (3) Prednisone: 20/3/63
46 (B.K.)	9/3/64 20/3/64	0.6 0.4	8 7	4 4	3 4	18 16	4 8	N N	6.0 6.2	4.0 3.8	2.0 2.4	2:1 1.6:1	N 0.18	N 0.81	N 0.62	N 0.78	4.2 3.6	(1) Cyclophosphamide: 10/3/64
47 (M.G.)	5/4/64 25/3/65 2/9/65 10/9/65 14/9/65 29/9/65	0.8 1.4 - - - -	7 26 - - - -	1 2 - - - -	- - - - - -	20 - - - - -	20 20 - - - -	- - - - - -	- 6.0 5.5 5.8 5.8 5.9	- - 2.8 3.0 3.5 3.3	- - 2.7 2.8 2.3 2.6	- - 1:1 1.1:1 1.4:1 1.3:1	- N 0.20 0.30 0.20 0.30	- N 0.60 0.60 0.80 0.80	- N 1.00 0.80 0.70 0.60	- N 0.90 1.10 0.70 0.90	- 4.2 - 3.3 - 2.6	(1) Cyclophosphamide: 3/9/65 (2) Stilboestrol 2/10/59 (3) Testosterone and Prednisone: 1/7/64

GROUP F : CARCINOMA OF BREAST (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
48 (A.W.)	1/3/65	0.7	6	3	-	-	-	-	6.9	3.1	3.8	1:1.1	++	+	N	N	-	(1) Cyclophosphamide: 11/3/65
	18/3/65	-	-	-	-	-	-	-	6.5	-	-	-	-	-	-	-	4.1	
	25/3/65	0.5	4	3	-	-	20	-	6.3	-	-	-	-	-	-	-	4.7	
	22/4/65	-	-	-	-	-	-	-	6.4	2.6	3.8	1:1.4	0.60	1.00	1.00	1.20	3.7	
	29/4/65	-	-	-	-	-	-	-	6.4	2.9	3.5	1:1.3	0.60	1.00	1.00	0.90	4.6	
	25/5/65	-	-	-	-	-	-	-	6.6	3.0	3.6	1:1.2	0.50	1.00	0.90	1.20	4.2	
	24/6/65	-	-	-	-	-	-	-	7.2	3.0	4.2	1:1.5	0.50	1.70	1.00	0.90	2.8	
	23/9/65	0.4	4	2	-	-	-	-	5.8	2.3	3.5	1:1.5	0.30	0.70	0.80	1.60	3.0	
	3/1/66	-	-	-	-	-	-	-	6.9	3.6	3.3	1:1	0.40	0.90	1.00	1.00	3.2	
49 (M.O.)	29/5/64	0.7	8	1	-	-	20	-	7.2	3.6	3.6	1:1	++	++	N	N	-	(1) Cyclophosphamide: 14/1/65
	4/6/64	0.6	7	1	-	-	20	-	5.1	2.1	3.0	1:1.4	++	++	N	N	-	
	13/1/65	0.8	8	1	-	-	20	-	7.0	3.2	3.8	1:1.1	0.60	1.60	0.80	0.80	7.4	
	18/1/65	-	-	-	-	-	-	-	6.5	2.5	4.0	1:1.8	0.80	1.60	0.80	0.80	6.8	
50 (M.S.)	13/9/65	0.4	14	7	6	-	-	-	6.9	3.7	3.2	1.1:1	0.20	0.90	0.80	1.30	-	(1) Cyclophosphamide: 21/9/65
	23/9/65	-	-	-	-	-	-	-	6.1	2.8	3.3	1:1.2	0.30	0.80	1.00	1.30	7.3	
	24/9/65	0.5	15	6	8	-	-	-	6.2	2.8	3.4	1:1.3	0.30	0.80	0.90	1.40	-	
	27/9/65	-	-	-	-	-	-	-	6.2	2.3	3.9	1:1.5	0.20	1.60	0.70	1.40	5.0	
	30/9/65	-	-	-	-	-	-	-	6.0	2.2	3.8	1:1.5	0.40	1.00	1.00	1.40	5.3	
	7/10/65	-	-	-	-	-	-	-	6.1	2.4	3.7	1:1.4	0.40	1.10	0.90	1.40	2.6	
	21/10/65	-	-	-	-	-	-	-	7.2	3.4	3.8	1:1.2	0.20	1.20	0.70	1.70	7.6	
	28/10/65	-	-	-	-	-	-	-	6.3	2.9	3.4	1:1.2	0.40	0.90	0.80	1.30	7.7	
51 (M.K.)	24/11/64	0.3	16	2	-	20	-	+	-	-	-	-	-	-	-	-	-	(1) Thiotepa: 12/8/63
	21/1/65	0.5	20	1	-	20	-	-	-	-	-	-	-	-	-	-	-	(2) Cyclophosphamide: 13/4/65
	30/3/65	1.1	26	1	-	20	-	-	-	-	-	-	-	-	-	-	-	
	14/4/65	-	-	-	-	-	-	-	6.0	2.7	3.3	1:1.2	0.50	0.80	0.80	1.2	11.7	(3) Testosterone and Cortisone: 24/1/65
	19/4/65	-	-	-	-	-	-	-	5.4	2.2	3.2	1:1.3	0.40	0.09	0.90	1.0	13.8	
	23/4/65	-	-	-	-	-	-	-	6.1	2.4	3.7	1:1.4	0.50	1.00	1.00	1.20	9.5	
	29/4/65	-	-	-	-	-	-	-	6.3	3.2	3.10	1:1	0.40	0.90	0.80	1.00	-	
	6/5/65	-	-	-	-	-	-	-	6.4	3.3	3.1	1.1:1	0.40	0.80	0.80	1.10	9.5	

GROUP F : CARCINOMA OF BREAST (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
51	25/5/65	-	-	-	-	-	-	-	6.1	2.9	3.2	1:1.1	0.40	0.80	0.90	1.20	10.6	(
(M.K.)	29/5/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9.0	
(cont.)	10/6/65	-	-	-	-	-	-	-	6.2	4.0	2.2	1.9:1	0.40	0.50	0.60	0.70	7.4	
	16/8/65	-	-	-	-	-	-	-	6.5	4.3	2.2	2:1	0.20	0.60	0.80	0.60	5.0	
	30/8/65	-	-	-	-	-	-	-	6.4	3.8	2.6	1.5:1	0.30	0.60	0.60	1.10	4.4	
	4/10/65	-	-	-	-	-	-	-	6.3	3.1	3.2	1:1	0.40	0.70	1.00	1.10	-	
	23/11/65	-	-	-	-	-	-	-	5.9	3.3	2.6	1.2:1	0.40	0.60	0.90	0.80	-	
52	18/9/64	0.3	14	1	-	-	-	20	5.6	2.7	2.9	1:1	0.30	0.90	0.70	0.90	3.0	(1) Thiotepa:
(S.O.)	2/12/64	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.7	28/8/64

TABLE 25

GROUP G : CARCINOMA OF OVARY

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α1 Globulin	α2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
53 (J.H.)	29/6/62	0.5	7.0	5	10	8	10	N	7.4	3.4	4.0	1:1.2	0.37	1.23	1.09	1.26	4.0	(1) Thiocolciran: 9/7/62
	13/7/62	0.6	7.8	1	6	-	-	N	6.8	3.2	3.6	1:1.2	0.32	1.20	0.92	1.20	4.3	(2) Cyclophosphamide: 5/11/62
	23/8/62	0.6	15	1	6	24	-	-	6.3	4.6	1.7	2.4:1	0.12	0.80	0.40	0.40	7.4	(3) Vinblastine Sulphate: 12/3/63
	5/3/63	0.4	10.0	1	4	28	-	-	7.3	4.9	2.4	2:1	0.14	1.00	0.50	0.50	6.2	
54 (A.E.)	13/8/62	0.1	6	2	5	10	4	N	6.0	3.9	2.1	1.8:1	+	+	N	N	-	(1) Thiocolciran: 14/8/62
	28/8/62	0.3	5	2	4	8	2	N	6.4	3.6	2.8	1.2:1	+	+	N	N	4.0	(2) Cyclophosphamide: 17/1/63
	14/10/62	0.2	37	1	3	16	-	-	7.4	5.3	2.1	2.5:1	0.30	0.70	0.60	0.60	4.8	(3) Thiotepa: 11/5/63
	12/12/62	0.2	6	1	7	14	-	-	-	-	-	-	-	-	-	-	-	(4) Vinblastine Sulphate: 30/5/63
	4/7/63	0.4	8	4	8	20	2	-	7.4	4.8	2.6	1.9:1	0.32	1.00	0.60	0.70	5.2	
55 (D.M.)	21/12/62	0.2	10.0	3	8	28	-	-	6.4	3.4	3.0	1.1:1	N	N	N	N	3.0	(1) Cyclophosphamide: 22/12/62
	7/1/63	0.4	8	4	7	20	-	-	6.5	3.6	2.9	1.2:1	N	N	N	N	3.2	(2) Thiotepa: 25/9/63
	27/9/63	0.5	11.0	8	6	22	-	-	6.9	4.6	2.3	2:1	N	N	N	N	-	(3) Vinblastine Sulphate: 8/10/63

TABLE 25

GROUP G : CARCINOMA OF OVARY (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
56	28/8/63	0.3	18.5	20	-	-	6	++	6.2	4.2	2.0	1.9:1	N	++	N	D	8.0	(1) Cyclophosphamide: 5/9/63
(S.G.)	13/9/63	0.5	12	12	15	-	-	++	6.1	4.4	1.7	2.6:1	D	+	N	D	6.4	
	15/10/63	0.6	18	14	16	40	-	-	6.2	4.1	2.1	2:1	N	+	N	D	6.2	
57	28/6/65	0.4	8	4	8	-	-	-	7.1	3.3	3.7	1:1.2	0.10	0.60	0.80	2.20	2.8	(1) Thiotepa:17/3/65
(M.C.)	29/7/65	-	-	-	-	-	-	-	6.8	2.4	4.4	1:1.9	0.40	0.80	0.80	2.50	3.8	(2) Cyclophosphamide: 24/6/65
	9/9/65	-	-	-	-	-	-	-	7.3	3.3	4.0	1:1.2	0.30	0.70	1.00	2.00	3.7	
	14/10/65	-	-	-	-	-	-	-	6.2	2.4	4.8	1:2.0	0.30	0.90	0.80	1.80	4.0	
	21/10/65	-	-	-	-	-	-	-	6.5	3.1	3.4	1:1.1	0.30	0.70	0.80	1.60	3.1	
	28/10/65	-	-	-	-	-	-	-	6.4	2.6	3.8	1:1.5	0.40	0.90	0.80	1.70	3.9	
	30/12/65	0.3	10	8	-	-	-	-	6.4	3.3	3.1	1:1	0.10	0.70	0.90	1.40	4.1	
	13/1/66	0.4	9	4	-	-	-	-	6.4	2.7	3.7	1:1.3	0.40	1.00	0.70	1.60	3.3	
58	29/6/64	0.4	7	1	-	-	20	-	6.0	3.5	2.5	1.4:1	0.40	0.90	0.70	0.50	-	(1) Thiotepa:11/7/64
(E.H.)	16/7/64	-	-	-	-	-	-	-	5.4	2.5	2.9	1:1.2	0.50	1.10	0.70	0.60	3.8	(2) Cyclophosphamide: 13/7/64
	20/7/64	-	-	-	-	-	-	-	5.2	2.5	2.7	1.1:1	0.50	0.90	0.70	0.60	-	
	22/8/64	0.3	6	1	-	-	20	-	5.2	2.2	3.0	1:1.4	0.40	1.00	0.80	0.70	3.6	
	31/8/64	0.5	9	-	-	20	20	-	-	-	-	-	-	-	-	-	-	
	4/9/64	1.0	10	1	-	-	20	-	5.2	2.0	3.2	1:1.4	0.50	1.00	0.70	1.00	-	

TABLE 25

GROUP H : TESTICULAR TUMOURS

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α1 Globulin	α2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
59 (D.H.)	5/10/62	0.5	15	4	5	18	-	N	7.1	4.8	2.3	2.1:1	N	++	N	N	-	(1) Mannitol Mustard: 10/11/62
	21/11/62	0.6	11	4	6	16	-	N	7.4	4.9	2.5	2:1	N	++	N	N	3.0	
60 (T.T.)	9/6/63	0.4	6	4	6	17	-	-	6.9	4.1	2.8	1.4:1	0.23	0.80	0.90	0.90	6.1	(1) Mannitol Mustard: 10/6/63
	13/8/63	0.5	7	6	6	17	-	-	7.8	5.4	2.4	2.1:1	0.18	0.82	0.82	0.80	6.3	(2) Vinblastine Sulphate: 13/8/63
	4/1/64	0.6	8	6	7	10	-	-	6.8	4.0	2.8	1.4:1	0.12	0.94	0.78	1.00	7.1	(3) Methotrexate: 13/8/63
	22/1/64	-	-	-	-	14	-	-	6.6	3.6	3.0	1.2:1	0.20	1.02	0.80	1.08	6.8	
61 (B.A.)	18/7/63	0.25	17.5	8	7	-	-	+	6.6	3.30	3.30	1:1	0.32	1.01	0.88	0.57	8.2	(1) Cyclophosphamide: 1/8/63
	20/8/63	0.50	18	9	11	28	-	+	6.8	3.5	3.3	1.1:1	0.34	1.10	0.76	0.54	7.4	(2) Vinblastine Sulphate: 19/7/63
	16/1/64	0.80	16	10	15	40	-	-	6.4	3.0	3.4	1.1:1	0.32	1.20	0.72	0.60	5.8	
62 (M.E.)	18/9/63	0.40	11.7	6	11	19	-	+	6.3	4.3	2.0	2.1:1	+++	++	N	D	5.0	(1) Mannitol Mustard: 19/9/63
	8/10/63	0.50	14	7	14	22	-	-	7.3	3.9	3.4	1.2:1	0.64	1.22	1.00	0.57	6.2	(2) Methotrexate: 19/9/63
	18/12/63	0.80	14	7	15	28	-	+	7.0	3.4	3.6	1:1	0.62	1.26	1.10	0.66	6.4	(3) Cyclophosphamide: 28/9/63
																		(4) Vinblastine Sulphate: 2/11/63

TABLE 25

GROUP I : RENAL CARCINOMA (HYPERNEPHROMA)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
64 (H.S.)	28/8/63	0.20	18	7	8	32	-	+	7.2	4.8	2.4	2:1	+	++	N	N	5.8	(1) Cyclophosphamide: 24/9/63
	9/10/63	0.25	25.6	9	9	28	-	+	7.3	4.9	2.4	2:1	++	++	N	N	6.2	
	17/10/63	-	-	-	-	-	-	-	8.1	4.0	4.1	1:1	0.51	1.25	1.03	1.32	-	(2) Vinblastine Sulphate: 16/1/64
	12/5/64	0.40	22	8	11	38	-	-	7.6	4.0	3.6	1.1:1	0.48	1.22	0.92	1.00	5.6	
65 (V.A.)	28/5/63	0.6	13.3	7	8	28	-	++	7.1	5.3	1.8	2.9:1	N	N	N	N	-	(1) Cyclophosphamide: 1/6/63
	14/6/63	0.6	14	7	9	22	-	++	6.8	4.4	2.2	2:1	0.18	0.82	0.54	0.70	6.7	
	22/8/63	1.0	18	8	10	-	-	-	6.3	4.0	2.3	1.8:1	0.20	0.78	0.60	0.70	4.6	(2) Vinblastine Sulphate: 4/6/63
66 (J.W.)	11/3/65	0.5	15	1	-	20	20	-	-	-	-	-	-	-	-	-	-	(1) Cyclophosphamide: 15/3/65
	13/3/65	0.5	17	1	-	20	20	-	5.6	2.5	3.1	1:1.2	+	+	N	N	8.4	
	17/3/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8.2	
	18/3/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.9	
	22/3/65	0.7	15	1	4	20	20	-	-	-	-	-	-	-	-	-	7.5	
	24/3/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6.1	
	26/3/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.9	
	13/4/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6.9	
	15/4/65	0.6	14	2	4	-	-	-	5.7	1.8	3.9	1:2.1	0.50	1.00	1.00	1.40	8.6	
	22/4/65	-	-	-	-	-	-	-	6.1	2.3	3.8	1:1.5	0.50	1.00	1.00	1.20	7.0	
	29/4/65	-	-	-	-	-	-	-	5.8	2.7	3.1	1:1.2	0.40	0.90	1.00	0.90	8.5	

TABLE 25

GROUP I : RENAL CARCINOMA (HYPERNEPHROMA) (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
67 (J.C.)	15/6/64	0.3	22	2	-	-	20	-	6.6	2.4	4.2	1:1.8	0.60	1.20	0.90	1.50	8.8	(1) Cyclophosphamide: 20/6/64
	27/6/64	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.8	
	6/7/64	1.0	18	1	-	-	20	-	-	-	-	-	-	-	-	-	3.9	
	20/7/64	0.7	30	1	-	-	20	-	6.1	2.2	3.9	1:1.8	0.50	1.00	0.90	1.50	4.8	
68 (H.S.)	4/11/65	-	-	-	-	-	-	-	7.0	3.2	3.8	1:1.1	0.40	1.30	0.90	1.30	5.2	(1) Cyclophosphamide: 29/9/65 (4/11/65)
	11/11/65	-	-	-	-	-	-	-	7.4	3.1	4.3	1:1.5	0.30	1.70	0.90	1.30	4.8	
	18/11/65	-	-	-	-	-	-	-	6.9	3.2	3.7	1:1.1	0.30	1.30	1.00	1.10	4.8	
	25/11/65	-	-	-	-	-	-	-	6.5	2.9	3.6	1:1.2	0.30	1.20	1.00	1.00	4.8	
	9/12/65	-	-	-	-	-	-	-	6.0	2.8	3.2	1:1.1	0.40	1.00	0.90	0.90	-	
	23/12/65	0.3	16	1	-	-	-	-	6.7	3.3	3.4	1:1	0.20	1.50	0.90	0.90	-	
	30/12/65	-	-	-	-	-	-	-	7.3	4.0	3.3	1.2:1	0.20	1.30	1.10	0.80	5.7	
	13/1/66	0.3	18	1	-	-	-	-	6.7	3.4	3.3	1:1	0.40	1.20	0.80	0.90	-	
	20/1/66	0.3	14	1	-	-	-	-	7.3	4.4	2.9	1.5:1	0.40	1.60	0.60	0.30	6.4	
	17/2/66	0.3	27	1	-	-	-	-	6.6	2.8	3.8	1:1.4	0.60	1.60	0.90	0.70	6.0	

TABLE 25

GROUP J : CARCINOMA OF BLADDER

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α1 Globulin	α2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
69 (W.K.)	10/4/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.8	(1) Cyclophosphamide: 14/6/65
	13/6/65	0.4	14	3	-	14	4	-	6.4	3.4	3.0	1.1:1	0.40	0.90	1.00	1.20	6.0	(2) 5-Fluouracil: 16/6/65
	14/6/65	-	-	-	-	-	-	-	6.0	3.1	2.9	1:1	0.30	0.90	0.80	0.90	5.5	
	15/6/65	0.5	12	4	-	16	8	-	6.6	2.4	4.2	1:1.8	0.40	1.10	1.20	1.60	6.8	
	16/6/65	-	-	-	-	-	-	-	5.8	2.6	3.2	1:1.2	0.30	1.00	0.80	1.00	7.9	
	17/6/65	-	-	-	-	-	-	-	6.5	3.6	2.9	1.2:1	0.20	1.00	0.80	0.80	8.7	
	18/6/65	-	-	-	-	-	-	-	6.4	3.3	3.1	1:1	0.30	0.90	1.10	0.80	8.3	
	19/6/65	-	-	-	-	-	-	-	6.7	3.8	2.9	1.3:1	0.20	0.90	1.00	0.90	8.8	
	21/6/65	-	-	-	-	-	-	-	5.7	3.3	2.4	1.3:1	0.20	0.80	0.70	0.70	-	
	23/6/65	-	-	-	-	-	-	-	6.3	3.6	2.7	1.3:1	0.20	0.80	0.80	0.90	9.3	
	24/6/65	-	-	-	-	-	-	-	5.9	3.4	2.5	1.4:1	0.40	1.00	0.40	0.80	9.3	
	25/6/65	-	-	-	-	-	-	-	5.9	3.4	2.5	1.4:1	0.30	0.80	0.70	0.80	11.8	
	26/6/65	-	-	-	-	-	-	-	6.1	3.5	2.6	1.4:1	0.20	0.90	0.60	0.90	11.8	
	29/6/65	-	-	-	-	-	-	-	5.6	2.7	2.9	1:1.1	0.40	0.80	0.70	1.00	12.5	
	30/6/65	-	-	-	-	-	-	-	5.7	2.3	3.4	1:1.4	0.50	1.00	0.80	1.00	12.2	
	2/7/65	-	-	-	-	-	-	-	5.6	2.8	2.8	1:1	0.40	1.10	0.70	0.60	6.4	
	3/7/65	-	-	-	-	-	-	-	6.1	3.1	3.0	1:1	0.40	1.30	0.60	0.80	9.7	
	5/7/65	-	-	-	-	-	-	-	6.2	2.9	3.3	1:1.1	0.50	1.20	0.70	1.00	-	
	8/7/65	-	-	-	-	-	-	-	6.1	2.8	3.3	1:1.1	0.40	1.10	0.80	1.00	6.9	
	19/7/65	-	-	-	-	-	-	-	6.6	2.9	3.7	1:1.3	0.40	0.80	0.90	1.60	5.7	

TABLE 25

GROUP K : CARCINOMA OF PROSTATE

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
70 (T.P.)	28/8/63	0.6	18.3	12	9	36	-	+	6.3	4.6	1.7	3.7:1	N	N	D	D	8.2	(1) Cyclophosphamide: 11/9/63
	9/9/63	0.4	11.1	8	7	28	-	-	5.9	4.3	1.6	2.7:1	D	N	D	D	7.4	
	20/9/63	0.8	18.0	10	10	-	-	-	5.6	4.1	1.5	2.6:1	D	N	D	D	7.6	

TABLE 25

GROUP L : ADRENAL CARCINOMA

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
71 (J.R.)	13/2/62	0.9	42.6	6	15	20	-	++	-	-	-	-	-	-	-	-	-	(1) Nitrogen Mustard: 24/2/62
	23/2/62	0.5	20.8	7	15	18	-	-	6.4	4.2	2.2	1.9:1	N	++	N	N	3.6	(2) Cyclophosphamide: 28/2/62
	8/3/63	0.25	27.4	2	9	-	-	+	6.6	4.5	2.1	2:1	N	+	N	N	4.0	
	17/4/63	0.3	25.3	3	8	20	-	-	6.6	4.5	2.1	2:1	0.12	0.98	0.54	0.70	3.2	
	23/7/63	0.5	12.2	3	5	-	-	-	6.9	5.0	1.9	2.7:1	N	+	D	D	3.0	
	23/9/63	0.4	16.1	7	7	22	-	-	6.3	4.0	2.3	1.8:1	0.18	0.92	0.60	0.70	2.8	
	11/11/63	0.25	18	7	6	28	-	-	6.4	4.0	2.4	1.7:1	0.20	0.96	0.60	0.62	4.0	
72 (C.M.)	19/9/62	0.20	10.4	1	5	20	-	N	7.2	4.0	3.2	1.2:1	0.46	1.12	0.70	0.90	7.2	(1) Mannitol Mustard: 22/10/62
	30/10/62	0.40	20.0	6	10	18	-	N	7.9	4.7	3.2	2.0:1	0.32	1.02	0.80	1.10	6.8	(2) Thiotepa: 23/10/62
	4/4/63	0.80	24	7	14	22	-	-	8.0	4.8	3.2	1.5:1	0.42	1.20	0.68	0.72	7.4	(3) Cyclophosphamide: 28/3/63
	26/6/63	0.80	28	7	15	28	-	-	7.8	4.3	3.5	1.4:1	0.43	1.22	0.76	0.84	7.6	(4) Methotrexate: 11/5/63

TABLE 25

GROUP M : CARCINOMA OF OESOPHAGUS

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α1 Globulin	α2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
73 (A.C.)	5/11/62	0.3	9.3	1	6	4	-	N	7.1	4.9	2.2	2.2:1	0.56	0.70	0.48	0.52	4.0	(1) Cyclophosphamide: 27/12/62
	28/12/62	0.3	14	4	1	15	-	-	6.9	3.8	3.1	1.2:1	0.52	0.84	0.72	1.00	6.4	
	1/1/63	0.2	38	3	8	-	-	+	5.2	3.3	1.9	1.7:1	+	N	N	D	7.4	
74 (J.P.)	18/7/63	0.9	15.3	7	7	14	-	-	7.3	5.0	2.3	2.2:1	+	++	N	N	6.3	(1) Thiotepa: 19/7/63
	4/8/63	8.1	16.6	7	13	15	-	-	6.2	4.3	1.9	2.2:1	0.20	0.82	0.40	0.50	6.2	(2) Cyclophosphamide: 23/7/63
	14/8/63	1.9	19.6	11	12	-	-	-	6.4	4.4	2.0	2.2:1	0.21	0.90	0.40	0.52	5.8	(3) Nitrogen Mustard: 10/8/63

TABLE 25

GROUP N : CARCINOMA OF STOMACH

Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α1 Globulin	α2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
75 (R.H.)	20/10/63	0.4	38.2	3	5	28	-	+	6.4	4.2	2.2	1.9:1	++	+	N	D	5.0	(1) Thiotepa: 21/10/63
	6/11/63	0.5	80.0	7	10	24	-	+	6.1	3.0	3.1	1:1	0.44	1.18	1.02	0.46	6.3	(2) Cyclophosphamide: 21/10/63
	12/11/63	0.8	10.4	8	14	42	-	-	6.0	3.2	2.8	1.2:1	0.36	1.10	1.00	0.40	7.7	
76 (T.H.)	12/10/64	0.7	17	-	-	-	20	-	-	-	-	-	-	-	-	-	-	(1) Thiocolciran and Methotrexate: 18/10/64
	14/10/64	-	-	-	-	-	-	-	6.9	3.0	3.9	1:1.2	0.70	1.20	0.60	1.30	7.7	
	26/10/64	0.9	21	1	-	-	20	-	-	-	-	-	-	-	-	-	-	
77 (W.M.)	23/10/64	0.8	9	1	-	-	20	-	5.3	1.9	3.4	1:1.7	0.50	1.10	1.00	0.90	3.3	(1) Thiocolciran and Methotrexate: 23/10/64
78 (I.M.)	5/1/65	0.7	10	1	-	-	20	-	-	-	-	-	-	-	-	-	-	(1) Thiocolciran and Methotrexate: 16/1/65
	16/1/65	0.7	10	1	-	-	20	-	-	-	-	-	-	-	-	-	6.3	
79 (R.C.)	3/3/65	-	-	-	-	-	-	-	6.6	3.6	3.0	1.2:1	N	N	N	N	2.9	(1) Thiocolciran and Methotrexate: 31/3/65
	24/3/65	1.5	12	1	-	-	20	-	-	-	-	-	-	-	-	-	-	
	22/4/65	-	-	-	-	-	-	-	5.8	2.3	3.5	1:1.5	0.50	0.90	0.90	1.20	2.5	
	29/4/65	-	-	-	-	-	-	-	6.2	2.9	3.3	1:1.2	0.40	1.10	0.90	1.00	2.8	
	6/5/65	-	-	-	-	-	-	-	5.8	2.6	3.2	1:1.3	0.50	1.00	0.80	0.90	3.0	
	20/5/65	-	-	-	-	-	-	-	5.4	2.9	3.5	1:1.1	0.30	0.90	0.60	0.60	2.3	
	27/5/65	-	-	-	-	-	-	-	6.1	3.6	2.5	1.5:1	0.40	1.00	0.60	0.50	2.8	
	3/6/65	-	-	-	-	-	-	-	6.0	3.2	2.8	1.1:1	0.40	0.90	0.60	0.90	3.5	
	19/6/65	-	-	-	-	-	-	-	5.9	3.7	2.2	1.5:1	0.20	0.90	0.50	0.60	3.3	
	28/6/65	-	-	-	-	-	-	-	5.6	3.5	2.1	1.5:1	0.30	0.90	0.50	0.40	5.0	
	29/6/65	-	-	-	-	-	-	-	5.3	3.2	2.1	1.5:1	0.10	1.00	0.60	0.40	6.5	
	2/7/65	-	-	-	-	-	-	-	6.0	2.7	3.3	1:1.2	0.50	1.10	0.80	0.90	10.2	
	3/7/65	-	-	-	-	-	-	-	5.3	2.4	2.9	1:1.1	0.30	1.30	0.90	0.50	7.2	

TABLE 25

GROUP N : CARCINOMA OF STOMACH (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
80 (E.C.)	17/2/65	1.2	14	1	-	-	20	-	-	-	-	-	-	-	-	-	-	(1) Thiocolciran and Methotrexate: 7/3/65
	7/3/65	0.6	12	1	-	-	20	-	5.9	2.6	3.3	1:1.4	0.50	1.20	0.60	1.00	3.1	
	18/3/65	-	-	-	-	-	-	-	6.2	-	-	-	-	-	-	-	2.9	
	15/4/65	-	-	-	-	-	-	-	6.2	2.3	3.9	1:1.5	0.70	1.10	0.90	1.20	4.2	
	22/4/65	-	-	-	-	-	-	-	5.4	1.6	3.8	2.1:1	0.60	0.70	1.10	1.40	3.4	
	29/4/65	-	-	-	-	-	-	-	5.2	2.9	3.3	1:1.2	0.50	0.70	0.60	0.50	-	
81 (P.D.)	16/4/65	0.4	8	1	-	-	20	-	-	-	-	-	-	-	-	-	-	(1) Thiocolciran and Methotrexate: 16/4/65
	26/4/65	-	-	-	-	-	-	-	5.7	3.3	2.4	1.3:1	0.20	0.80	0.80	0.60	3.5	
	3/5/65	-	-	-	-	-	-	-	5.3	2.9	2.4	1.1:1	0.40	0.70	0.80	0.50	4.2	
	10/5/65	-	-	-	-	-	-	-	5.9	3.0	2.9	1:1	0.50	0.70	1.00	0.70	4.5	
	19/5/65	-	-	-	-	-	-	-	6.2	3.2	3.0	1:1	0.40	1.00	1.10	0.60	5.8	
	26/5/65	-	-	-	-	-	-	-	6.0	3.2	3.0	1:1	0.40	0.80	0.90	0.70	4.5	
	9/6/65	-	-	-	-	-	-	-	6.3	3.6	2.7	1.2:1	0.30	0.80	0.90	0.80	4.2	
82 (A.W.)	24/5/65	0.6	8	3	-	-	20	-	6.0	3.1	2.9	1:1	0.30	1.00	0.60	0.70	3.8	(1) Thiocolciran and Methotrexate: 27/5/65
	10/6/65	0.4	6	3	-	-	20	-	6.2	3.1	3.1	1:1	0.22	1.10	0.78	0.80	4.6	
	12/7/65	-	-	-	-	-	-	-	6.4	3.0	3.4	1:1.1	0.32	1.12	0.80	1.20	4.8	

TABLE 25

GROUP O : CARCINOMA OF COLON AND RECTUM

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
83	29/5/61	0.4	8	2	3	-	-	N	6.2	4.1	2.1	1:1	N	+	N	N	4.0	(1) Thiocolciran: 14/6/61
(J.S.)	25/10/61	0.4	10	2	2	9	-	N	-	-	-	-	-	-	-	-	-	(2) Vinblastine Sulphate: 4/4/63
	3/11/61	0.6	8	3	4	11	-	-	-	-	-	-	-	-	-	-	-	(3) Thiotepa: 20/9/63
	19/4/63	0.3	11.3	6	4	-	-	-	6.3	4.5	1.8	2.5:1	N	+	N	N	4.2	(4) Cyclophosphamide: 9/1/64
	26/9/63	0.3	9.0	7	10	1.25	5.1	-	6.9	3.5	3.4	1:1	0.25	1.08	1.10	1.05	3.6	
	8/1/64	0.3	9.0	9	9	-	-	-	7.4	4.8	2.6	1.9:1	0.20	1.10	0.60	0.70	3.2	
84	10/11/62	0.3	6.8	2	5	-	-	N	5.6	2.6	3.0	1:1.1	0.50	1.10	0.80	0.60	6.4	(1) Cyclophosphamide: 16/11/62
(I.L.)	31/12/62	0.4	6.3	3	6	18	-	N	6.0	3.0	3.0	1:1	0.48	1.00	1.00	0.60	6.2	(2) Vinblastine Sulphate: 3/11/63
	4/1/63	0.6	7.0	3	8	22	-	-	5.8	2.8	3.0	1:1.1	0.50	1.20	1.01	0.30	9.0	
85	17/12/62	0.4	8.6	3	8	-	-	-	6.6	4.7	1.9	2.5:1	N	+	N	D	5.0	(1) Mannitol Mustard: 2/1/63
(A.T.)	8/3/63	0.1	8.0	3	9	-	-	-	6.6	3.0	3.6	1:1.2	0.41	1.06	0.90	1.23	4.6	(2) Cyclophosphamide: 2/2/63
	18/10/63	0.2	7.0	4	8	18	-	-	6.4	3.2	3.2	1:1	0.46	1.10	0.92	0.80	4.3	(3) Thiotepa: 13/11/63
	13/1/64	0.6	13.3	7	5	-	-	-	6.4	4.3	2.1	2:1	0.30	1.00	0.40	0.40	6.1	
86	8/7/63	0.15	5.1	3	2	-	-	-	7.0	4.0	3.0	1.25:1	0.32	1.20	0.60	0.90	4.2	(1) Cyclophosphamide: 12/8/63
(E.W.)	1/8/63	0.20	6.0	3	2	20	-	-	7.2	4.2	3.0	1.3:1	0.30	1.18	0.70	0.80	4.3	
	2/2/64	0.30	6.0	4	3	18	-	-	6.8	3.6	3.2	11.2:1	0.20	0.80	1.20	1.00	4.8	

TABLE 25

GROUP O : CARCINOMA OF COLON AND RECTUM (contimued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
87 (A.S.)	24/10/63	0.4	64.5	2	3	-	-	++	7.1	4.8	2.3	2:1	+	++	N	N	7.2	(1) Cyclophosphamide: 16/12/63
	22/11/63	4.6	34.6	7.0	8	128	231	+++	5.3	3.7	1.6	2.3:1	D	+	N	D	7.4	
	17/12/63	15.6	91.5	19	11	109	108	-	6.3	4.0	2.3	1.7:1	N	++	N	D	7.6	
	9/1/64	13.2	10.5	40	8	-	-	-	6.1	3.5	2.6	1.4:1	0.20	1.20	0.68	0.52	8.2	
88 (E.H.)	13/9/63	0.5	40	4	6	20	46	+	7.3	4.2	3.1	1.3:1	0.50	0.82	1.00	0.80	6.4	(1) Cyclophosphamide: 25/10/63
	18/10/63	0.5	8.3	5	6	-	-	-	6.1	2.9	3.2	1:1.1	0.75	0.83	0.83	1.13	6.8	
	6/11/63	1.0	41.5	7	10	-	-	+	5.6	3.6	2.0	1.8:1	0.32	0.60	0.40	0.68	4.8	
89 (E.D.)	18/12/63	0.5	8.0	6	6	20	18	-	6.4	4.6	1.8	2.9:1	+	N	N	N	-	(1) Vinblastine Sulphate:21/12/63 (2) Cyclophosphamide: 27/2/64
	6/1/64	0.4	9.8	7	6	-	-	-	6.3	3.4	2.9	1:1:1	0.35	0.81	1.03	0.93	4.8	
90 (P.N.)	28/12/63	0.4	8	3	2	-	-	-	6.8	3.6	3.2	1.1:1	N	N	N	N	3.0	(1) Cyclophosphamide: 18/12/63 (2) Thiotepa:9/1/64
91 (R.G.)	10/3/65	0.5	11	1.0	-	-	20	-	-	-	-	-	-	-	-	-	-	(1) Thiocolciran and Methotrexate: 26/3/65
	26/3/65	-	-	-	-	-	-	-	6.5	3.5	3.0	1.2:1	+	N	N	N	4.0	
	20/4/65	-	-	-	-	-	-	-	6.4	3.1	3.3	1:1	0.40	0.90	0.80	1.10	5.0	
	29/4/65	-	-	-	-	-	-	-	6.2	2.6	3.8	1:1.5	0.50	1.00	0.90	1.20	4.0	
	13/5/65	-	-	-	-	-	-	-	7.0	3.4	3.6	1:1	0.40	1.10	0.90	1.30	6.0	
	20/5/65	-	-	-	-	-	-	-	6.7	2.1	4.6	1.2:1	0.40	1.10	1.20	1.90	4.5	
	25/5/65	-	-	-	-	-	-	-	6.6	3.6	3.0	1.1:1	0.30	0.70	0.80	1.30	5.5	
	6/5/65	-	-	-	-	-	-	-	6.5	3.4	2.1	1:1.5	0.50	1.00	0.80	1.00	5.2	
	3/6/65	-	-	-	-	-	-	-	5.7	2.7	3.0	1:1.1	0.50	0.80	0.60	1.00	5.9	
	17/6/65	-	-	-	-	-	-	-	6.8	4.3	2.5	1.7:1	0.20	1.00	0.60	0.70	5.3	
	24/6/65	-	-	-	-	-	-	-	6.6	3.7	2.9	1.2:1	0.30	0.90	0.80	0.90	4.3	
	22/7/65	-	-	-	-	-	-	-	6.2	3.4	2.8	1.2:1	0.30	0.60	0.80	1.00	5.3	
	27/1/66	0.5	11	2	-	-	27	-	7.7	4.0	3.7	1.1:1	0.20	0.60	1.00	1.80	7.3	
	17/3/63	0.3	12	1	-	-	27	-	-	-	-	-	-	-	-	-	-	

TABLE 25

GROUP P : CARCINOMA OF PANCREAS

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
92 (F.R.)	15/2/63	0.9	37	1	2	28	-	+	7.8	3.2	3.6	1:1.1	0.47	0.93	0.93	1.32	7.2	(1) Mannitol Mustard: 22/2/63
	12/3/63	3.0	33	1	1	30	-	+	5.5	3.7	1.8	2:1	0.10	0.60	0.60	0.50	6.8	(2) Cyclophosphamide: 28/2/63
	22/3/63	4.8	40	2	4	28	-	-	5.6	3.2	2.4	1.4:1	0.24	0.90	0.60	0.70	6.7	(3) Vinblastine Sulphate: 29/2/63
																		(4) Thiotepa: 19/3/63
93 (E.L.)	7/12/64	0.2	12	2	-	-	20	-	-	-	-	-	-	-	-	-	4.7	(1) Cyclophosphamide: 7/12/64
	7/1/65	0.4	14	2	-	-	20	-	-	-	-	-	-	-	-	-	3.0	
	21/1/65	0.3	17	2	-	-	20	-	7.4	2.7	3.7	1:1.4	0.70	0.80	0.90	2.3	3.8	
	18/2/65	0.6	16	3	-	-	20	-	6.4	-	-	-	-	-	-	-	3.9	
	11/3/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.6	
	15/4/65	-	-	-	-	-	-	-	6.8	2.3	4.5	1:2	0.70	1.00	1.10	1.70	4.7	
94 (J.K.)	19/11/64	0.7	13	1	-	-	31	-	5.8	2.3	3.5	1:1.4	0.50	1.10	0.60	1.30	3.4	(1) Cyclophosphamide: 26/11/64
	30/12/64	0.7	15	1	-	-	20	-	-	-	-	-	-	-	-	-	3.9	
95 (J.T.)	14/12/64	0.5	20	1	-	-	54	-	6.2	5.2	3.0	1:1	+	++	N	N	-	(1) Cyclophosphamide: 14/12/64
	28/12/64	0.8	28	1	-	-	36	-	-	-	-	-	-	-	-	-	6.0	
	21/1/65	5.6	35	2	-	-	31	-	-	-	-	-	-	-	-	-	3.1	
	5/2/65	11.5	40	4	-	-	36	-	7.4	3.9	3.5	1.1:1	0.60	1.20	0.70	0.90	-	
	12/2/65	5.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	16/2/65	4.0	30	1	-	-	25	-	-	-	-	-	-	-	-	-	8.2	
	22/2/65	2.5	17	1	-	-	20	-	-	-	-	-	-	-	-	-	-	
	8/3/65	1.1	-	-	-	-	-	-	5.9	-	-	-	N	++	N	N	-	
	18/3/65	1.0	35	2	-	-	20	-	5.9	-	-	-	N	++	N	N	5.3	
	1/4/65	-	-	-	-	-	-	-	5.9	-	-	-	N	++	N	N	4.8	

TABLE 25

GROUP 9 : MALIGNANT MELANOMA

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
96 (R.C.)	16/12/62	0.6	4.0	3	7	8	6	-	7.3	4.3	3.0	1.4:1	N	N	N	N	3.2	(1) Phenyl-alanine Mustard: 19/12/62
	2/1/63	0.6	3.0	4	6	-	-	-	7.1	4.0	3.1	1.3:1	N	N	N	N	3.0	(2) Cyclophosphamide: 22/12/62
97 (M.S.)	18/5/65	0.5	7	4	-	-	-	-	7.5	4.2	3.3	1.3:1	0.30	1.10	1.00	1.00	3.2	(1) Methotrexate: 4/6/65
	29/6/65	0.4	10	3	-	-	-	-	6.7	4.0	3.7	1:1	0.20	0.90	0.90	0.70	-	(2) Phenyl-alanine Mustard: 4/6/65
	23/8/65	0.6	14	3	-	-	-	-	7.3	3.9	3.4	1.1:1	0.30	0.80	1.10	1.10	-	(3) 2-Ethyl-hydrazine: 14/1/65
	20/9/65	-	-	-	-	-	-	-	6.5	3.6	2.9	1.2:1	0.30	0.80	0.70	1.00	-	
	1/11/65	-	-	-	-	-	-	-	6.0	3.1	2.9	1:1	0.30	0.80	0.80	1.10	3.0	
	13/12/65	-	-	-	-	-	-	-	6.6	3.6	3.0	1.2:1	0.40	0.90	0.80	0.90	3.4	
	22/12/65	0.7	13	2	-	-	-	-	-	-	-	-	-	-	-	-	2.4	
	6/1/66	0.7	25	2	-	-	-	-	6.4	3.4	3.0	1.1:1	0.30	0.80	1.00	0.80	3.9	
	21/1/66	0.5	23	2	-	-	-	-	5.6	3.4	2.2	1.5:1	0.30	0.70	0.80	0.50	4.2	
	1/2/66	-	-	-	-	-	-	-	5.2	2.5	2.7	1:1	0.40	0.90	0.80	0.70	3.0	
98 (J.S.)	23/12/65	0.4	11	3	-	-	-	-	6.7	3.8	2.9	1.3:1	0.20	0.90	0.90	0.9	4.1	(1) Phenyl-alanine Mustard: 7/1/66
	3/1/66	-	-	-	-	-	-	-	7.7	4.1	3.6	1.1:1	0.40	1.10	1.10	1.0	-	(2) 2-Ethyl-hydrazine: 24/1/66
	10/1/66	-	-	-	-	-	-	-	6.5	3.7	2.8	1.2:1	0.30	1.00	1.10	0.5	4.1	
	13/1/66	-	-	-	-	-	-	-	6.4	3.8	2.6	1.3:1	0.20	0.80	0.70	0.9	2.8	
	24/1/66	-	-	-	-	-	-	-	6.6	3.6	3.0	1.1:1	0.20	1.10	0.90	0.8	3.8	
	25/1/66	-	-	-	-	-	-	-	6.8	3.9	2.9	1.3:1	0.20	0.90	1.10	0.7	4.9	
	7/3/66	-	-	-	-	-	-	-	6.3	3.0	3.3	1:1.1	0.40	1.10	0.90	1.0	3.6	
	21/3/66	-	-	-	-	-	-	-	6.3	2.9	3.4	1:1.1	0.40	1.20	1.00	0.9	-	
	2/4/66	-	-	-	-	-	-	-	6.1	3.4	2.7	1.2:1	0.30	1.10	0.80	0.6	3.5	
	28/4/66	0.3	12	2	-	-	-	-	5.9	3.1	2.8	1.1:1	0.40	1.00	0.70	0.8	5.7	
	12/5/66	0.2	10	2	-	-	-	-	-	-	-	-	-	-	-	-	-	
	19/5/66	0.4	10	2	-	-	-	-	5.5	2.3	3.2	1:1.1	0.50	1.00	0.90	0.9	8.1	

TABLE 25

GROUP R : CARCINOMA OF UNKNOWN PRIMARY

Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	∝ 1 Globulin	∝ 2 Globulin	β Globulin	γ Globulin		Cytotoxic Agent(s) and Date of Commencement
99 (C.B.)	23/3/63	0.8	10	3	3	18	12	N	6.2	3.1	3.1	1:1	+	++	N	N	4.8	(1) Cyclophosphamide: 25/3/63
	8/4/63	0.9	8	4	3	-	-	N	6.0	2.8	3.2	1:1.1	0.40	1.20	0.70	0.90	6.7	
	12/6/63	0.7	8	3	3	14	8	-	6.4	2.7	3.7	1:1.3	0.48	1.30	1.00	0.90	6.8	
100 (J.A.)	29/8/63	1.0	5.3	7	8	-	-	-	7.8	5.0	2.8	1.8:1	+	++	N	N	6.5	(1) Vinblastine Sulphate: 1/1/64
	10/9/63	-	-	-	-	-	-	-	7.9	3.5	4.4	1:1.2	0.57	1.75	1.10	1.0	5.4	(2) Cyclophosphamide: 3/1/64
	15/1/64	0.9	8	7	11	18	22	-	7.4	3.4	4.0	1:1.2	0.50	1.60	1.02	0.90	6.0	(3) Thiotepa: 14/1/64 (4) 5-Fluouracil: 10/2/64
101 (J.McI)	18/2/65	0.7	10	3	-	-	20	-	-	-	-	-	-	-	-	-	-	(1) Cyclophosphamide: 14/3/65
	25/2/65	0.4	10	2	-	-	20	-	6.7		raised 2 globulin							
	13/3/65	0.5	18	2	-	-	20	-	5.6	1.9	3.7	1:2	0.60	0.90	1.10	1.20	6.1	
	16/3/65	-	-	-	-	-	-	-	5.6		raised 2 globulin						5.6	
	18/3/65	0.5	11	1	-	-	20	-	5.6		raised 2 globulin						-	
	29/3/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.5	
102 (J.W.)	11/1/65	0.1	17	1	-	-	20	-	5.6	2.6	3.0	1:1.2	0.40	1.20	0.80	0.60	-	(1) Nitrogen Mustard: 22/1/65
	22/1/65	0.1	13	1	-	-	20	-	-	-	-	-	-	-	-	-	3.1	(2) Cyclophosphamide: 15/2/65
	27/1/65	-	-	-	-	-	-	-	6.2	2.6	3.6	1:1.4	0.50	1.40	0.90	0.80	3.2	
	29/1/65	-	-	-	-	-	-	-	6.4	3.4	3.0	1:1.1	0.70	1.30	0.50	0.50	3.0	
	3/2/65	0.6	19	1	-	-	20	-	6.9	3.2	3.7	1:1.1	0.70	1.60	1.00	0.40	2.4	
	15/2/65	-	-	-	-	-	-	-	6.0		raised 2 globulin						3.0	
	25/2/65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.0	
	3/3/65	0.7	20	1	-	-	20	-	6.2	2.9	3.3	1:1.1	raised 2 globulin				5.2	

TABLE 25

GROUP S : OTHERS

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case No.	Date	Serum Bilirubin	Alkaline Phosphatase	Thymol Turbidity	Zinc Sulphate Turbidity	S.G.O.T.	S.G.P.T.	B.S.P. Retention	Total Proteins	Albumin	Globulin	A/G Ratio	α 1 Globulin	α 2 Globulin	β Globulin	γ Globulin	Serum Uric Acid	Cytotoxic Agent(s) and Date of Commencement
103 (S.P.)	7/12/63	0.8	5.0	1	9	20	8	N	7.2	3.4	3.8	1.1:1	0.34	1.00	1.30	1.20	6.4	(1) Mannitol Mustard: 11/2/63
	8/3/63	0.7	6.0	1	6	-	-	N	7.2	3.6	3.6	1:1	0.40	1.10	1.10	1.00	6.4	(2) Thiotepa: 12/2/63
	10/9/63	1.1	6.5	3	5	-	-	-	7.8	5.3	2.3	2.3:1	0.30	1.00	0.50	0.50	6.2	(3) Cyclophosphamide: 11/9/63
																		(4) Vinblastine Sulphate: 1/10/63
104 (D.O.)	10/1/63	0.6	-	2	7	10	4	-	6.7	4.0	2.8	1.7:1	N	N	N	N	-	(1) Cyclophosphamide: 12/1/63
	8/3/63	0.5	5.4	1	3	-	-	-	6.6	5.2	1.4	3.6:1	N	N	N	D	-	(2) Vinblastine Sulphate: 15/1/63
	12/3/63	0.25	6.0	1	2	-	-	-	6.8	5.1	1.7	3:1	N	N	N	D	-	(3) Cyclophosphamide: 7/2/64
	12/2/64	0.40	6.8	5	7	8	8	-	7.3	4.6	2.7	1.8:1	0.38	0.65	0.81	0.81	-	
105 (J.W.)	14/8/63	1.4	8	2	6	20	11	-	-	-	-	-	-	-	-	-	4.8	(1) Mannitol Mustard: 29/3/63
	24/11/63	1.5	7.9	2	3	-	-	-	6.1	3.5	2.6	1.2:1	0.32	0.56	0.72	0.96	8.6	(2) Cyclophosphamide: 25/11/63
	3/12/63	1.8	12	3	6	18	12	-	5.8	4.0	2.8	1.6:1	0.30	0.62	0.80	1.02	10.2	

TABLE 25

GROUP S : OTHERS (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
106 (M.H.)	6/9/63 20/9/63	1.30 1.10	6.5 7	5 5	4 3	- -	- -	- -	6.9 6.8	3.7 3.4	3.2 3.4	1.1:1 1:1	0.30 0.36	0.75 0.82	0.94 0.98	1.20 1.30	- -	(1) Mannitol Mustard: 10/9/63
107 (J.P.)	26/10/63 7/11/63	1.3 1.4	6.8 8	5 4	7 6	10 8	8 6	- -	6.9 6.8	3.7 3.6	3.2 3.2	1.1:1 1.1:1	0.34 0.40	1.10 1.08	0.81 0.78	1.02 1.00	4.0 4.2	(1) Cyclophosphamide: 28/10/63

KEY

N = Normal or Negative

D = Decreased

\+ = Slight increase

++ = Moderate increase

+++ = Marked increase

\- = Not carried out

CHEMOTHERAPY OF CANCER

POST-MORTEM EXAMINATIONS - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS

TABLE 26

POST-MORTEM EXAMINATIONS	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
	M	4	8	2	-	-	2	5	1	7	29	42
	F	-	1	-	-	5	5	2	-	-	13	

CHEMOTHERAPY OF CANCER

OCCURRENCE OF PLEURAL AND PERITONEAL EFFUSIONS - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS

PLEURAL AND PERITONEAL EFFUSIONS	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
	M	1	2	1	-	-	3	3	-	5	15+	32
	F	-	1	-	-	1	3	-	2	-	7*	

+ 10 Pleural and 5 peritoneal

* 5 Pleural and 2 peritoneal

ASSESSMENT OF RESPONSE TO CYTOTOXIC THERAPY - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS

TABLE 27

NATURE OF RESPONSE*	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Subjective Response Only	M	1	2	-	-	-	6	4	-	2	15	23 (21%)
	F	-	-	-	-	2	2	2	1	1	8	
2. Objective Response Only	M	-	-	-	-	-	-	1	-	-	1	2 (2%)
	F	-	-	-	-	-	1	-	-	-	1	
3. Both Subjective and Objective Response	M	4	5	2	1	-	1	2	-	4	19	33 (31.5%)
	F	1	1	-	-	7	4	-	1	-	14	
4. Harmful	M	-	-	-	-	-	1	1	1	1	4	7 (6.5%)
	F	-	-	-	-	2	-	1	-	-	3	
5. No Benefit	M	1	6	1	3	1	2	5	-	4	22	42 (39%)
	F	-	-	-	-	11	1	3	-	4	20	

* (a) Subjective Response: Symptomatic improvement maintained for minimum period of 8 weeks

(b) Objective Response: Definite tumour regression maintained for minimum period of 8 weeks

(c) Objective and Subjective Response: Combination of (a) and (b) above

(d) Harmful: Death thought to be accelerated by cytotoxics

(e) No Benefit: No symptomatic improvement or improvement maintained for less than 8 weeks

: None or minimal tumour regression

: Insufficient treatment

PATTERNS OF ∝2 GLOBULIN AND URIC ACID BY PRINCIPAL TUMOUR GROUPS

TABLE 28

PATTERNS OF 2 GLOBULIN AND URIC ACID		PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Normal Initially	∝2	-	2	-	2	15	5	5	1	4	34*	32%
	U.A.	4	9	1	2	15	10	10	2	9	62	59%
2. Remaining Normal	∝2	-	2	-	-	11	3	4	1	3	24	22%
	U.A.	2	7	-	-	14	6	5	2	3	39	37%
3. Raised Initially	∝2	7	13	3	2	5	13	10	2	11	66*	63%
	U.A.	3	6	2	2	5	8	4	-	5	35	33%
4. Remained Raised	∝2	5	13	3	1	3	10	6	-	9	50	48%
	U.A.	-	5	1	2	2	6	4	-	5	25	23%
5. Changing Patterns	∝2	2	-	-	3	6	5	5	2	3	26	24%
	U.A.	5	3	2	2	4	6	5	-	6	33	31%
6. Hepatic Metastases	M	3	6	6	3	-	4	6	-	5	33	47
	F	-	1	-	-	6	3	2	-	2	14	45%

* Insufficient results in 7 Patients of total of 107 Cases

KEY ∝2 = ∝2 Globulin
U.A. = Uric Acid
M = Male
F = Female

PATTERNS OF LIVER FUNCTION TESTS BY PRINCIPAL TUMOUR GROUPS

TABLE 29

PATTERNS OF LIVER FUNCTION TESTS	PRINCIPAL TUMOUR GROUPS									TOTALS	
	Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Normal Initially	5	5	3	2	13	6	8	3	7	52*	49%
2. Remaining Normal	3	1	3	-	11	2	5	2	3	30	28%
3. Raised Initially	2	10	-	2	7	12	7	-	8	48*	46%
4. Remained Raised	2	8	-	2	7	10	6	-	8	43	41%
5. Changing Patterns	2	6	-	2	2	6	4	1	4	27	25%
6. Hepatic Metastases Male	3	6	6	3	-	4	6	-	5	33	47
6. Hepatic Metastases Female	-	1	-	-	6	3	2	-	2	14	45%

* Incomplete results in 7 Patients - i.e. 5% of total from total of 107 cases

TABLE 30

THE CHEMOTHERAPY OF CANCER

NATURE AND INCIDENCE OF TOXIC EFFECTS

Nature	Number of Cases	
	Male	Female
1. Gastro-intestinal	20	5
2. Bone Marrow	12	7
3. Integuments	14	14
4. Central Nervous System	3	4
5. Cardio-vascular System	10	3
6. Genito-urinary System	5	1
7. Others	15	6
Total	79	40

CHEMOTHERAPY OF CANCER

NATURE, INCIDENCE AND SEVERITY OF TOXIC EFFECTS - RESULTS BY SEX AND AGENTS USED

TABLE 31

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
			Gastro-Intestinal				Bone-Marrow				Integuments			C.N.S.				C.V.S.			G.U.S.		Others					
Case No.	Primary Tumour	Agents Used	Vomiting	Diarrhoea	Pain	Bucco-labial Ulceration	Anaemia	Leucopaenia	Thrombocytopaenia	Failure	Alopecia	Rashes	Injection Ulcer	Neuritis	Depression	Hallucinations	Paranoia	Bleeding	Thrombophlebitis	Pericarditis	Cystitis	Renal Failure	Fungal Infection	Chest Infection	Wound	Septicaemia	Hepatic	Endocrine
2	Hodgkin's Disease	D.V.N.C.U.	2	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	2	-	-	1	-	2	-	-	-
3	"	N.D.V.C.	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	"	V.N.D.I.	2	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
5	"	N.D.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
6	"	N.D.Cl.C.V.	-	-	-	-	2	2	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-
7	"	N.C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-
9	Lung	C.V.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-
10	"	Cl.C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-
11	"	C.	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	2	-	-	-	-	-	-	-	-	-
12	"	Th.C.	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-
13	"	N.C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	2	-	-	-	-
14	"	C.	2	2	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	"	D.C.	2	1	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16	"	C.V.	1	-	-	1	-	3	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17	"	C.	1	-	-	-	-	-	-	-	2	-	-	-	1	-	-	-	-	-	2	-	-	-	-	-	-	-
18	"	D.C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-
20	"	C.	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
22	"	C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-
23	Lympho-sarcoma	Th.N.V.C.	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-
24	"	Cl.	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25	"	C.V.	-	-	-	-	-	-	-	-	2	-	-	-	-	2	-	-	-	-	-	-	3	-	-	-	-	-

CHEMOTHERAPY OF CANCER

NATURE, INCIDENCE AND SEVERITY OF TOXIC EFFECTS - RESULTS BY SEX AND AGENTS USED (continued)

TABLE 31

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
27	Leukaemia	C.V.	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-
30	Myeloma	C.	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	2	-	-
31	Breast	C.V.	-	-	-	-	-	2	2	1	3	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-
33	"	D.	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35	"	D.C.	-	-	-	-	-	2	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39	"	D.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-
42	"	C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-
45	"	C.V.	-	-	-	-	2	2	1	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46	"	C.	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
51	"	Th.C.	-	-	-	-	-	-	-	-	1	-	-	-	-	-	3	-	-	1	-	-	-	-	-	-	-	-
53	"	Tc.C.V.	-	-	-	-	-	-	-	-	3	-	-	-	2	-	-	-	-	-	-	1	-	-	-	2	-	-
54	"	Tc.C.Th.V.	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	1	-	-	2	-	-	-	-
55	Ovary	C.Th.V.	-	-	-	-	2	2	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-
56	"	C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-
57	"	Th.C.	-	-	-	-	1	2	-	-	1	-	-	-	-	-	1	2	-	-	-	-	-	-	-	-	-	-
58	"	Th.C.	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
60	Testis	D.V.M.	2	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
61	"	C.V.	2	-	-	-	1	2	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-
62	"	D.M.C.V.	2	-	-	-	1	1	-	-	1	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-
63	"	D.M.C.V.	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
64	"	C.V.	2	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65	Kidney	C.V.	-	-	-	-	-	-	-	-	2	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-
66	"	C.	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-
67	"	C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-
70	Prostate	C.	-	-	-	-	2	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
71	Adrenal	N.C.	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72	"	D.Th.C.M.	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-
74	Stomach and Oesophagus	Th.C.N.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-
75	"	Th.C.	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
76	"	Tc.M.	2	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
77	"	Tc.M.	2	-	1	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
78	"	Tc.M.	2	2	-	1	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

NATURE, INCIDENCE AND SEVERITY OF TOXIC EFFECTS - RESULTS BY SEX AND AGENTS USED (continued)

TABLE 31

79	Stomach and Oesophagus	Tc.M.	2	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
81	"	Tc.M.	2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
82	Colon and Rectum	Tc.V.Th.C.	1	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83	"	Tc.V.Th.C.	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
84	"	C.V.	2	2	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
86	"	C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-
88	"	C.	2	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
89	"	V.C.	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
91	"	Th.M.	2	-	1	-	1	1	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
92	Pancreas	D.C.V.Th.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-
93	"	C.	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
95	"	C.	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
96	Melanoma	P.C.	-	-	-	1	1	1	1	-	-	2	-	-	2	-	-	2	-	-	-	-	-	-	2	-	-	-
97	"	M.P.E.H.	-	-	-	-	1	1	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-
99	Unknown	C.	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-
100	"	V.C.Th.F.	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102	"	N,C.	2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
105	Others	D.C.	-	-	-	-	1	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-
106	"	D.	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

KEY 1 = Mild to moderate

2 = Moderate to severe

3 = Very severe

TABLE 32

NATURE OF SUPPORTIVE THERAPY - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS

NATURE OF SUPPORTIVE THERAPY	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Blood Transfusion	M	5*	4*	1	-	-	8	7	-	9	33	56
	F	-	1	-	-	9	6	2	1	4	23	
2. Platelet Transfusion	M	1	-	-	-	-	-	-	-	-	1	1
	F	-	-	-	-	-	-	-	-	-	-	
3. Antibiotics	M	3	4	-	2	-	-	1	-	1	11	14
(a) Tetracycline	F	-	-	-	-	1	-	-	2	-	3	
(b) Penicillin	M	4	7	1	-	-	2	4	1	6	25	29
	F	-	-	-	-	1	1	1	1	-	4	
(c) Streptomycin	M	-	-	1	-	-	-	3	1	1	6	8
	F	-	-	-	-	-	1	1	-	-	2	
(d) Erythromycin	M	3*	1*	-	-	-	1	1	-	1	6	6
	F	-	-	-	-	-	-	-	-	-	-	
(e) Chloramphenicol	M	1	-	-	-	-	1	1	-	-	3	3
	F	-	-	-	-	-	-	-	-	-	-	
(f) Others	M	-	1	-	-	-	-	1	-	1	3	7
	F	-	-	-	-	1	2	1	-	-	4	
4. Analgesics	M	1	2	-	-	-	3	3	-	6	15	22
	F	-	1	-	-	1	3	-	2	-	7	

* 1 case with Hodgkin's disease and carcinoma of lung

CHEMOTHERAPY OF CANCER

CAUSES OF DEATH - RESULTS BY SEX AND PRINCIPAL TUMOUR GROUPS

TABLE 33

CAUSES OF DEATH	SEX	PRINCIPAL TUMOUR GROUPS									TOTALS	
		Hodgkins (A)	Lung (B)	Lympho-sarcoma (C)	Leukaemia (D)	Breast (F)	G.U.T. (G-K)	G.I.T. (M-O)	Melanoma (Q)	Others (E.P.L.R)		
1. Progress of Disease	M	2	6	1	1	-	3	6	-	4	23	46 (59%)
	F	-	2	-	-	6	7	3	2	3	23	
2. Cardio-Respiratory Failure	M	3	4	-	-	-	1	2	-	3	13	16 (21%)
	F	-	-	-	-	2	-	-	-	1	3	
3. Septicaemia	M	-	-	-	2	-	2	-	1	1	6	8 (10%)
	F	-	-	-	-	1	-	1	-	-	2	
4. Haemorrhage	M	-	-	-	1	-	-	-	-	-	1	2 (2.5%)
	F	-	-	-	-	-	1	-	-	-	1	
5. Bone-Marrow Failure	M	-	-	-	-	-	-	1	-	-	1	2 (2.5%)
	F	-	-	-	-	-	-	1	-	-	1	
6. Renal Failure	M	-	-	1	-	-	-	-	-	1	2	2 (2.5%)
	F	-	-	-	-	-	-	-	-	-	-	
7. Others	M	-	2	-	-	-	-	-	-	-	2	2 (2.5%)
	F	-	-	-	-	-	-	-	-	-	-	
												78*

* Total Cases = 107 of which 29 were still alive at last review.

ASSESSMENT OF RESPONSE TO TREATMENT IN PRINCIPAL TUMOUR GROUPS

The benefits obtained by the use of cytotoxic drugs vary with the nature and extent of the tumour, with the particular agent used and, to a lesser extent, with the mode and route of administration employed. The results obtained in this study largely accord with those reported by other workers. [22,23,24,37,40,41,46,78.]

1. Malignant Disorders of the Reticulo-endothelial System and Blood-forming Organs (14 Cases)

a) Hodgkin's Disease (7 Cases)

Even with the small numbers available, it is clear that cytotoxic agents are of value in controlling the symptoms and progress of Hodgkin's Disease. The alkylating agents, nitrogen mustard, mannitol mustard and cyclophosphamide were found to be the most useful in this condition. Vinblastine sulphate and, in one case, uracil mustard have proved of benefit in producing further remission when relapse occurs with other agents.

b) Lymphosarcoma (3 Cases)

Cyclophosphamide and vinblastine sulphate produced worthwhile remission in two of the three cases of lymphosarcoma but were without effect in the third case. This virulent form of malignant disease requires the application of all modalities of treatment of which /

which chemotherapy is perhaps the most important. Evenso, prognosis remains uniformly bad.

c) Leukaemia (4 Cases)

Worthwhile remission was obtained in one case of acute myeloid leukaemia using 6-mercapto-purine but in the remaining three cases, one of which was acute monocytic leukaemia, nitrogen mustard and cyclophosphamide were used without effect.

In each of the above groups, the use of cortico-steroids has a definite part to play in the control of symptoms and in the maintenance of remission. They are of particular value in patients who develop haemolytic anaemia or thrombocytocaemia. There is no evidence, however, that they prolong life and the complications of their use are considerable.

2. Carcinoma of the Lung (15 Cases)

Subjective and objective improvement was obtained in approximately 50 per cent of the cases of carcinoma of the lung treated in this study. The principal agents used were cyclophosphamide and nitrogen mustard. The greatest benefit was obtained in those patients who had not received prior radiotherapy or in whom radiotherapy had been given a minimum of three months previously. Remissions were usually short-lived, but in two cases the disease was controlled for one year.

3. /

3. Carcinoma of Breast (22 Cases)

Cytotoxins have a definite part to play in the control of advanced carcinoma of breast as confirmed by this study. In addition, carcinoma of breast lends itself to the prophylactic use of cytotoxic drugs and although the patients in this series have not been followed for a sufficient period of time, there is evidence from other centres [31,55,58,60] that definite benefit accrues from such use. The agents most useful have been cyclophosphamide, thiotepa and vinblastine sulphate. The combination of cyclophosphamide systemically and thiotepa intrapleurally or intraperitoneally is of particular value. Cyclophosphamide and vinblastine have also proved a satisfactory and effective combination. Some of the most satisfactory and complete remissions were obtained in this group and, in two cases, extended over a period of one year. Approximately 30 per cent of the patients obtain a good to excellent subjective and objective response and a further 10 per cent experience subjective benefit. Two of the cases of carcinoma of the breast in this series were considered to have been harmed in that their deaths were probably accelerated by the use of cytotoxic drugs.

4. Malignant Tumours of the Genito-urinary system (18 Cases)

a) Carcinoma of Ovary (6 Cases)

Carcinoma of the ovary is particularly amenable to cytotoxic /

cytotoxic therapy with agents such as cyclophosphamide and thiotepa. In the six cases in this series, good tumour regression and prolonged control were obtained in four. In the remaining two cases slight subjective benefit was obtained in one and no effect in the other.

b) Testicular Tumours (5 Cases)

Malignant disease of the testis, once it escapes the control of surgery and radiotherapy, is only slightly influenced by the use of cytotoxic agents including methotrexate, vinblastine sulphate and cyclophosphamide. Transient subjective control was obtained in two cases, but objective benefit was not evident.

c) Renal Carcinoma (5 Cases)

In the five cases of renal carcinoma treated, subjective improvement was obtained in two cases with the use of cyclophosphamide by intra-arterial injection. Objective improvement alone was obtained in one case using intravenous cyclophosphamide. Marked resolution of pulmonary metastases was, however, accompanied by the development of severe toxic effects and the patient remained throughout her course in hospital (Case No. 65. Fig. 3).

d) Carcinoma of Bladder (1 Case) and Prostate (1 Case)

No benefit was obtained in the one case of carcinoma of the bladder using 5-fluouracil or in the one case of carcinoma of the /

the prostate with cyclophosphamide. In this last case severe depression of the bone marrow occurred and accelerated the patient's death.

5. Malignant Lesions of the Gastro-intestinal Tract (19 Cases)

The response of gastro-intestinal tumours to cytotoxic therapy has been studied with particular interest. These tumours are generally regarded as non-sensitive to radiotherapy and to chemotherapy. Some benefit has, however, been obtained in 40 per cent of the cases of gastro-intestinal malignancy treated in this series. The principal chemotherapeutic agents used were methotrexate and thiocolciran in combination, and cyclophosphamide alone or in combination with thiotepa or vinblastine.

5-Fluouracil[54,56] was not used in this series, but reports in the literature suggest that this is the most satisfactory agent available for treating tumours of the gastro-intestinal tract.

a) Carcinoma of Oesophagus (2 Cases)

No benefit was obtained in either of the two cases of carcinoma of the oesophagus using cyclophosphamide.

b) Carcinoma of Stomach (8 Cases)

The response of gastric carcinoma to cytotoxic agents has been poor, but subjective benefit lasting for periods of three to five months was obtained in three cases using methotrexate and thiocolciran. /

thiocolciran.

c) Carcinoma of Colon and Rectum (9 Cases)

In carcinoma of the colon subjective benefit was obtained in three cases and objective benefit in two, using combinations of methotrexate and thiocolciran, cyclophosphamide and vinblastine sulphate, or cyclophosphamide alone.

d) Carcinoma of Pancreas (4 Cases - Group 'P' included under "Others" in principal tumour groups)

Four cases of carcinoma of the pancreas, included under the Group headed "Others", were treated, one with a combination of cyclophosphamide, vinblastine and mannitol mustard and three with cyclophosphamide alone. Short-lived subjective benefit was obtained in one case, but no benefit in the others.

6. Malignant Melanoma (3 Cases)

In the three cases of malignant melanoma in the series, little or no benefit was obtained with the use of phenylalanine mustard (melphelan) or 2-ethyl hyrazine. In one patient (Case No. 16) the prolonged use of melphelan is thought to have been a factor precipitating a fatal subarachnoid haemorrhage.

7. Others (8 Cases)

Included under this heading are examples of bone, cerebral and retro-peritoneal /

retro-peritoneal tumours and cases of unknown primary origin. These cases were mainly treated with cyclophosphamide alone or in combination with vinblastine, thiotepa or mannitol mustard. Subjective benefit was obtained in two of these cases and objective benefit in one, but only one patient in the group survived for more than a year from diagnosis.

In summary, it may be stated that cancer chemotherapy is of definite benefit in malignant diseases of the reticulo-endothelial system and blood-forming tissues, of the breast, ovary and lung. It is of less value, but still has a useful part to play in the management of tumours of the gastro-intestinal and genito-urinary tracts. Occasional benefit may be obtained in tumours of the pancreas, in melanomas and in tumours of unknown origin. No benefit derives from the use of cytotoxins in sarcomas and in tumours of the oesophagus, adrenal gland and larynx.

SECTION VI

DISCUSSION

a) The assessment of Response to Treatment with Cytotoxic Agents.

I Subjective Assessment
II Objective Assessment

b) The Toxic Effects of Cancer Chemotherapeutic Agents.

I Nature
II Incidence
III Significance
IV Mechanisms
V Management: rôle of supportive therapy.

c) Significance of Hepatic Metastases.

d) Causes of Death.

TABLES VIIand VIII

and

Pages 60 - 105

TABLE VII

CHEMOTHERAPY OF CANCER

MEANS USED OF ASSESSING RESPONSE

1. **Subjective Assessment**

   (a) Improved appetite
   (b) Improved wellbeing
   (c) Reduction or loss of pain
   (d) Improved function

2. **Objective Assessment**

   (a) Arrest of tumour growth
   (b) Measurable decrease in size or volume of a tumour or its metastases
      (i) visible
      (ii) by X-ray

   (c) Biochemical changes
   (d) Weight gain
   (e) Reduced pyrexia, bleeding or discharge

TABLE VIII

CHEMOTHERAPY OF CANCER

TOXIC SIDE-EFFECTS OF TREATMENT

1. Gastro-intestinal Tract

   (a) Nausea and vomiting
   (b) Diarrhoea
   (c) Pain
   (d) Bucco-labial ulceration and bleeding ("sore gums")
   (e) Sloughing of mucosa
   (f) Liver damage

2. Bone Marrow

   (a) Anaemia
   (b) Leucopenia
   (c) Thrombocytopenia
   (d) Complete failure

3. Integuments

   (a) Dry, scaly skin
   (b) Alopecia
   (c) Ulceration at injection site
   (d) Rashes

4. Central Nervous System

   (a) Neuritis
   (b) Depression
   (c) Hallucinations and paranoia

5. Others

   Lowering of host resistance to infection

   (a) Respiratory infection
   (b) Genito-urinary tract infection
   (c) Wound infection and wound healing
   (d) Gram-negative septicaemia

   Suppression of immunity

DISCUSSION

The advent of effective chemotherapy has provided a further approach to the management of malignant disease. Used alone, or as an adjunct to surgery or irradiation, the agents at present available have much to offer. While principally indicated in the management of the advanced case, cytotoxins may now be employed to prevent or control spread and recrudescence. By using combinations of drugs, attacking different metabolic pathways within the cell, effectiveness may be increased and toxicity reduced. Sophisticated techniques, such as perfusion, alterations of oxygen tension[84] or pH[85], and autologous marrow infusion[86] are of value in specialised units, but, in the practical management of cancer, simplified, low-cost, out-patient chemotherapy is the desired aim.

Objective means of assessing response are essential if results obtained in different series are to be compared and observer bias is to be eradicated. Biochemical changes in blood and urine, following the exhibition of cytotoxic agents, constitute the most fruitful line of research and it should be possible to identify, at an early stage, those patients being benefitted. Almost as important, is the identification of those patients in whom continued use of cytotoxins is unlikely to prove beneficial, so that treatment may be withdrawn and hazards avoided.

The incidence and severity of toxic effects may also be reduced by /

by controlled maintenance therapy at sub-toxic dose levels. The occurrence of these effects, however, will continue to limit the application of cytotoxic agents and much research will be required before ideal agents become available.

The assessment of response to treatment, the incidence, severity, significance and management of toxic effects, the significance of hepatic metastases in relation to response and toxicity and the cause of death in treated patients, are considered the outstanding problems in cancer chemotherapy. These aspects constitute the main points of this discussion.

DISCUSSION

a) The Assessment of Response to Treatment with Cytotoxic Agents (Tables VII and 27).

The assessment of response to treatment constitutes one of the most difficult aspects of cancer chemotherapy. So many problems are involved in the management of patients with advanced malignant disease, that surmise, impression and observer bias cannot be entirely eradicated from the assessment of a controversial treatment. The mere placebo effect of an interested medical attendant, regularly reviewing a patient with advanced cancer, may be considerable. The physician may convey his own enthusiasm to the patient with the result that the correct interpretation of symptoms and even of clinical signs is delayed or avoided. Particular stress has accordingly been placed, throughout this study, on achieving an accurate and unbiased assessment of response to treatment. This may be discussed under the two broad headings of Subjective Assessment and Objective Assessment.

I. SUBJECTIVE ASSESSMENT

a) Improved appetite

b) Improved well-being

c) Reduction or loss of pain

d) Improved function.

a) /

a) Improved appetite and b) Improved well-being

Improvement in appetite and general well-being may represent no more than the effect of such measures as bedrest, reassurance, correction of anaemia, or intercurrent infection, or result from a palliative surgical procedure. They are of little real value in assessing response to cytotoxic therapy.

c) Reduction or loss of pain

The significance of reduction or loss of pain may be difficult to determine and may equally well result from the use of simple supportive measures such as rest, sedation and analgesia. If, however, pain has been severe and previously unrelieved by analgesics, then relief following rapidly on the exhibition of cytotoxic drugs may be reasonably ascribed to their effects.

d) Improved function

Improvement in function of an affected system, organ or limb, for example, improvement in liver function, reduction of dyspnoea following correction of a malignant pleural effusion, or return of function in a limb by relief of tumour compression of nerve roots, following cytotoxic therapy, is also difficult to assess. The mere mechanical removal of fluid from the chest or abdomen may be sufficient to account for any improvement which ensues, while reduction of associated oedema and infection may simulate reduction in /

in tumour mass.

While subjective improvement following the exhibition of cytotoxic agents has been carefully noted throughout this study, little significance can be attached to the findings recorded (Table No.27.)

II. OBJECTIVE ASSESSMENT

a) Arrest of tumour growth.

b) Measurable decrease in size or volume of a tumour or its metastases.

c) Biochemical changes: significance of changes in α_2 globulin and serum uric acid.

d) Weight gain.

e) Reduced pyrexia, bleeding or discharge.

f) Morphological changes in tumours.

The only acceptable means of assessing tumour response to cytotoxic drugs are objective and include a) the demonstration of arrest of a tumour or its metastases when, previously, growth had been rapid and obvious; b) a decrease in size or volume of a tumour or its metastases on direct measurement or on serial X-ray examination. The results detailed in Table 27 fulfil these criteria.and little significance can be attached to published reports, unless the results obtained are based on similar assessments.

c) Biochemical changes; the determination of biochemical changes either in the blood or urine, e.g. changes in serum or urine uric acid, in serum protein patterns or in certain serum enzymes, constitutes /

constitutes the most effective and most promising line of objective assessment. Changes in plasma proteins, serum electrophoretic patterns and serum uric acid levels, form an important aspect of this study.

Significance of changes in α_2 globulin and serum uric acid.[79,80]

It is believed that a definite relationship exists between tumour response and changes in the serum electrophoretic pattern and that tumour breakdown results in measurable changes in serum uric acid levels.

It can be seen from Table 28 that in 60% of the cases in this series, the α_2 globulin fraction of the serum electrophoretic pattern was raised, often to a marked degree, when the patient first presented. If cases demonstrating advanced disease or metastases were considered alone, then the percentage showing a raised α_2 globulin fraction was 75.

From this table it can also be seen that the serum uric acid was initially raised in 30% of the patients and could be further altered by treatment with cytotoxic drugs.

The significance of these changes in the α_2 globulin and uric acid levels in relation to the chemotherapy of malignant disease has already been made the subject of a separate study.[79] The main conclusions of this study were that changes in the α_2 globulin fraction of the serum electrophoretic pattern are a guide to tumour activity following treatment with cytotoxic drugs. A persistently raised level /

level suggests continued activity and a falling level, tumour control. Changes in the serum uric acid level were similarly considered to represent alterations in tumour breakdown.

Combining the changes in α_2 globulin and serum uric acid levels, estimated before and at frequent intervals during the administration of cytotoxic drugs, is considered a valuable objective means of assessing tumour response. Furthermore, this assessment can be made within two to three weeks of commencing treatment in those cases in which response is likely to occur. By this means the small percentage of patients with solid tumours likely to be improved by continued cytotoxic therapy can be identified and the remainder spared the potential hazards of treatment which will not be beneficial. This work remains incomplete and continued studies are necessary.

d) Weight gain

One of the most sensitive indices of active malignant disease is anorexia. Loss of appetite results in loss of weight and while improvement in appetite may result from a number of other factors, as discussed above, positive gain in weight may be regarded as an objective indication of improvement. Patients in this study have accordingly been weighed before and at intervals during treatment and gain in weight included under "Objective benefit" in Table 27.

e) Reduced pyrexia, bleeding or discharge

If /

If infection can be excluded, then reduction of pyrexia, bleeding or discharge from a tumour may also be regarded as objective evidence of response. Their importance in this context is, however, largely confined to the assessment of response in malignant disorders of the reticulo-endothelial system and blood-forming organs.

f) Morphological changes in tumours following cytotoxic therapy [76]

As detailed in an earlier section, this aspect of the study, because of the difficulties involved in processing post-mortem material and in getting a series of suitable biopsies for study, was abandoned and it is hoped will be taken up in due course.

In the final assessment of tumour response to chemotherapy the only criterion of success is the extent by which a patient's endurable and useful life may be prolonged. Less emphasis has been placed in this study on the total duration of response or survival (Table 20) than on the quality of response obtained over even short periods. Little significance has been attached to the time spent as a hospital in-patient. The aim of treatment has been to maintain the patient on an out-patient regime and, whenever possible, to restore the patient to normal activities. Such assessment requires repeated out-patient review, the correction of associated conditions, such as anaemia, intercurrent infection and intermittent bouts of vomiting

or /

or diarrhoea and continuous reassurance. By these means, patients have frequently remained at home and active when they would otherwise have been admitted to hospital for terminal care. In cancer chemotherapy, the tumour being treated will, with few exceptions, inevitably escape control within a matter of weeks or months. It is believed by some that if remission is obtained treatment should be stopped until relapse commences when a further course of therapy is given in an attempt to achieve further remission. By this means two, three or more courses of the same or of a different agent may be employed at intervals of a few weeks to a few months. Others believe that if remission is obtained, treatment should be continued to prevent relapse and that maintenance treatment with a small dose is unlikely to produce severe toxic effects without adequate warning. Both methods have been employed in this study and the weight of evidence is in favour of a regime which combines an initial intensive intravenous, intra-arterial or intra-cavitary course of treatment as an in-patient, with low-dose oral or intravenous out-patient therapy.

b) THE TOXIC EFFECTS OF CANCER CHEMOTHERAPEUTIC AGENTS
(Figs. 1-8) Tables VIII, 30 and 31.

The hazards associated with the administration of cytotoxic drugs is the most important factor limiting their usefulness, while the incidence and severity of the toxic effects produced frequently determine the total dosage and the duration of treatment. This toxicity derives, not from an inherent property, but from the similarity of their action on normal and malignant cells. The principal toxic effects involve, therefore, the rapidly dividing tissues such as those of the bone marrow, liver and gastro-intestinal tract. The minor qualitative differences which exist between malignant and normal cells, cannot yet be exploited clinically and at this stage the occurrence of toxicity is inseparable from the use of anti-cancer drugs.

I & II Nature and Incidence of Toxic effects

The toxic effects encountered in this study may be grouped under five main headings as detailed in Table VII

1. Gastro-intestinal Tract

   a. Anorexia, nausea and vomiting.

   b. Diarrhoea.

   c. Pain.

   d. Bucco-labial ulceration and bleeding.

   e. /

e. Sloughing of mucosa. f. Liver damage.

Disturbances of gastro-intestinal function are common during treatment with cytotoxic drugs, particularly with those of the alkylating group. Although the effects produced are more severe with some drugs, e.g. nitrogen mustard, than with others, e.g. cyclophosphamide, the incidence and severity of these effects are more closely related to duration of treatment and total dosage than to the agents themselves.

Anorexia and nausea were experienced at some stage by most of the patients in the study. Usually mild and of short duration, these symptoms were readily controlled by anti-emetics and did not necessitatechanges in treatment. Vomiting, which could be directly attributed to cytotoxins, occurred in twenty-four patients (23%). In three cases it was mild to moderate and required temporary reduction in dosage only; in the remaining twenty-one cases vomiting was of sufficient severity to warrant cessation or prolonged reduction in dosage during maintenance therapy. From the patient's point of view, nausea and vomiting are among the most distressing of the effects produced by anti-cancer drugs. While patients may remain unconcerned by low white cell or platelet counts they are often reluctant to continue with treatment producing nausea, loss of appetite and vomiting.

Diarrhoea, directly attributably to anti-cancer drugs, has occurred in 7 (6%) of the patients studied. In 6 it was considered severe and /

and required cessation of treatment; in the remaining case treatment was continued, but with a lower dose. This side effect was most commonly seen in association with drugs of the antimetabolite group. The agents particularly associated with diarrhoea were Thiocolciran, 5-fluorouracil and Methotrexate. As might be expected, diarrhoea occurred most frequently in those patients with primary gastro-intestinal tumours.

Severe pain at the site of the primary tumour or a large metastasis was experienced in 9 patients (8%) following intravenous or intra-arterial injection of cytotoxins. In 6 cases the pain was mild to moderate and could be controlled by simple analgesics, in the remaining three cases it was severe, associated with marked pallor, near collapse and only incompletely relieved by pethidine or morphine. The pain usually commenced within twenty minutes to one hour of the injection, persisted for two to six hours and then gradually subsided.

Severe bucco-labial ulceration and bleeding occurred in 6 (5%) of the patients treated and, in each case was associated with the use of Methotrexate. This distressing toxic effect was only seen when the total white cell and platelet counts were depressed. The occurrence of bucco-labial ulceration in the patients under study has been regarded as an indication to reduce or temporarily stop treatment, but in three cases treatment was subsequently resumed without further incident. Most commonly, the lesions developed

along /

along the line of lip closure in the bucco-labial sulcus or on the edges and under surface of the tongue. The invariable complaint of the patients was "soreness of the mouth" and in three cases was of sufficient severity to prevent ingestion of food or fluids.

Sloughing of the mucosa of the gastro-intestinal tract is a severe effect of certain drugs of the antimetabolite group, particularly Methotrexate. This is an extreme manifestation of the toxic effects of anti-cancer drugs on the gastro-intestinal tract and was seen in only two cases in this series. Mucosal destruction in these two cases was associated with profuse diarrhoea, dehydration, severe electrolyte imbalance, profound collapse and death. At post-mortem the appearances of the small bowel were similar to those of a necrotising enteritis. Bacteriological culture of the stools was negative in both cases, but it is believed that they represent examples of superinfection following depression of the body defence mechanisms by cytotoxic drug.
It is possible that some of the other cases of diarrhoea seen in this series were milder forms of gastro-intestinal mucosal damage, but direct proof of this is lacking.

2. <u>Bone Marrow</u>

a. Anaemia.

b. Leukopenia.

c. Thrombocytopenia.

d. Complete failure.

The/

The effects of cytotoxic agents on the bone marrow and peripheral blood picture have been studied in detail by a number of workers. In this study, examination of the bone marrow was carried out in 82 (80%) patients and of the peripheral blood in all patients prior to commencing treatment and at intervals thereafter. The changes occurring in the marrow and peripheral blood were noted and the incidence and severity of toxic depression recorded (see Table 31).

In 12 (11%) cases, most of whom received cytotoxins as a prophylactic measure only, the bone marrow showed little or no change and this was reflected by persistently normal peripheral blood counts. The principal finding in 80% of cases was a depression of all the blood forming elements of the marrow and in these cases the peripheral blood picture showed varying degrees of anaemia, leucopenia or thrombocytopenia. These changes were most frequently associated with the alkylating agents, but the antimetabolites were, by their nature, more specifically effective against the white cell series. Within these groups, certain agents are more toxic to one cell series than to others. For example, cyclophosphamide affects the white cell series without affecting the thrombocytes to the same degree. Myleran shows a selective destruction of the myeloid series as compared with the lymphoid series and is therefore of value in the treatment of chronic myeloid leukaemia.

The effects of cytotoxic agents on the blood-forming organs are largely a function of dose and duration of treatment. In three

cases/

cases (77, 78 and 70), however, an apparent sensitivity developed so that severe depression of all cell series was produced with even small amounts of drug. Complete bone marrow failure, although uncommon, may therefore occur in the very early stages of treatment, and be associated with pancytopenia and a rapid downhill course. It may also develop as a terminal event following prolonged cytotoxic therapy as in cases 31 and 71 and this stage is usually associated with severe intercurrent infection involving chest, skin and intestine.

Frequent estimations of white cell count, differential white cell count, platelet count and haemoglobin constitute the principal means of controlling cytotoxic therapy. In the majority of cases it is the effects on the bone marrow and peripheral blood which ultimately limit the application, duration of treatment and dosage of many of the cytotoxic agents. It is essential that frequent and accurate counts are available whenever patients are being treated with these drugs. If the development of toxic effects on the bone marrow are detected at an early stage, their severity may be limited by reducing the drug dosage or by temporarily withdrawing treatment. Although the effects of the drug may continue for many days after withdrawal, the bone marrow will usually recover within ten to thirty days (see Graphs of Case 65) and thereafter treatment can be resumed at the same or reduced dosage. For the purposes of this study, a white cell count of 2,000 or below, a haemoglobin of 50% or below, and /

and a platelet count of 50,000 or below have been taken as the levels at which drug therapy should be greatly reduced or withdrawn. While patients may remain active, out of hospital, and apparently well with counts below these ranges, the risk of intercurrent infection is extremely high and three deaths in the series occurred from this cause when the patient's tumour was otherwise under control.

3. Integuments

a. Alopecia.

b. Dry scaly skin.

c. Ulceration at injection site.

d. Rashes.

a. Alopecia

Although less serious in their consequences, the toxic effects of anti-cancer drugs on the skin and its appendages are a frequent concern to the patient. The most important of these effects is alopecia which may occur with any of the drugs, but is most commonly associated with alkylating agents such as thiotepa and cyclophosphamide. Hair loss may be any degree from mild to complete. It appears to be a function of dosage and duration of treatment since, cyclophosphamide, for example, if given in great enough dose for a long enough period will produce alopecia in almost every patient. This distressing side effect has been considered by some as a serious /

serious contra-indication to the use of anti-cancer drugs. It is claimed that to add an embarrassing condition to the problems of a patient dying of malignant disease is unjustified. A wig, however, is a readily prescribed and easily fitted prosthesis. Even if alopecia is marked, hair regrowth will usually occur within a period of two to four months, despite the patient remaining on treatment. Alopecia produced by anti-cancer drugs should be regarded in the same light as major ablative surgery for such conditions as osteogenic sarcoma which frequently require the fitting of a complicated, cumbersome prosthesis.

Alopecia occurred in 25 (24%) of the patients under treatment (14 female and 11 male) and in each case was associated with the prolonged use of cyclophosphamide alone, or with cyclophosphamide and thiotepa in combination. On one occasion a marked degree of hair loss was associated with the use of thiocolciran, vinblastine sulphate and a small amount of cyclophosphamide. In 8 (7%) patients hair loss was mild to moderate, and regrowth occurred in all cases within four months. In these patients treatment was continued throughout but at a reduced dosage. Moderate to severe alopecia occurred in a further 13 (12%) patients and very severe or complete hair loss in the remaining 4 (3.5%) of cases. Many of the 25 patients expressed concern when hair loss commenced, but marked distress was only evident in two, while four patients remained unconcerned by moderate to severe alopecia. As would be expected, the females were more perturbed by even minimal hair loss than were the males.

Wigs /

Wigs were provided for four patients in whom epilation was severe (Fig. 2) but in three cases the prosthesis was discarded within three months, while the fourth patient died before regrowth occurred.

In three cases alopecia occurred on two occasions, in association with courses of cyclophosphamide therapy separated by intervals of 5 months, 8 months and 11 months. In each case hair loss was more marked and occurred at an earlier stage on the second than on the first occasion. In two cases the second episode of alopecia was associated with the terminal stages of cancer and hair loss was still marked at death.

b. Dry, scaly skin

The development of a dry scaly skin in association with cytotoxic therapy was seen in 48 (46%) of the patients treated. In many of these the skin changes were considered to largely reflect the nature and extent of the malignant process and to be only partly attributable to the action of the drugs. Varying degrees of brown pigmentation of the skin was also a common feature and in only two cases could be ascribed to metastatic lesions involving the adrenal glands. Few patients complained of these skin changes, but accepted them as part of their general illness.

c. Ulceration at injection site

An indolent ulcer at the site of intravenous injection occurred in two cases in this study. In both cases the ulcer was associated with /

with accidental extra-vascular injection of an alkylating agent, being used prophylactically. The agent concerned in one case was mannitol mustard and the injection site was the dorsum of the foot, the injection being given during the course of a general anaesthetic. The ulcer failed to heal and excision and grafting were ultimately required. In the second case nitrogen mustard was used in an ante-cubital vein and produced a small shallow, indolent ulcer which healed with conservative therapy over a period of three months.

The avoidance of this troublesome complication requires continuous care during the intravenous or intra-arterial injection of cytotoxic drugs, particularly those of the alkylating group. If the least pain is experienced at the injection site the injection should be stopped and given elsewhere; when using agents such as nitrogen mustard or mannitol mustard they must always be diluted with sterile water or normal saline.

d. Rashes

Three patients in the series developed skin rashes considered due to the administration of anti-cancer drugs. In two cases the rash took the form of a generalised papular eruption most marked on the face and forehead (Fig. 3). In both cases the underlying disorder was Hodgkin's disease and drug being used was vinblastine sulphate (velbe). In the third case, a patient with carcinoma of the /

the stomach, a haemorrhagic-purpuric rash, confined to the trunk and upper arms developed in association with the use of methotrexate (Fig. 4). The platelet count remained normal in this case, but there was a severe depression of the white cell count at the height of the rash. In all three cases the rash slowly cleared following temporary cessation of treatment and did not recur when treatment was resumed with reduced dosages.

Central Nervous System (Neuritis, depression, hallucinations and paranoia)

Toxic effects on the central nervous system, directly attributable to the use of anti-cancer drugs, were uncommon in this study. Two patients, one with lymphosarcoma (Case No.23) and the other with carcinoma of the lung (Case No.11), developed marked peripheral neuritis while on treatment with cyclophosphamide. Neurological changes are known, however, to occur as a feature of malignant disease and the part therefore played by cytotoxins in these cases is uncertain. Mild to moderate depression was a common symptom among the patients under study. In many it resulted from failing general health, from the patients increasing awareness of the true situation and from the increasing limitations imposed on normal activities by advancing malignant disease. In five cases (4.3%), however, endogenous depression developed at an early stage and was of marked degree. Three of these patients were receiving vinblastine sulphate (Cases No. 2, 53 and 72), one cyclophosphamide (Case /

(Case No. 17) and one phenylalanine (Case No. 96). In all of these patients depressive symptoms persisted while drug therapy was maintained, but responded to the use of tranquillizer drugs and the temporary cessation of treatment.

Hallucinations, resulting particularly from the use of vinblastine sulphate were severe, in Cases No. 23, 25 and 65, and in one preceded coma resulting from hyperuricaemia (Case No. 25). In the other two cases hallucinations occurred with the first few doses of vinblastine sulphate, but coincided with a dramatic improvement in general state and marked regression of the disease process. One patient (Case No. 51) demonstrated severe paranoid tendencies while on long term maintenance therapy with cyclophosphamide and required temporary admission to a mental hospital. These symptoms resolved spontaneously within three weeks of discontinuing cyclophosphamide and instituting therapy with chlorpromazine. Mild paranoid states were evident in a further two patients, one (Case No. 57) receiving a combination of cyclophosphamide and thiotepa and one (Case No. 65) receiving vinblastine sulphate. Psychiatric disturbances are common in patients suffering from malignant disease, even when cytotoxins are not exhibited and exact role of these agents in producing such clinical states is therefore uncertain.

Other Side-effects

1 /

Fig. 1: Cyclophosphamide induced alopecia: Case 55.

Fig. 2: Same case with wig.

Fig. 3: Vinblastine induced rash: Case 4.

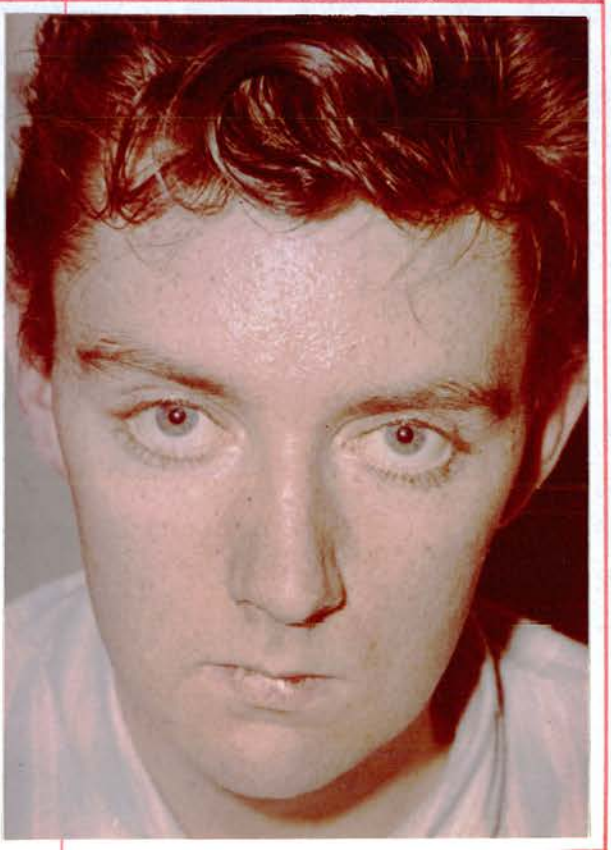


Fig. 4: Buccal bleeding and ulceration: Methotrexate.

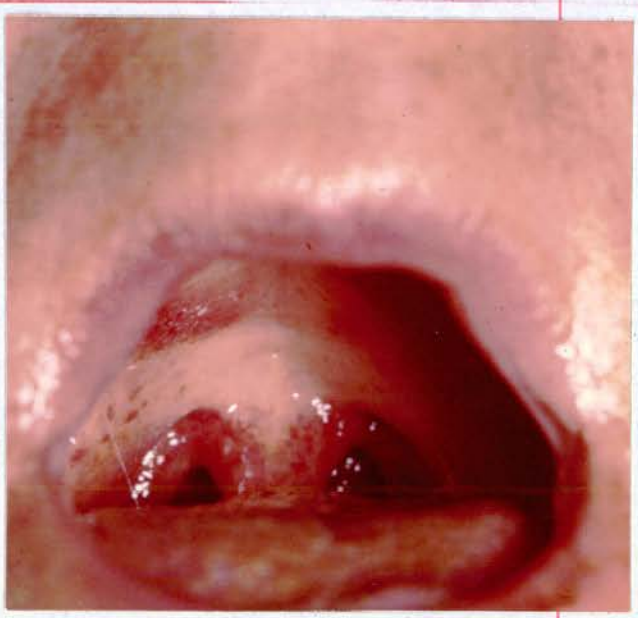


Fig. 5: Haemorrhagic rash - Methotrexate (Case not included in series).

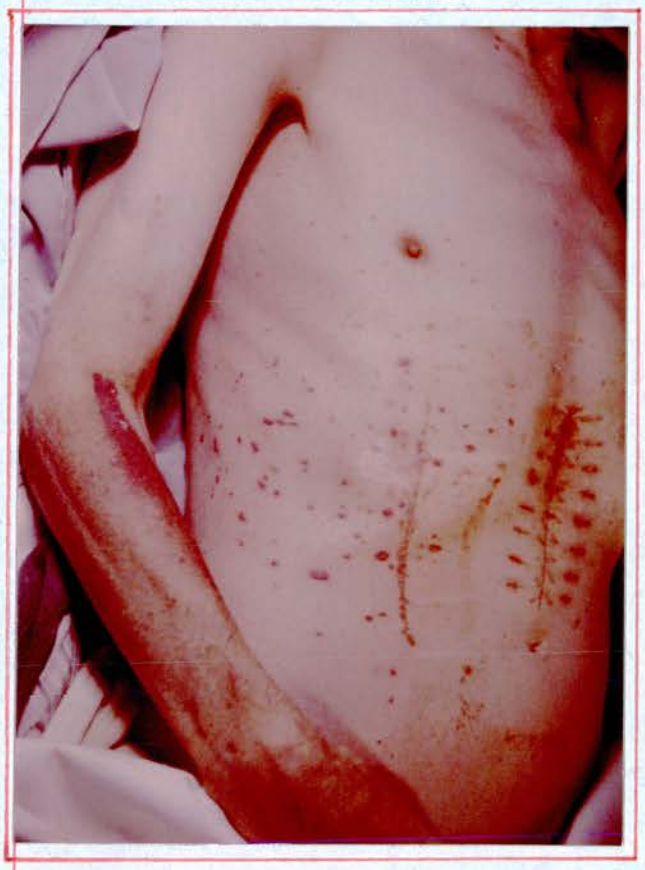


Fig. 6: Indolent induration at site of injection of vinblastine sulphate - dorsum of hand.

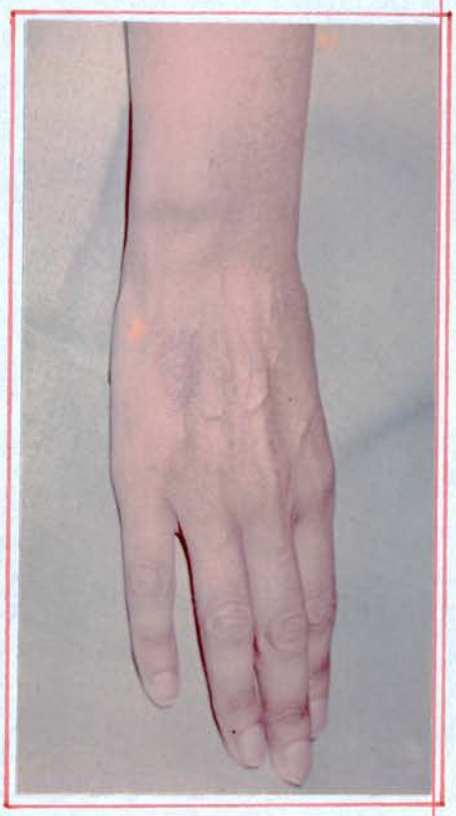


Fig. 7: Radical mastectomy: infusion of cyclophosphamide via internal mammary artery: Case 42: 10 days post-operation.

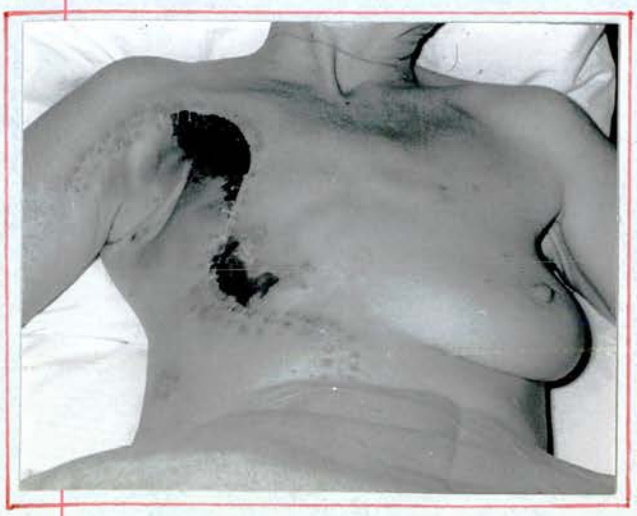
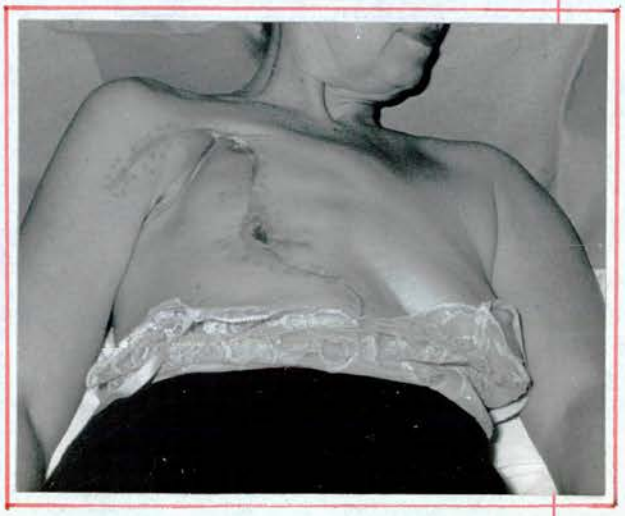


Fig. 8: Same case: 6 weeks post-operation.



1. Lowering of Host Resistance to Infection

Declining general health from progressive malignant disease is frequently associated with an increased incidence of respiratory tract, urinary tract, wound and skin infection. In patients receiving cytotoxic drugs the effects on the blood-forming elements and reticulo-endothelial system are likely to increase the incidence and severity of such infections. It is considered, however, that the part played by low white blood counts in producing infection has been over-emphasised. Many patients in this series remained well and active with total white cell counts below 3,000 per cubic millimetre. In three patients (Cases nos. 2, 27 and 31) with white cell counts below 1,500 and exposed to a hospital environment for long periods, ulceration and infection developed around the nose and mouth and resisted attempts at healing until the peripheral blood picture improved.

a. Respiratory Infection

The incidence of significant respiratory tract infection (6%) was no higher in this group of patients than in a group of post-operative patients not receiving cytotoxic drugs. It was, however, noted that many patients complained of persistent coryzal symptoms which were often difficult to eradicate and one patient (Case No.91) experienced symptoms of chronic sinusitis for five months.

b. /

b. Genito-urinary Tract Infection

The incidence of urinary tract infection was found to be no higher in patients treated with cytotoxic drugs than in control patients. With the exception of haemorrhagic cystitis, seen on three occasions (Cases Nos. 10, 67 and 99) in association with cyclophosphamide therapy and resolving on cessation of drug therapy, major infections of the genito-urinary tract were not encountered in this study. In the 22 cases in which the urine was examined bacteriologically, pathogenic organisms were cultured in 9 (40%). The majority of these patients were symptomless and the urine was rendered sterile by sulphonamide or antibiotic therapy. Two cases, 17 and 53, developed moderately severe non-haemorrhagic cystitis with positive urine cultures. These were both associated with the use of cyclophosphamide but responded to antibiotic therapy.

c. Wound Infection and Wound Healing

It has been stated that cytotoxins delay healing of wounds and predispose to a high incidence of wound infection. All wound complications occurring in the series have been attributed to the use of cytotoxins despite the possibility of other factors playing a part. Three patients (Cases nos. 39, 42 and 86) demonstrated delayed wound healing and one of these is illustrated (Figs 7 and 8 Case no. 42). The incidence of wound dehiscence does not appear to be increased by treatment with anti-cancer drugs and occurred in only /

only two patients in the series. One of these, Case no. 56 had received cytotoxins for three weeks before operation, but the second, Case no. 86, had received only one dose of mannitol mustard prior to the episode of wound dehiscence. In the great majority of cases primary, uncomplicated wound healing occurred despite patients, in some cases, receiving cytotoxins, for many weeks prior to operation. If surgical technique is good, the occurrence of these side effects should not influence the use of anti-cancer drugs or the timing of a surgical operation.

d. Gram-negative Septicaemia

An E-coli septicaemia was established as the cause of death in two of the patients (Cases nos. 30 and 102) dying in hospital. In these two cases the E-coli septicaemia was the final event in a terminal illness. In three cases (32, 77 and 78) overwhelming clinical infection developed within a short time of commencing cytotoxic therapy but bacteriological proof of Gram-negative septicaemia was lacking. Septicaemia was believed to be the final event in a further four patients (Case nos. 2, 3, 96 and 100) in or approaching the terminal stages of their disease, but blood cultures were again negative. In all cases the onset of clinical septicaemia was preceded by moderate to severe depression of bone marrow function. It is believed that overwhelming Gram-negative infection is an important cause of death in patients receiving cytotoxic therapy and will be further discussed in a later section.

2. /

2. "Suppression of Immunity" [3,81]

The possibility that cytotoxic drugs may act in a harmful manner by suppressing the "immunity mechanisms" of the host has been investigated by a number of workers both in the experimental animal and, on a much smaller scale, in the human patient. The anti-cancer drugs, cyclophosphamide and imuran are employed in renal homotransplantation to suppress the antigen-antibody reactions involved in host rejection of a transplant. These drugs must similarly suppress antibody mechanisms in those patients being treated for cancer. If it is accepted that a host-tumour relationship exists and that this relationship may be adversely affected by suppression of host resistance, then, from the above analogy, it is clear that certain cytotoxic agents may actually favour the growth and spread of tumours. In the experimental animal it has been shown that pre-treatment with, or con-current administration of, nitrogen mustard will suppress the antibody response to typhoid antigen in the rabbit (Spier, 1947).[3] Philips et al. (1947)[81] found antibody response to a booster dose of antigen in previously immunised goats was delayed in onset, or decreased in extent after pre-treatment with nitrogen mustard. Preston and others (1960)[82] found that there was no suitable reduction in the natural resistance to the development of lymphosarcoma in rats when treated with nitrogen mustard, but there was considerable depression of /

of this resistance with steroids, cyclophosphamides and 5-fluouracil. Similar results have been obtained by other workers, using a wide variety of experimental animals including goats and chickens, the most marked effects being obtained with such agents as 6-mecapto-purine, cyclophosphamide, nitrogen mustard and 5-fluouracil. In eight patients with advanced malignant disease Woodruff and Nolan (1965) showed that injections of homologous splenic cells produced detectable tumour regression in one case; again suggesting the presence of an immune mechanism. Particular note was taken throughout this study of any feature or event which might suggest the existence of, or changes in, tumour-host resistance. In this context, it was noted that within a short time of commencing cytotoxic therapy six patients demonstrated rapid and widespread dissemination of a previously slowly-growing tumour. This suggests a possible break-down in host immunity mechanisms in favour of the tumour. Proof of this is, however, lacking and further study of the problem is required. It was also noted that many patients remained well and active with normal appetite and increasing weight, despite a steadily growing and progressively disseminating tumour. This commensal-like relationship between host and tumour suggests suppression of defence mechanisms, the normal functioning of which might be responsible for some of the features of the "cancer illness." Tumour growth continues uninhibited, but the patient is spared the metabolic burden /

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burden of maintaining active resistance and reserves are utilised for other purposes. If this hypothesis is tenable, then much of the negative nitrogen balance, the increasing weight loss, toxaemia and the feeling of general malaise associated with cancer may represent the toll of host resistance. A final point of interest is that, in some cases, the bulk of tumour found at post-mortem was of a degree quite unsuspected clinically. Compared with the post-mortem findings in a small group of comparable patients by age and tumour type the increased bulk of tumour in patients receiving anti-cancer drugs suggests that this feature is of significance. It may again indicate a lowering of the host resistance, favouring rapid growth of the widespread primary tumour and the development of widespread metastases.

II Incidence of Toxic Effects

The incidence of toxic effects, in relation to nature and duration of drug treatment, in the patients studied is detailed in Table 31.

III The Significance of Toxic Effects

It has been repeatedly stated that anti-cancer drugs must be given to "toxic levels" in order to produce clinical effect. The development of toxic side-effects, however, implies impairment of the patient's condition, the development of unpleasant symptoms, a reduction /

reduction in appetite, food intake and disturbances of fluid and electrolyte balance from vomiting and diarrhoea. It is manifest, therefore, that the occurrence of toxic effects detracts from the principle aim of treatment. This aim should be the production of maximal palliation of the disease and its effects with minimal distress to the patient. If tumour-host resistance is depressed by cytotoxic therapy, then it is again evident that more harm than good may ensue by continuing treatment to toxic levels. The belief that anti-cancer drugs must be given to toxic levels before clinical response is produced pre-supposes that these represent the most effective therapeutic levels. I believe that a good response may be obtained with sub-toxic levels of a drug in the same proportion of patients as would be obtained with levels producing severe side-effects. As indicated by this study, only 20 to 30 per cent of patients treated will achieve significant benefit from the use of cytotoxins. It is clearly undesirable to subject the remaining 70 to 80 per cent of patients to the hazards of high dosage therapy when there is no possibility of benefit being produced. Throughout this study an attempt has been made to relate response to toxic effects and to obtain support for the hypothesis that toxic levels are unnecessary to produce clinical benefit. The incidence and severity of side-effects are closely related to the agent used, the total dose given and the duration of treatment. In some cases, however, they develop acutely and closely /

closely mimic a hypersensitivity reaction. Severe and often fatal effects may therefore appear within a short time of commencing treatment, or may only develop after a prolonged period of treatment during which the patient receives a large dose of cytotoxins. This study has shown that sub-toxic levels of anti-cancer drugs are compatible with a good and sustained clinical response, but it is equally clear that the most dramatic results occurred in those cases receiving a large amount of drug over a short period of time and who survived the development of severe toxic effects such as bone marrow depression, vomiting, epigastric pain and buccal ulceration. In some of these patients marked tumour regression occurred and persisted for periods of up to six months, during which small doses of maintenance therapy were continued. The distress occasioned by the occurrence of toxic effects, together with the period of in-patient treatment required for their control, further support the belief that therapy should aim at sub-toxic levels so that the patient may remain active and reasonably well while receiving treatment for an inevitably fatal condition. Cancer chemotherapy should not be employed to prolong a miserable existence.

IV Mechanisms of Production of Toxic Side Effects

These may be summarised as follows:-

1. Direct irritant action on cells and tissues.

2. /

2. Central effects on brain-stem centres.
3. Depression or inactivation of cell enzymes systems - "cytotoxic" action.
4. Inhibition or antagonism of co-enzymes and other essential metabolites in cellular metabolism.
5. Effects resulting from presence of breakdown products in blood and urine.
6. Effects of action on specific cells, e.g. small lymphocytes.

1. Direct Irritant Action

Certain of the cytotoxic agents, particularly those belonging to the alkylating group, have a powerful irritant or vesicant action on tissues. This is well demonstrated when even a small amount of an agent such as nitrogen mustard or mannitol mustard, escapes into the tissues during an intravenous or intra-arterial injection. An area of induration develops around the injection site and extends into the surrounding tissues one or two centimetres (Fig. 6). The centre of this area becomes necrotic and breaks down to leave a shallow, indolent ulcer which may take many weeks to heal. The irritant nature of these agents is also demonstrated by the frequency of superficial vein thrombosis following the single injection of a large dose or repeated use of the same vein . Direct irritant action probably explains many cases of nausea /

nausea, vomiting and diarrhoea associated with the use of cytotoxic drugs. This is most likely to occur when the drugs are administered by mouth.

2. Central Effects

Central effects on brain-stem centres probably account for such features as nausea, vomiting and anorexia which occur almost invariably on commencing cytotoxic therapy by whatever route. The exact mechanism of these effects is unknown, but is possibly related to changes in cellular tonicity.

3. Direct Toxic Action on Cell-enzyme Systems

Many of the toxic effects of anti-cancer drugs are due to their action as non-specific cell-poisons resulting in depression, inactivation or destruction of cell enzyme systems and ultimately to disruption of cellular metabolism. This "cytotoxic"action is particularly marked on the nucleic acids and their precursors so that the vital processes of cell division and reproduction are disrupted and the cell destroyed. The wide distribution of cytotoxic agents in all tissues accounts for many of the effects, such as depression of bone marrow function, hair loss, disturbance of cerebral function and ulceration of epithelial surfaces, which accompany their use.

The biochemical differences which exist between malignant and normal /

normal cells are mainly of a quantitative nature and only a few minor differences have so far been discovered between the two types of cell. It is unlikely, therefore, that drugs will be readily discovered that will be effective against malignant cells and leave normal cells unharmed. The effects of cytotoxic agents on normal cells will continue, therefore, to limit their usefulness, but with further research it is to be hoped that exploitable differences between malignant and normal cells will progressively emerge.

4. Inhibition or Antagonism of Essential Metabolites

The inhibition or antagonism of co-enzymes and certain metabolites, essential to the economy of the cell, is the mechanism of action of the antimetabolite group of agents. They are particularly active against the rapidly dividing cells of the bone marrow and gastro-intestinal mucosa and the development of severe toxic effects is readily understood. Employed as effective agents in the management of disorders of the reticulo-endothelial system and blood-forming organs, the margin between therapeutic and toxic levels is small and limits dosage and duration of their administration.

5. Breakdown Products in Blood and Urine

The destruction of rapidly dividing cells results in an excess of /

of metabolic breakdown products, particularly potassium, uric acid and amino acids, in the blood and urine. The use of cytotoxic agents in highly sensitive tumours, for example, in lymphosarcoma, may precipitate a state of acute mental confusion associated with drowsiness and, in some cases, acute renal failure from hyperuricaemia and the deposition of uric acid crystals in the renal tubules. It is possible that less marked degrees of cerebral disturbance, malaise and depression may result from the presence of excess breakdown products, particularly potassium and certain amino-acids in the circulation. It has been noted in this study that patients receiving a single large dose or infusion of a cytotoxic agent have occasionally demonstrated such effects and that in some of these the serum uric acid has reached levels of two or three times normal.

6. Effects on Specific Cells

Many of the effects of cytotoxic drugs on the bone marrow may be explained on the basis of non-specific cell-poisoning, but certain agents such as Busulphan (myleran) and chlorambucil (leukeron) are particularly effective against specific cell lines in the myeloid and lymphoid series respectively.

If suppression of "immunity mechanisms" by cytotoxic drugs is accepted, then it is possible that part of this effect results from the inhibition or alteration of the small lymphocytes in the reticulo-endothelial /

reticulo-endothelial system. This is a problem which is currently being studied by other workers and has not been elaborated in this study.

In the lowering of resistance to infection, direct toxic effects on cell metabolism in respiratory and genito-urinary epithelium may play a part. It is also possible that the lowering of mucosal resistance in such sites as the alimentary tract may allow the ingress of viruses and other organisms which would normally fail to cross cell barriers. This may account for the few cases of influenzal-like illness, gastro-enteritis and myocarditis occurring in association with the use of cytotoxic drugs. Ultimately, the effects of all the anti-cancer drugs are demonstrated on the metabolism of normal and malignant cells and it is the balance required between therapeutic and toxic dose levels which renders their use hazardous and demands repeated monitoring of the peripheral blood count, liver function tests, protein and uric acid patterns and reassessment of the clinical state.

V. Management of Toxic Side Effects

In the management of toxic effects resulting from the treatment of cancer by drugs, two main measures may be applied. In the first of these, an attempt is made to eradicate or minimise the incidence and severity of side effects and, in the second, measures are undertaken to control or combate the effects produced.

1. /

1. Measures to Eradicate or Minimise the Incidence and Severity of Toxic Effects.

a) Small-dose regime

The simplest measure is the use of small doses at repeated intervals over short periods of time so that side effects are unlikely to develop. The therapeutic dose of many cytotoxic agents is, however, very close, or even equal, to the toxic dose and good results will seldom be obtained by using the drugs in this manner.

b) Reduction of dosage

A more effective means is the reduction of dosage as soon as toxic effects, such as depression of white cell count, hair loss or oral ulceration, first appear. By this means a good therapeutic response may be obtained and the severity of the side effects reduced. In some cases it is necessary to completely withdraw treatment and resume, with smaller doses of the same drugs, when toxic effects have subsided. Alternatively, treatment may be resumed with another agent of a related or different group. It has been shown in this study, that further treatment can safely be given, even after the development of severe toxic effects and that the use of cytotoxic drugs in short intensive courses separated by intervals of a few weeks or few months is an important means of reducing the incidence and severity of such effects.

c) /

c) Use of drug combinations

The use of two or more drugs in combination allows each drug to be given in a smaller dose than would be effective if used singly. Used in this manner, side effects of the individual drugs may be minimised or eradicated. In this study the use of drug combinations has been particularly exploited and it can be seen from Table 31 that the incidence of toxic effects in these cases is less than when treatment has been maintained on a single drug. A less effective means of reducing the incidence of toxic effects is to stop treatment with one drug before signs of toxicity appear and to continue treatment with another closely related agent. The actions of similar drugs may, however, be summated and while the occurrence of side effects is occasionally delayed they are not prevented.

d) Single dose infusion technique

Of less significance than depression of bone marrow function or suppression of immunity, the occurrence of nausea, vomiting, anorexia and diarrhoea frequently cause more distress and disturbance to the patient. In an attempt to minimise these effects the administration of a single large amount of drug, by continuous intravenous infusion over a period of 24 to 36 hours, has been undertaken in a number of patients in this series. During the course of the infusion small regular doses of phenobarbitone or chlorpromazine /

chlorpromazine have been given to produce a sedative-anti-emetic effect. There is some evidence that chlorpromazine may also act as an un-coupling agent, permitting more effective action of such drugs as cyclophosphamide.[87] It is, therefore, the anti-emetic of choice.

It has been found that the incidence and severity of nausea and vomiting has been greatly reduced by the use of this technique and, in many cases they did not occur at all. Following a single dose infusion, treatment has been resumed on an out-patient basis using intermittent intravenous injection or oral maintenance therapy. The dose given can then be maintained at subtoxic levels, although the accumulative effects of treatment over many months may result in a slow, progressive depression of bone marrow function, loss of hair, the development of a dry, scaly skin and other effects. Of all the measures applied to reduce the incidence and severity of side effects this is at the same time the simplest and most effective. It does, however, require that the patient should occupy a hospital bed for a minimum period of 24 to 48 hours, but even in a busy surgical unit this can usually be arranged.

e) Use of antagonists

The toxic effects of a few agents may be minimised by using the drug in combination with its antagonist.[52,53] The best known example of such use is folinic acid (citro vorum factor) in combination /

combination with the folic acid antagonist methotrexate. By saturating the normal tissues with folic acid it is hoped that the effects of methotrexate on the normal cell will be minimised, while its action on the malignant cell remains unaffected. This technique has been widely used by other workers, but its efficacy is doubtful and it has not been employed in this study.

f) Protection of bone marrow

Of the many toxic effects produced by using anti-cancer drugs, those on the bone marrow are possibly the most significant and most serious. Any measure which will protect the bone marrow is, therefore, of value. In this study this has been attempted in a few cases by extraction of the bone marrow and replacing it at some stage following the administration of cytotoxic agents. There are two principal ways in which this technique was carried out. a) In the first, the bone marrow was extracted, stored at 4° C. for 24 hours, then immediately replaced by intravenous infusion. During the period of 24 hours between extraction and replacement, a single large dose of a cytotoxic drug is given by continuous infusion. This technique was carried out in 5 patients with no serious consequences and in 3 with obvious benefit from reduction in incidence and severity of side effects. In the second method bone marrow was extracted, concentrated, sealed in 20ml. ampoules and a total cell count carried out. The marrow was then cooled /

cooled in step-wise manner to minus 79° C. and stored at this temperature. The marrow can be maintained in a viable state for up to three months at this temperature. Chemotherapy was then administered parenterally or by mouth over a period of weeks or months until toxic effects appeared, when the patient's bone marrow was taken out of storage, rewarmed and replaced. In those cases in which toxic effects did not develop within the period of marrow viability, the marrow was used for homologous transfusion in any genotypically related patients demonstrating severe effects. This technique of marrow extraction and storage was employed in 12 cases, but autologous marrow was replaced in only 3 cases and homologous marrow in 2 cases.

With the use of autologous marrow, replaced after twenty-four hours storage, no adverse reactions were observed. In one case of autologous marrow replacement after a period of two months' storage the patient (Case No. 31) complained of mild headache, slight sweating and precordial discomfort but no other significant effects. In two cases receiving homologous marrow replacement after periods of ten and twelve weeks' storage, sweating, precordial discomfort and pyrexia developed. In one of these the symptoms were sufficiently severe to abandon the infusion after 200 ml. had been replaced.

The techniques of bone marrow extraction, storage and replacement are detailed in appendix III, but no obvious benefits accrued from this method and because of the time, cost, and hazards involved, its /

its use was ultimately abandoned.

Autologous Splenic Tissue

Injection of autologous splenic tissue has been employed by Woodruff and Nolan (1965) as a means of obtaining regression in cases of advanced malignant disease. On the basis that the spleen may be the site of anti-tumour antibodies, this would seem a rational method of reducing the incidence and severity of toxic effects. This technique has not, however, been employed in the study and its indications would appear limited.

2. Measures for the Control of Existing Side Effects

Many supportive measures may be employed to control the side effects of cytotoxic therapy.

a) Antibiotics

The use of appropriate antibiotics to treat chest or urine infections, wound infections, and skin lesions has an obvious place.

b) Haematinics

The control of anaemia by haematinics, including iron, vitamin B_{12} and folic acid, is essential.

c) Blood transfusion

The timely use of blood transfusion may restore not only the /

the haemoglobin level but also a degree of vigour and vitality beyond that which might be expected. The discriminate use of blood transfusion may also allow continued treatment when bone marrow depression, low peripheral blood counts and a poor general state would otherwise require its withdrawal.

d) Nutritional factors

Protein supplements, vitamins and a high calorie diet are readily prescribed and the patient should be encouraged to continue their use.

e) Short in-patient periods

If toxic effects are severe, then a few days in hospital, during which intravenous therapy, blood transfusion and appropriate sedation are employed, will do much to alleviate distress and restore the patient to a state where out-patient treatment may be continued.

f) Anti-emetics and analgesics

Anti-emetics such as chlorpromazine, promazine and stemetil; analgesics such as aspirin, codeine and ponstan, and gastro-intestinal sedatives such as nacton and probanthine all play a part in reducing the gastro-intestinal and central effects of cytotoxic therapy.

The /

The proper use of supportive measures in the control of the effects produced by anti-cancer drugs offers a wide scope for the considerate practice of good medical care.

Much can, therefore, be done to reduce the incidence and severity of toxic effects and to relieve the distress and discomfort occasioned by those that develop. It remains the responsibility of the physician, however, to ensure that the most effective agent with the least likelihood of producing severe or irreversible damage is being used, in a suitable dose, by the most appropriate route. /

c) Significance of Hepatic Metastases

Forty-two patients (40%) in this series were known or believed to have metastases in the liver. The significance of hepatic metastases in relation to cancer chemotherapy, requires further consideration.

It has been stated that jaundice or extensive hepatic metastases contra-indicate /

contra-indicate the use of cytotoxic agents. In that they act on all rapidly dividing cells, the effect of cytotoxins on the remaining liver parenchyma in these cases, is likely to precipitate hepatic failure. It can be seen from the results of the liver function tests, Table 25, however, that only a few cases in this study demonstrated evidence of impaired hepatic function following the use of cytotoxic drugs, even in large doses over long periods of time. Three cases were jaundiced prior to commencing cytotoxic therapy. In two of these the condition rapidly deteriorated, but in the third, reduction in size and tenderness of palpable liver metastases, was associated with resolution of the jaundice.

It must, however, be accepted that when marked impairment of liver function results from the presence of extensive metastases, cytotoxic agents are unlikely to produce benefit and they may precipitate hepatic failure. Such cases, are usually in the terminal stages of their illness and should not be considered for cytotoxic therapy.

The presence of hepatic metastases has been said to increase the incidence and severity of toxic effects due to the inability of the liver to metabolise the drugs or to remove excess breakdown products from the blood. From details contained in Tables 1-19 and Table 31 it can be seen, however, that there is no increase in the incidence or severity of toxic effects in patients with metastases in the liver. A few patients with proven hepatic deposits did not develop /

develop toxic effects at any stage. This merely confirms that, providing the stress is not too severe or prolonged, the presence of even a small amount of functioning hepatic tissue is adequate for most metabolic purposes.

Finally, the changes occurring in the α_2 globulin fraction of the serum electrophoretic pattern have been attributed to changes in hepatic function and to the presence of hepatic metastases. It can be seen from Table 29 that the presence of hepatic metastases is not directly related to changes in the α_2 globulin level. A point of interest arising from Tables 28 and 29 is the correlation between the presence of metastases in the liver and simultaneously elevated levels in all three; liver function tests, α_2 globulin and serum uric acid levels.

The significance of hepatic metastases may be summarised as follows:- when present to an extent causing severe impairment of hepatic function, they are usually related to an advanced stage of the disease and cytotoxic agents should not be exhibited. When present in lesser degree, cytotoxins may be safely used without causing further impairment of hepatic function. The influence of hepatic metastases and impaired hepatic function on the patterns of the α_2 globulin is uncertain but does not appear to be direct. There is no increase in the incidence or severity of side effects in those patients with hepatic metastases compared to those without.

d) <u>Causes of Death</u> /

Causes of Death

Seventy-eight patients (76% of total series) died during the course of this study. In 42 of these (54% of those dying) post-mortem examination was carried out. The principal cause of death recordedwas "Progress of Disease" and 46 of the 78 patients (59%) died from the direct effects of primary or metastatic malignant disease. A further 16 patients (20%) died from cardio-respiratory failure - mostly bronchopneumonia accelerating an otherwise inevitable end.

The remaining 16 cases (20%) died at a stage in the progress of their disease when cancer was not the immediate cause of death. In some of these, death was sudden and occurred unexpectedly when the prognosis was otherwise in terms of several months. Gram negative septicaemia was considered the possible cause of death in 8 of these 16 cases and in two was established by blood culture. The remaining patients (8 of 78) were positively harmed by the use of anti-cancer drugs and died from haemorrhage, complete bone marrow failure or renal failure. It must be accepted, therefore, that the use of cytotoxic agents will be associated with an accelerated death in a small percentage of the patients treated. Preventable deaths, however, must be avoided when dealing with cancer as with any other condition. While the majority of cases died as a direct result of their disease, it is essential that effective supportive therapy is administered to prevent deaths from other causes, at a stage when the patient remains otherwise well and active.

ASPECTS OF CANCER CHEMOTHERAPY

SECTION VII

CONCLUSIONS

Pages 105 - 108.

CONCLUSIONS

The results of treating malignant disease by chemical means leave much to be desired. The agents at present available, if administered in adequate dosage, with careful attention to the avoidance of toxic effects and to the correction of associated disorders, will produce worthwhile benefit in 20-30% of the cases treated. Occasionally a dramatic result is obtained which provides encouragement to continue.

Effectiveness may be improved and toxicity reduced by using cytotoxic agents in combination and by delivering them in high local concentration to the tumour. A few agents, e.g. 5-fluorouracil, are best given in intermittent courses, but the majority are best administered by an initial in-patient intravenous, intra-arterial or intra-cavitary course, followed by out-patient oral or intravenous maintenance therapy.

The prevention of tumour spread and implantation is an important indication for the use of cytotoxins, but the principal aim of cancer chemotherapy must remain the control of distressing symptoms resulting from advanced malignant disease. To protract a miserable existence is unjustifiable. These agents should never be used for this purpose, nor exploited in terminal patients. A few cases of prolonged remission are reported, but in the majority of cases remission lasts a few months at the most before the disease pursues an unrelenting course. Once tumour remission has been obtained and recrudescence /

recrudescence occurs, it is unlikely that a further good response will be obtained by using another agent of the same or different group.

Cancer chemotherapy is of definite benefit in malignant diseases of the reticulo-endothelial and haemopoietic systems and of the breast, ovary and lung. Less benefit is obtained in tumours of the gastro-intestinal and genito-urinary tracts, but chemotherapy still has a useful part to play in their management. Occasional benefit may derive from the use of cytotoxic agents in cancer of the pancreas and testis, and in malignant melanomas, but they are of no value in oesophageal, laryngeal and adrenal carcinomas.

Sophisticated techniques, such as arterial perfusion and autologous bone marrow replacement, play little part in the over all use of chemotherapeutic agents in the management of malignant disease. This study is an attempt to demonstrate the value of cancer chemotherapy, practiced largely on an out-patient basis, using simplified techniques and avoiding the cost of expensive equipment and prolonged periods of hospital treatment.

Assessment of response is one of the most difficult aspects of treating cancer by drugs. It requires objective unbiased means of measuring change in size or activity of a tumour or its metastases and the determination of biochemical changes in blood and urine appears the most fruitful line for further research. In the final assessment of response to chemotherapy, quality of life is of more importance than length of survival and the only criterion of success is the extent /

extent by which a patient's endurable and useful life is prolonged.

The incidence and severity of toxic effects remains the limiting factor in the application of chemical agents to the management of malignant disease. It is, however, considered that they can be prevented, minimised or controlled by using sub-toxic dose levels and by meticulous attention to supportive therapy. Toxicity is not an accurate index of therapeutic activity and the occurrence of severe toxic effects detracts from the principal aim of cancer chemotherapy. The development of mild to moderate bone-marrow depression is not necessarily an indication to cease treatment and, in some cases, treatment may be safely resumed even after the occurrence of severe toxic effects.

The possibility that cytotoxic agents may produce harmful suppression of body "defence mechanisms", requires further research, but this action may also permit a commensal-like relationship to exist between tumour and host. The tumour continues to grow and to metastasise, but the patient remains active and apparently well for many weeks or months.

When present in sufficient degree to cause severe impairment of function, hepatic metastases are usually associated with an advanced stage of the disease and cytotoxic agents should not be employed. If there is little or no impairment of liver function, the presence of metastases does not contra-indicate their use and they are unlikely to produce a higher incidence of toxic effects.

The management of advanced cancer requires close co-operation between /

between general practitioner, surgeon, radiotherapist and physician. Patient and relatives must bear the immensity of the human problems involved and require every assistance. The place of chemotherapy in this pattern, is in the control of the disease when other modalities of treatment are no longer effective or cannot be employed. Its use requires specialised knowledge of the agents available, the methods and routes of administration, dosages and toxic effects.

The ideal agents have not yet been found, but chemotherapy offers an avenue for at least the symptomatic relief of certain malignant conditions. The patient should not be allowed to die of intercurrent infection or toxic effects simply because the underlying disease is cancer. The opportunity to remain active and at home, the control of pain, bleeding, discharge and other distressing symptoms and the moral-lifting affect of an interested medical attendant, justify the continued use of chemotherapy in cancer.

The approach to the future is beautifully defined in the words of Gordon Gordon-Taylor:-

> "....."the vision splendid," which for us is that long desired day, perhaps not too far distant, when in the cure of cancer gross mechanical destruction and cruel mutilation of human tissues shall no longer be required, nor the scorching methods and machinery of Hephaestus the blacksmith god, or Prometheus who stole fire from heaven! "When the biologist shall know the laws that govern cell-growth with a knowledge akin in its sweep and accuracy to that of the astronomer," he will then have a power denied to those who scan the stars in the firmament, and that power will enable him to prevent, to control, and to cure cancer."
>
> Gordon-Taylor 1948.

ASPECTS OF CANCER CHEMOTHERAPY

SECTION VIII

SUMMARY

SUMMARY

A total of 107 cases (62 male and 45 female), with histologically proven malignant disease and all receiving cytotoxic therapy were studied.

A brief review of the history of cancer chemotherapy is given, together with a detailed account of the principal agents currently available, methods and routes of administration, means of assessing response to treatment and the necessary routines of investigation.

The results obtained are presented, mainly in tabular form. Assessment of response, incidence, severity, significance, mechanisms and management of toxic effects, the significance of hepatic metastases and causes of death in relation to cancer chemotherapy, are discussed in detail.

Finally, the conclusions derived from the study of these cases are presented.

ASPECTS OF CANCER CHEMOTHERAPY

SECTION IX

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ACKNOWLEDGEMENTS

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The /

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ASPECTS OF CANCER CHEMOTHERAPY

SECTION X

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ASPECTS OF CANCER CHEMOTHERAPY

SECTION XI

APPENDICES

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APPENDIX I

ABBREVIATIONS USED THROUGHOUT

A. Cancer Chemotherapeutic Agents

1.	Nitrogen Mustard	N.
2.	Cyclophosphamide	C.
3.	Phenyl-Alanine Mustard (Melphelan)	P.
4.	Mannitol Mustard (Degranol)	D.
5.	Uracil Mustard	U.
6.	Chlorambucil (Leukeran)	Cl.
7.	Tri-Ethylene-Thiophosphoramide (Thiotepa)	Th.
8.	Ethoglucid (Epodyl)	E.
9.	Busulphan (Myleran)	My.
10.	Methotrexate	M.
11.	6-Mercapto-Purine	M.P.
12.	5-Fluouracil	F.
13.	Vinblastine Sulphate	V.
14.	2-Ethyl-Hydrazine	E.H.
15.	Thiocolciran	Tc.
16.	Imuran	I.

B. Systems

1.	Cardiovascular System	C.V.S.
2.	Respiratory System	R.S.
3.	Gastro-Intestinal System/Tract	G.I.S/T.
4.	Gastro-Urinary System/Tract	G.U.S/T.
5.	Reticulo-Endothelial System	R.E.S.

C. Others

1.	Post-Mortem	P.M.
2.	Intravenous Injection	I.V.I.
3.	Intra-Muscular Injection	I.M.I.

APPENDIX II

NORMAL VALUES OF LIVER FUNCTION TESTS, PROTEINS, SERUM ELECTROPHORESIS AND URIC ACID

1. Liver Function Tests*

Function	Range
Serum Bilirubin	0.1-1.0 mg/100 ml.
Alkaline Phosphatase	3-12 King-Armstrong Units
Thymol Turbidity	0.4 Units
Zinc Sulphate Turbidity	8-12 Units (Kunkel)
Serum Glutamic-Oxalic Transaminase (S.G.O.T.)	8-40 Sigma-Frankel Units
Serum Glutamic Pyruvic Transaminase (S.G.P.T.)	5-35 Sigma-Frankel Units
Bromsulphthalein Retention (B.S.R.)	< 10% after 30 minutes < 3% after 45 minutes

* Local Laboratory Values

2. Proteins and Serum Electrophoresis

	Total Protein	Albumin	1 Globulin	2 Globulin	Globulin	Globulin
1	7.14±0.33	3.65±0.13	0.42±0.10	0.67±0.12	0.91±0.13	1.53±0.18
2	-	51.6%-68.1%	1.4%-3.3%	6.3%-13.7%	8%-16%	9.5%-21.9%

1. After Sunderman (1964): results = mean ± standard deviation
2. After Albert Recht (1959): results = "X" ± x standard deviation

3. Serum Uric Acid

Mean Value = 3.7 mg/100 ml.+
Range = 1.0-5.0 mg/100 ml.+

+After Jamieson and Kay, 1965.

APPENDIX III

Techniques of Bone-Marrow Extraction, Storage and Replacement

(a) Bone-Marrow Extraction.- With the patient anaesthetised, bone-marrow was extracted from sternum, anterior and posterior iliac spines and from the sacrum by multiple punctures using a wide bore aspirating needle. The needle was connected through a three-way valve to a suction machine through a collecting bottle and a bottle of sterile tissue culture fluid. By this technique quantities of 400-600 ml. of marrow could be obtained which, when separated from the tissue culture fluid and concentrated, yielded between 50 and 70 ml. of marrow concentrate.

(b) Bone-marrow storage and replacement.- The extracted marrow was first separated from tissue culture fluid and concentrated to a volume of 50 to 70 ml. Small amounts of heparin were added during extraction to avoid clotting. The marrow was then gradually cooled over a period of two hours to a temperature of -79°C, a temperature achieved by freezing with carbon dioxide snow. A small amount of the marrow was extracted for subsequent genotyping and the remainder held at a low temperature until required. In those cases in which the marrow was to be replaced after twenty-four hours, the extracted specimen was again concentrated, but was rapidly cooled to 4°C and held at this temperature for the required period.

When/

When required for replacement the marrow was reconstituted with normal saline 200-400 ml. and slowly infused over a period of two to four hours using a wide bore needle in a large vein. The patient was carefully observed for the occurrence of reactions during and for twenty-four hours after the infusion. Although the benefits of long-term marrow storage appeared minimal and the technique was largely abandoned, the value of replacement after twenty-four hour storage was felt to warrant its continued use in selected cases.

APPENDIX IV

CHEMOTHERAPY OF CANCER

COMPLETE LIST OF TABLES