METABOLIC AND NUTRITIONAL IMPLICATIONS OF CANCER AND CHEMOTHERAPY

by

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DECLARATION

I declare that the work presented in this thesis has been carried out solely by me, except where indicated in the text and below.

The work on the effects of cancer and chemotherapy on animal metabolism was performed jointly with Dr. G.E. Raines, and has been presented at a meeting of the British Association for Cancer Research in March, 1983, and is awaiting publication as a full paper.

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To my husband,

ED

WITH MY LOVE AND THANKS
FOR YOUR PATIENCE,
SUPPORT AND CONTINUAL
ENCOURAGEMENT DURING
THE WRITING OF THIS THESIS

"Depend upon it, Sir, when
a man knows he is to be
hanged in a fortnight, it
concentrates his mind
wonderfully"

"A man will turn over half
a library to make one book"

Dr. Samuel Johnson

1709-1784

SUMMARY

METABOLIC AND NUTRITIONAL IMPLICATIONS OF CANCER AND CHEMOTHERAPY

Cancer and chemotherapy are well known to cause metabolic and nutritional alterations in patients; the culmination of these being the syndrome of cancer cachexia. Theories abound to explain the causes of the altered metabolism, however many of the problems encountered in the cancer patient remain unresolved. The aims of this thesis are to explore, in more detail, some of these metabolic and nutritional problems.

The problem of nutritional assessment was considered, and dietary histories, clinical evaluation and biochemical estimations of nutritional deficiencies were compared and contrasted in a search for the best, easiest and most reliable method of nutritional assessment for the cancer patient. The best method of assessing patients was found to be a combination of all three types of evaluation. Each type of assessment broadly agreed with the others, however clinical and biochemical evaluations of nutritional state tended to reflect long-standing deficiencies, while 24 hour dietary recall histories could be used to predict potential nutritional problems. Twenty-four hour dietary recall histories with computer analysis used on several occasions allow fluctuations in dietary intake and hence nutritional state to be recorded, and provide a fast, easy and reliable way of evaluating present nutritional state and anticipating and correcting future nutritional problems.

The effects of cancer and chemotherapy on nutritional and metabolic status of cancer patients and tumour-bearing animals were considered in a number of studies.

Muscle biopsies were performed on cachectic cancer patients and showed considerable disruption of muscle fibres with particularly striking changes seen in the mitochondria. These changes were shown to be unique to cancer patients, illustrating the specific metabolic alterations in this group.

A preliminary study to investigate the problems of dry mouths, with difficulty in chewing and swallowing food, and changes in taste sensations, anorexia, and decreased enjoyment of food, looked at saliva composition and production. Cancer patients were found to have decreased saliva volumes, amylase content, lysozyme and IgA content and increased microbacteria and yeasts present in the saliva, compared to healthy controls. Patients followed over three months from initial chemotherapy showed decreasing saliva flow rates and increasing microflora colonisation of the mouth over this time. Cisplatin, Adriamycin and Mitomycin-C were particularly implicated in micro-organism colonisation; Cyclophosphamide and Methotrexate were more likely to produce decreased saliva volumes and dry mouths. Further work is required to correlate the incidence of dry mouths, altered taste sensations and anorexia with the changes found in saliva production and composition. The results obtained, however, confirm that there is decreased saliva flow in cancer patients receiving

chemotherapy; and that the mouth harbours organisms which are potentially virulent if host defences are impaired.

Metabolic consequences of tumour growth and chemotherapy were considered in studies using Wistar rats. The animals were given tumour alone, tumour plus Cyclophosphamide or Cisplatin, or drug alone. All showed metabolic alterations with weight loss, decreased carcass nitrogen content, decreased plasma protein, albumin and iron content, increased levels of ketone bodies and deranged liver enzymes. The tumour produced the greatest metabolic insult; the drugs also produced deterioration in metabolic state. The tumour and drug groups showed less metabolic upset, demonstrating the beneficial effects of response to treatment; where there is no response to treatment there are increased metabolic problems caused by cumulative effects of drugs and tumour. These results can be extrapolated to cancer patients.

Cisplatin was studied in more detail using preliminary animal studies which showed that Cisplatin affects all organs in the body but particularly the kidney; and causes mitochondrial disruption at the cellular level. These cellular changes may account for the metabolic upsets seen in animals and patients treated with Cisplatin, and future studies should look more closely at this aspect.

Clinical studies on Cisplatin looked at the effects of treatment in patients with teratoma. Trace metal levels showed little change during and over four courses of treatment: serum iron levels rose with

each course and corresponded with the incidence of anaemia. Serum magnesium levels consistently fell over four courses of treatment, and further studies compared routine magnesium supplementation over four courses of treatment with no supplementation over the same period. Magnesium supplements had no effect on response to treatment, rate of fall of tumour markers, or final outcome. Both supplemented and non-supplemented groups had similar weight loss, nausea, vomiting and anorexia during treatment. Dietary intake was shown to decrease markedly, to less than 50% pre-treatment level, following Cisplatin, and to remain low for 8-12 days following treatment. This allowed only 4-7 days of normal intake prior to the next course of treatment. There is a cumulative effect of Cisplatin on appetite over the four courses of treatment, and there may be significant nutritional depletion by the end of this regime which may prevent further aggressive treatment of the tumour, if required. Future studies should examine the usefulness of early nutritional support to prevent these problems.

Benefits of magnesium supplementation were fewer treatment delays due to neutropenic episodes following treatment, higher serum magnesium and potassium levels, and less deterioration in renal function as measured by N-acetylglucosamine and Beta-2-microglobulin levels in urine. These factors will allow regular and aggressive treatment with Cisplatin while keeping the safe therapeutic margin as wide as possible. Future studies should monitor renal function during and after Cisplatin treatment using N-acetylglucosamine and beta-2-microglobulin levels and should examine in more detail the routine use of magnesium supplments.

Magnesium supplements were given intravenously during inpatient treatment, and orally when discharged home. The oral supplements were not entirely satisfactory and compliance was poor. Further work is required to find the optimum level of supplementation, and a suitable, palatable oral supplement.

Anorexia was a major complaint in 43% patients attending the oncology outpatient clinic at Gartnavel General Hospital, Glasgow. A double blind crossover study of appetite stimulation using prednisolone against placebo over a two week period showed a significant improvement in appetite and well-being with prednisolone. Further studies should examine the use of prednisolone over longer periods; and compare prednisolone with other appetite stimulants.

In conclusion, this thesis has examined some of the effects of cancer and chemotherapy on nutrition and metabolism. Many of the results obtained beg further studies, and there remains a lot of work to be done to fully understand the nutritional and metabolic implications of cancer and its treatment.

ABBREVIATIONS

Very few abbreviations have been used and all are explained when they first appear in the text. Those most commonly referred to are:

Aceto	–	Acetoacetate
ALT	–	Alanine transaminase
AST	–	Aspartate transaminase
BOH	–	Beta-Hydroxybutyrate
Cisplatin	–	Cisdichlorodiammine Platinum (II)
Cyclo.	–	Cyclophosphamide
Fe	–	Iron
K	–	Potassium
NAG	–	N-Acetyl glucosamine
Pt	–	Cisdichlorodiammine Platinum (II)
T	–	Tri-iodothyronine

METABOLIC AND NUTRITIONAL IMPLICATIONS OF CANCER AND CHEMOTHERAPY

CHAPTER 1: INTRODUCTION - BACKGROUND AND AIMS OF THESIS

A. INTRODUCTION AND BACKGROUND

The implications of cancer extend beyond the cells in which it develops to involve the metabolic, nutritional and psychological constituents of the host. The resulting alterations in function may be caused both by the tumour itself and by many of the types of treatment used to combat it.

The syndrome of cancer cachexia - the word "cachexia" from the Greek "kakos" and "hexis" meaning bad condition - well describes the popular concept of the cancer patient: pale, anaemic, weak, listless, wasted and depressed, with malabsorption, diarrhoea and massive weight loss (Calman, 1982; Hall, 1979; Strain, 1979; Theologides, 1979). The number of deaths attributed to cachexia has varied little from 10-23% patients with cancer reported in the 1930's by Warren (1932), who originally described the condition (Inagaki, Rodriguez & Bodey, 1974).

The frequency of cachexia has been reported in 8-84% all patients with cancer (Strain, 1979), although not every patient with cancer will develop cachexia. It is often difficult to predict which patients will become cachectic; however, many patients have evidence of weight loss at some stage of their disease, and 43% patients in a survey carried out at the Department of Oncology, Glasgow University, complained of anorexia - both cardinal features of the "cachexia syndrome". Cachexia and weight loss are considered to be poor prognostic signs in

the cancer patient, indicating progressive tumour growth and a decreased tolerance to treatment, with corresponding reduction in its effectiveness (DeWys, 1980; Kisner, 1982; Strain, 1979).

Weight loss may occur as an isolated sign in the absence of obvious tumour and has been found in 29-66% patients starting chemotherapy (Gold, 1974; Kisner, 1982). It may occur despite a normal appetite and normal or increased intake of food, and is another indication of the disturbed internal metabolism of the patient (Strain, 1979; Brennan, 1977) (Fig. 1). Decreased intake of food is often present in cachexia and may account for the weight loss seen. It may be due to mechanical difficulties in chewing, swallowing, digesting or absorbing food caused by surgery, radiotherapy or chemotherapy or by the tumour itself altering normal anatomical and physiological pathways in the gastrointestinal tract. Anorexia may also contribute to poor intake (q.v.) (Fig. 2).

Cancer cachexia has been described in patients with tumours of all sizes, sites and stages and its symptoms and signs are markers of the underlying, fundamental changes in the metabolism of the patient. It has no correlation with food intake (Theologides, 1979; Cohen et al., 1978; Sudjian, 1980; Costa, 1977).

The metabolic changes may begin early in the growth of the tumour, at a stage not clinically identifiable, and progress insidiously to the

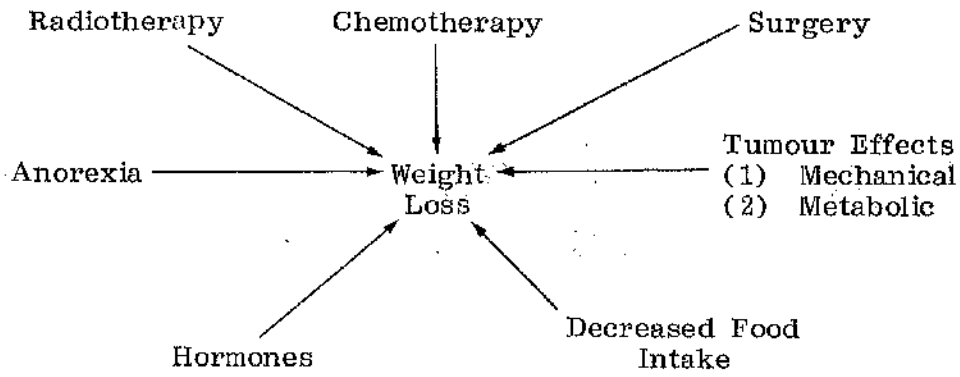

FIGURE 1: FACTORS CAUSING WEIGHT LOSS IN CANCER PATIENTS

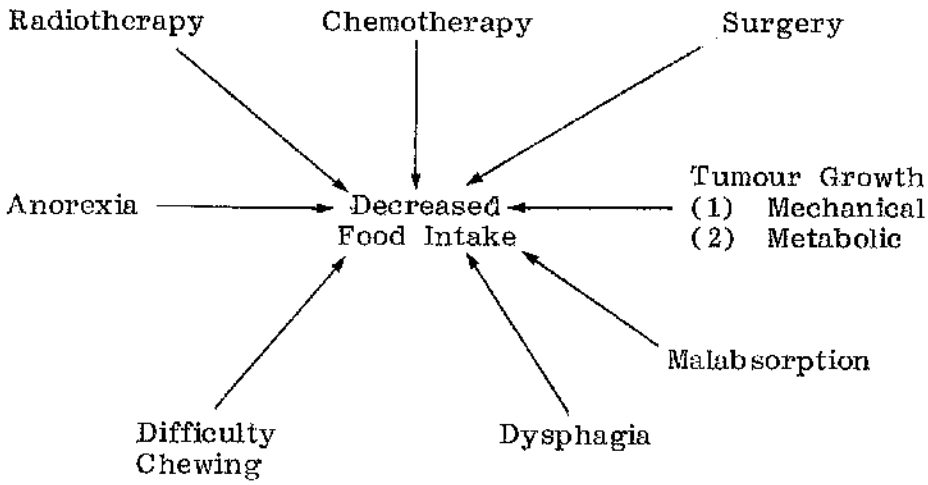

FIGURE 2: FACTORS AFFECTING FOOD INTAKE IN CANCER PATIENTS

gross alterations of metabolic and nutritional status seen in the cachectic patient (DeWys, 1970). These alterations may be temporarily slowed down or even reversed by feeding - either enteral or parenteral - but this serves to produce only a short-term improvement in the patient (Brennan, 1981). The only method for complete reversal of the changes of cachexia is successful treatment of the tumour (Costa, 1963; Terepka & Waterhouse, 1956; Brennan,1981; Calman, 1982). The problem is not simply that of increased energy expenditure exceeding intake (Theologides, 1972), there are other factors either induced in the host or produced directly by the tumour causing the "metabolic chaos" of the cachectic host. Theologides (1976) proposes that small molecular weight proteins or peptides are produced by the tumour or its influence on the host which interfere with the normal protein, fat and carbohydrate interrelationships, causing a failure of host adaptation to the tumour presence (Waterhouse, 1974; Morrison, 1976). A lipolytic factor (toxohormone-L) is among a number of factors isolated in experimental animals with cancer, and it produces increased fat mobilisation when injected into control animals (Chalmers, Kekwick & Pawan, 1958; Costa & Holland, 1962; Liebelt et al., 1974; Manuno, Yamasaki & Okuda, 1981). Another peptide, which induces anorexia has been found in the urine of patients with widespread malignant disease (Chalmers et al., 1958) and has been isolated from the urine of fasted rats. It was originally thought that these peptides were produced by the pituitary, however they have been identified in animals without a pituitary gland (Beaton, Szlavko & Stevenson, 1964). This provides some support for the theory of tumour-produced substances

affecting host metabolism.

Tumours are well known to produce hormones which may influence host homeostasis (DeWys, 1982). Small cell lung tumours, adrenal, pancreatic, breast, ovarian and endometrial tumours are among those implicated in hormone production (Strain, 1979; Weller, 1972); and the effects of the tumour derived hormones may upset fluid and electrolyte balance, glucose regulation and steroid metabolism. Other less well known hormones have been identified in cachectic patients such as somatostatin, bombesin, cholecystokinin, neurotensin, endorphins and encephalin. These hormones have effects both on the central nervous system appetite centres and on the gastrointestinal tract and may influence the intake and absorption of food (Theologides, 1981; DeWys, 1979).

Ratcliffe et al. (1978) found that in 33% patients with lung cancers of various histological types there was a significant decrease in triiodothyronine (T_3) levels in serum compared to control patients with other lung disease. This was correlated with a poor prognosis. Their work has been confirmed by Axelrod & Costa (1980) who suggest that the decreased levels of T_3 in cancer patients may reflect a compensatory mechanism for the decreased energy intake in these patients.

Liver function is generally found to be impaired in cachectic patients, and there is an increase in liver weight even in the absence

of metastases (Theologides, 1979; Abels et al.,1942; Walsh & Kissane, 1968). Fatty infiltration of the liver has been described (Lanza & Nelson, 1968) and this may be due in part, to increased fat mobilisation and ketone body production (Tisdale, 1982). Decreased synthesis of plasma albumin is common, although there may be normal or increased synthesis of other liver proteins such as the acute phase reactants and immunoglobulins. This continued hepatic synthesis may account for a large energy expenditure (DeWys, 1982; Raines et al., 1981; Steinfeld, 1960; Ekman, 1981). Abnormal levels of liver enzymes have been found which have no correlation with the degree of cachexia (Lemon, Holland & Holland, 1965; Waterhouse, 1974).

One explanation for the continued weight loss in cancer patients, despite normal intake, has been an increase in the basal metabolic rate in these patients (Warnold, Lundholm & Schersten, 1978; Manson, 1976; Waterhouse, 1974). Katz, Wals & Rognstad, (1978) suggest that "futile" metabolic processes caused by the tumour produce the increased energy expenditure. However a number of authors (Knox et al., 1983; Strain, 1979) maintain that there is no uniform increase in basal metabolic rate in cancer patients and, indeed, Knox et al (1983) found in a group of 200 heterogeneous cancer patients that 26% were hypermetabolic, while 33% had low metabolic rates. They suggest that the duration of disease may have a major influence on energy metabolism: the patients with the longer duration of disease,

although not necessarily with increased tumour spread, tended to be hypermetabolic. It seems, therefore, that at present, energy expenditure cannot be confidently predicted in cancer patients.

Carbohydrate metabolism

Carbohydrate metabolism is deranged in cachectic patients with most showing a diabetic-type glucose tolerance curve and poor utilisation of exogenous glucose (Young, 1977; Bishop & Marks, 1959; Jasani et al., 1978; Kisner et al., 1978). The fasting cachectic patient may, however, have a normal blood sugar (DeWys, 1982). There is evidence both for impaired release of insulin from the pancreas (Jasani et al., 1978; Bishop & Marks, 1959) and for insulin resistance in the peripheral tissues (Kisner et al., 1978). The inhibitory effects of insulin on lypolysis, however, are normal (Schein et al., 1979). Some patients show increased levels of glucagon in the plasma, antagonising the effects of insulin.

Lundholm, Bylund & Schersten (1977) found cellular evidence of altered carbohydrate metabolism with decreased levels of glycolytic enzymes in skeletal muscle biopsies of cancer patients compared to countrols. Evidence of decreased utilisation of glucose was provided by Waterhouse (1974) giving radio-labelled glucose orally and finding decreased levels of exhaled radio-labelled carbon dioxide in cancer patients compared to controls.

At least some tumours derive their energy solely from glycolysis (Gold, 1974; Waterhouse, 1974) and so rely heavily on supplies of glucose from the host. Once liver glycogen supplies are exhausted, in a relatively short period of time, the liver having enough glycogen stored for about 2 hours of continuous activity, the process of gluconeogenesis begins. The tumour produces lactate from the anaerobic oxidation of glucose, and this is recycled via the liver and kidney to glucose, requiring 6 moles ATP for each lactate molecule, with 2 lactate molecules required for each glucose molecule. The tumour derives 2 moles ATP from each glucose molecule and hence the host loses a net 14 moles ATP for each molecule of glucose metabolised (Gold, 1974). This lactate-glucose cycle, the Cori cycle, is greatly increased in patients with cachexia and progressive tumour growth, and with weight loss; patients with no weight loss show no change in Cori cycle activity (Waterhouse 1974; Holroyde et al., 1975; Reichard et al., 1963). A high glucose turnover rate with a slight overall increase in glucose production rates has been described in cachectic patients.

The relative contribution of this increase in oxidative metabolism to the overall energy expenditure of the host is the subject of some debate. Young (1977) maintains that the Cori cycle will account for only about 10% daily energy expenditure; Waterhouse (1974) and Reichard et al. (1963 and 1964) contend that in those patients with increased Cori cycle activity there is an increase of 50% in its contribution to daily energy expenditure, which they consider to be a

significant contribution to increased basal metabolic rate.

There may be another energy-expensive cycle in cachectic patients when glucose, instead of being used directly is converted first to triglyceride in adipose tissue, then oxidised as free fatty acid in the host. This may account for up to 20% extra daily energy expenditure for the cancer patient (Flatt & Blackburn, 1974; Fields et al., 1982).

Confirmatory evidence that some tumours use glucose for energy can be found in those tumours which produce hypoglycaemia in the host. These tumours tend to be large, weighing from 1-9 kilograms, and are often retroperitoneal tumours, usually hepatocellular carcinomas or fibrosarcomas. Their effects may be mediated through the extraction of excess glucose from the bloodstream or by producing products which have an insulin-like effect (Kreisberg et al., 1970; Costa, 1977). Fig. 3 summarises the changes seen in carbohydrate metabolism in cancer patients.

Protein metabolism

Protein metabolism is markedly altered in patients with cachexia with 33-100% of all patients with advanced cancer having a negative nitrogen balance (Blackburn et al., 1977). There is a progressive loss of muscle proteins to provide amino acids for gluconeogenesis. Some patients with non-gastrointestinal cancers show a decrease in the protein content of muscles and viscera as one of the first signs of

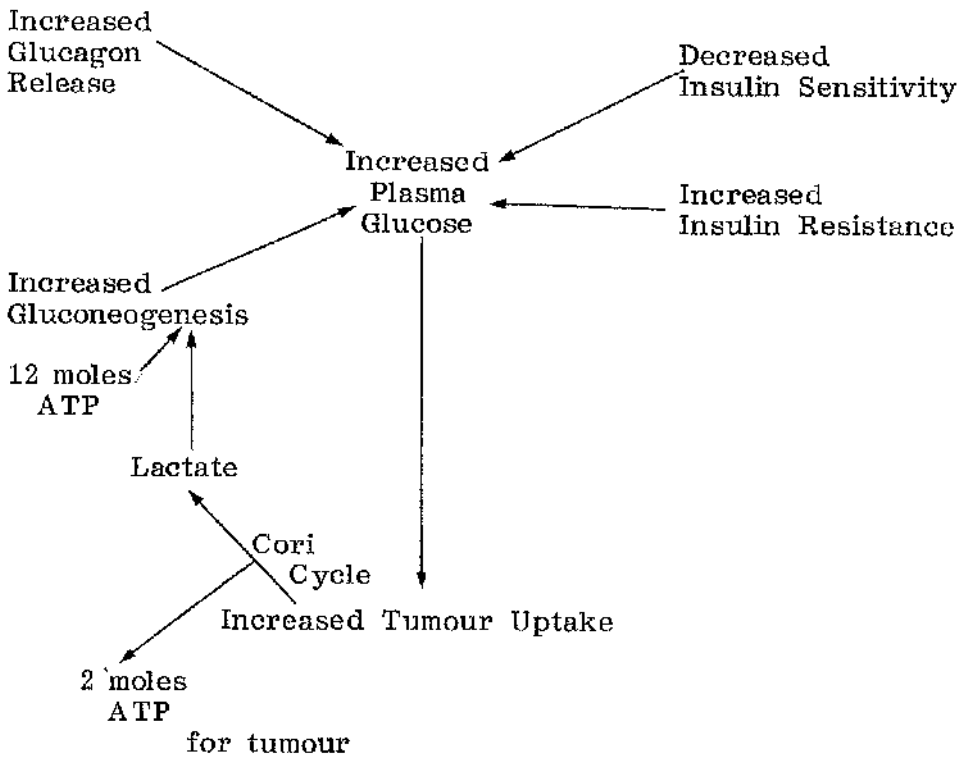

FIGURE 3: ALTERATIONS IN CARBOHYDRATE METABOLISM IN CANCER PATIENTS

malnutrition, even before fat loss is obvious (Bozzetti et al., 1982). Patients with cancers of the gastrointestinal tract have often, in addition to the effect of tumour on metabolism, a mechanical block to or abnormal absorption of food due to the surgery, radiotherapy, chemotherapy or disease (Blackburn et al., 1977). These patients show similarities to protein-calorie malnourished patients with early loss of body fat, then later loss of muscle and visceral proteins (Bozzetti et al., 1982). Hypoalbuminaemia is common and is due to low synthesis rates and normal or increased rates of albumin catabolism (Raines et. al., 1981). Those patients with gastrointestinal cancers showing similarities to protein-calorie malnutrition in their metabolism may produce an increased synthesis rate of albumin in response to feeding. However, so far this has not been shown to be sufficient to reverse the long-term net catabolism of albumin (Trotter & Calman, 1981). There may be losses of plasma albumin into extracellular fluid or into the gastrointestinal tract via fistulas or tumours or treatment-induced damage to the gastrointestinal mucosa (Strain, 1979). Costa (1977) has correlated the degree of hypoalbuminaemia in cancer patients with the appearance and number of metastases.

The decreased protein synthesis has been shown by Costa (1977) to correspond with decreased survival, depressed immune response, decreased tolerance to chemotherapy, radiotherapy and surgery, and decreased drug-carrying ability in the blood causing problems of drug toxicity and difficulties in prescribing appropriate drug doses for the patient.

It has been proposed that some tumours act as "nitrogen traps" taking all available amino acids for their own use, and depriving the host of essential amino acids, with consequent decreased utilisation of amino acids for protein synthesis in the host (Costa, 1977; Mider, 1951): the host amino acids are then channelled to gluconeogenesis or oxidation, with gluconeogenesis predominating (Stein, 1978). The amount of nitrogen "trapped" by the tumour may not account for the total loss of protein seen in patients since, although in animals, tumours may account for up to 40% body weight and hence may trap large amounts of nitrogen, human tumours, at most, will account for 5% body weight and would not therefore be anticipated to cause the large nitrogen deficit seen (Strain, 1979; Waterhouse, 1974). Norton et al. (1980) found evidence of increased uptake of amino acids by tumours in studies of blood flow in a tumour-bearing limb compared to its normal partner. They found that the tumour bearing limb retained up to 50% more of each amino acid than did the control limb. The release of gluconeogenic amino acid precursors from the control limb correlated with the glucose uptake recorded in the tumour-bearing limb. They suggest that this implies the breakdown of host muscle to provide precursors for gluconeogenesis in the liver and for tumour protein synthesis. Lundholm et al. (1976) confirm this view by finding, in vitro, an increased breakdown of protein in muscle fibres of cancer patients compared to controls.

Numerous studies have shown abnormal patterns of amino acids in

the blood of cachectic cancer patients (Stein, 1978; Trotter, Carlyle & Calman, 1980; Clarke, Lewis & Waterhouse, 1972; DeWys, 1970) and these may, in addition to causing upset protein metabolism, cause anorexia via an effect on the central nervous system (Theologides, 1972).

Fig. 4 summarises the alterations in protein metabolism in cancer patients.

Lipid metabolism

Lipid metabolism alters to compensate for the deranged protein and carbohydrate metabolism, according to DeWys (1982). Lipid absorption in the gastrointestinal tract may be abnormal (Strain, 1979), and Delaney et al. (1982) suggest there is abnormal lipid absorption, or disturbed oxidative metabolism in cancer patients prior to clinical signs of malnutrition. Costa (1977) showed that early fat loss tends to occur in cancer patients: muscle biopsies taken during first operation on patients with carcinomas of breast or colon showed, on average, 50% of the fat content of control biopsies from patients with a variety of acute and chronic surgical conditions. Warnold, Lundholm & Schersten (1978) showed decreased body fat in women with various cancers when compared to hospitalised controls.

Theologides (1979) found an early increase in cholesterol and phospholipid content of carcass, skeletal muscle and intestine of tumour animals and there was a concomitant decrease in fat stores with increased mobilisation of free fatty acids. Levels of free fatty acids in the blood may be normal or increased, and fall normally in

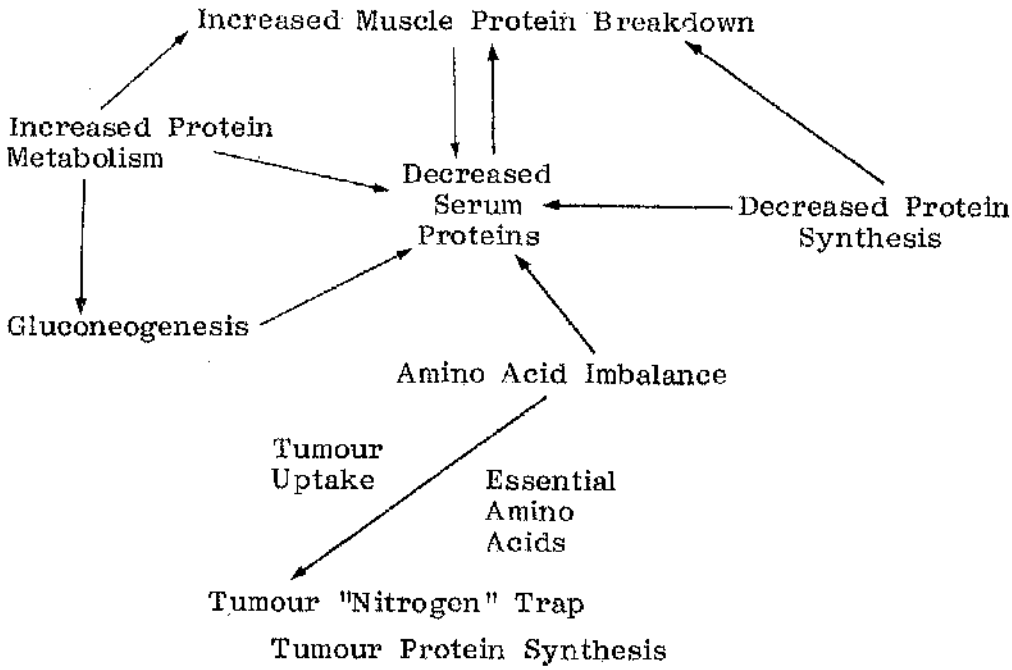

FIGURE 4: ALTERATIONS IN PROTEIN METABOLISM IN CANCER PATIENTS

response to insulin (Holroyde et al., 1978; Schein et al., 1979). Changes may be found in the composition of circulating lipoproteins and in the activity of plasma lipase (Theologides, 1979). At a cellular level, this loss of body fat may affect the lipid content of host cells and impair synthesis of cellular membranes (Costa, 1977).

There is an increased rate of removal of infused lipid from the circulation and decreased suppression of free fatty acid oxidation by infused glucose in cancer patients (Waterhouse & Nye, 1961; Waterhouse & Kemperman, 1971). The tumour itself appears to have no direct effect on free fatty acid levels in the blood as Norton et al. (1980) found no difference in free fatty acid levels in blood between tumour bearing and control limbs.

The increase in free fatty acid oxidation allows the production of ketone bodies and of co-enzyme A which stimulates the gluconeogenic cycles (Stein, 1978). Ketone bodies may be used as a source of energy by most of the body tissues including the central nervous system, although there is some debate as to whether tumours can utilise ketones. Some animal tumours have certainly the capacity to oxidise ketone bodies to the same extent as heart muscle (Tisdale, 1982). Ketone bodies normally inhibit continued lipolysis either directly or via stimulation of insulin secretion, however this does not happen in cancer patients. This may be due to impaired insulin secretion (Bishop & Marks, 1959) or decreased response of adipose tissue to ketones, and is another indication of the failure of host homeostatic

mechanisms (Tisdale, 1982).

Fig. 5 summarises the alterations in lipid metabolism in cancer patients.

These changes in carbohydrate, protein and lipid metabolism have some similarities both with protein-calorie malnourished patients and with patients who have had major injury or sepsis. In the starved patient there are two phases of metabolic adaptation (Strain, 1979). Initially there is increased gluconeogenesis designed to compensate for the rapid depletion of liver glycogen stores. Protein catabolism increases to provide glucose precursors and there is increased uptake of amino acids by the liver. Since this would rapidly lead to death, an adaptive mechanism which conserves protein is switched on in chronic starvation. Ketone bodies replace glucose as the fuel for cells, and there is decrease in gluconeogenesis. Both synthesis and catabolism of albumin decrease and there is a fall in oxidative metabolism, metabolic rate and carbon dioxide output. This "fat-fuel economy" allows survival for long periods under conditions of near starvation, using fat stores for energy (Brennan, 1977) (Fig. 6).

In major injury or sepsis, there is continued protein breakdown and high basal metabolic rate which persists until the injury or its complications are relieved. There is a high rate of gluconeogenesis and also loss of body fat for energy (Brennan, 1977).

The metabolic changes occurring in cancer patients are difficult

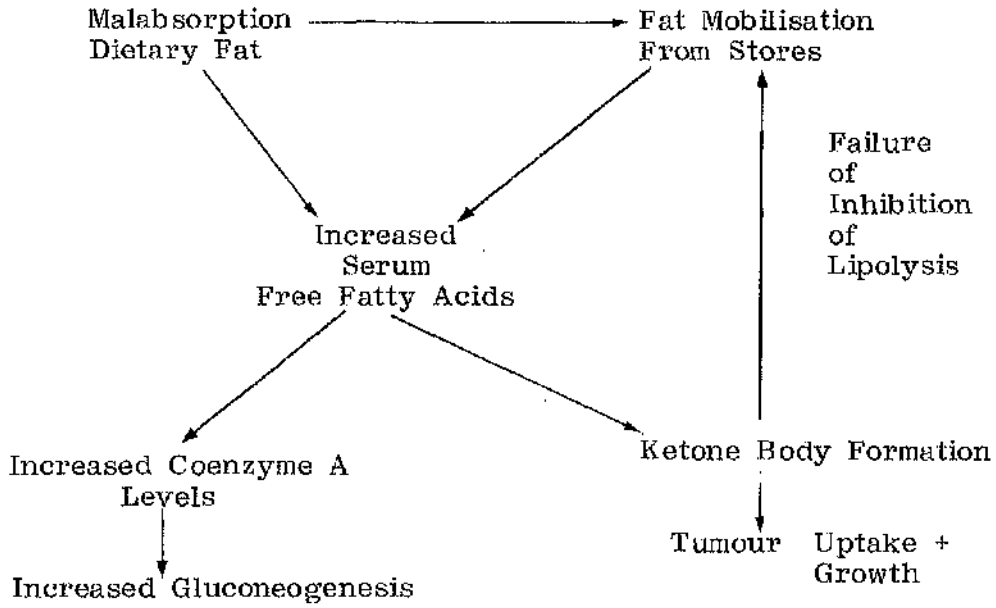

FIGURE 5: ALTERATIONS IN LIPID METABOLISM IN CANCER PATIENTS

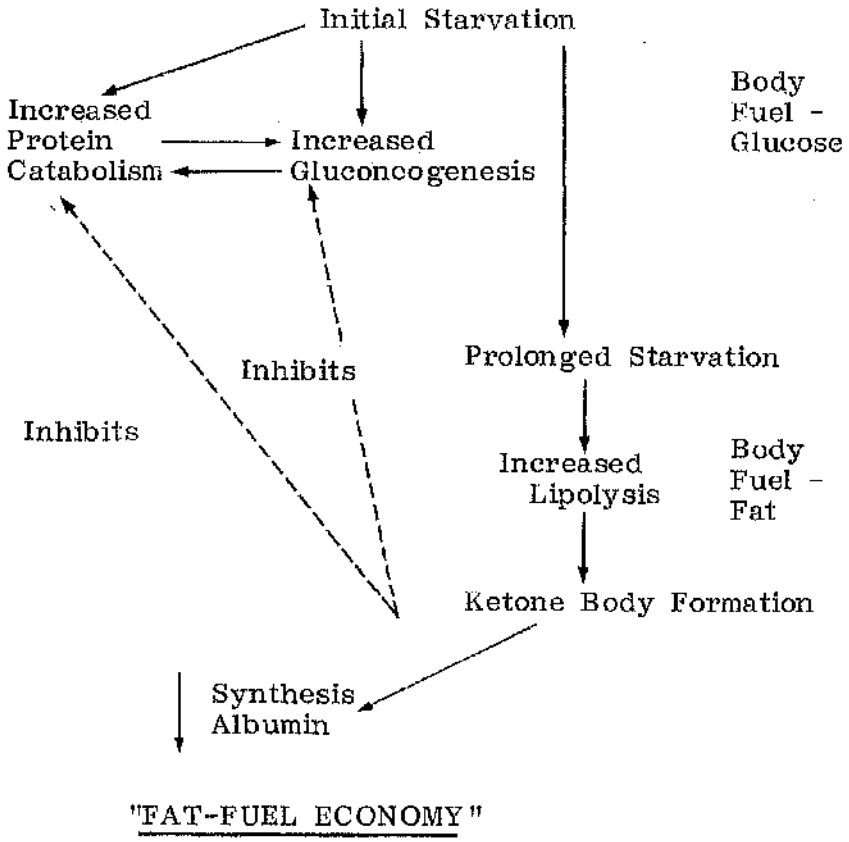

FIGURE 6: ADAPTIVE MECHANISMS IN STARVED PATIENTS

to define precisely - patients who have the disease for the longest time have more obvious abnormalities. Those who show weight loss have similar metabolic reactions to non cancer patients with weight loss, but there are differences with decreased utilisation of exogenous glucose and continued use of amino acids for energy via gluconeogenesis in the cancer patients. It appears thus that there is incomplete adaptation to decreased food intake; and failure of normal homeostatic mechanisms in the presence of tumour (Waterhouse, 1974) (Fig. 7).

Electrolytes, minerals and vitamins

Fluid and electrolyte balance may be altered in cancer patients with increased retention of both intracellular and extracellular water. This obscures the amount of weight lost by the patient making him appear better nourished than he actually is (Craig & Waterhouse, 1957; Rechcigl, Grantham & Greenfield, 1960). Cameron and Hunter (1983) have observed increases in intracellular sodium content of host cells in three different mouse tumours which were producing anorexia and cachexia; and they postulate that this may act to produce or maintain cachexia. Rat tumours have shown a similar sodium-retaining effect (Rechcigl et al., 1960). In man, low serum sodium levels are found in patients with advanced disease, and increased levels of sodium and potassium have been reported in the urine of patients with weight loss and increased catabolism (Blackburn et al., 1977; Theologides, 1979). Oat cell carcinoma of the lung and other hormone-secreting tumours may affect sodium and electrolyte balance.

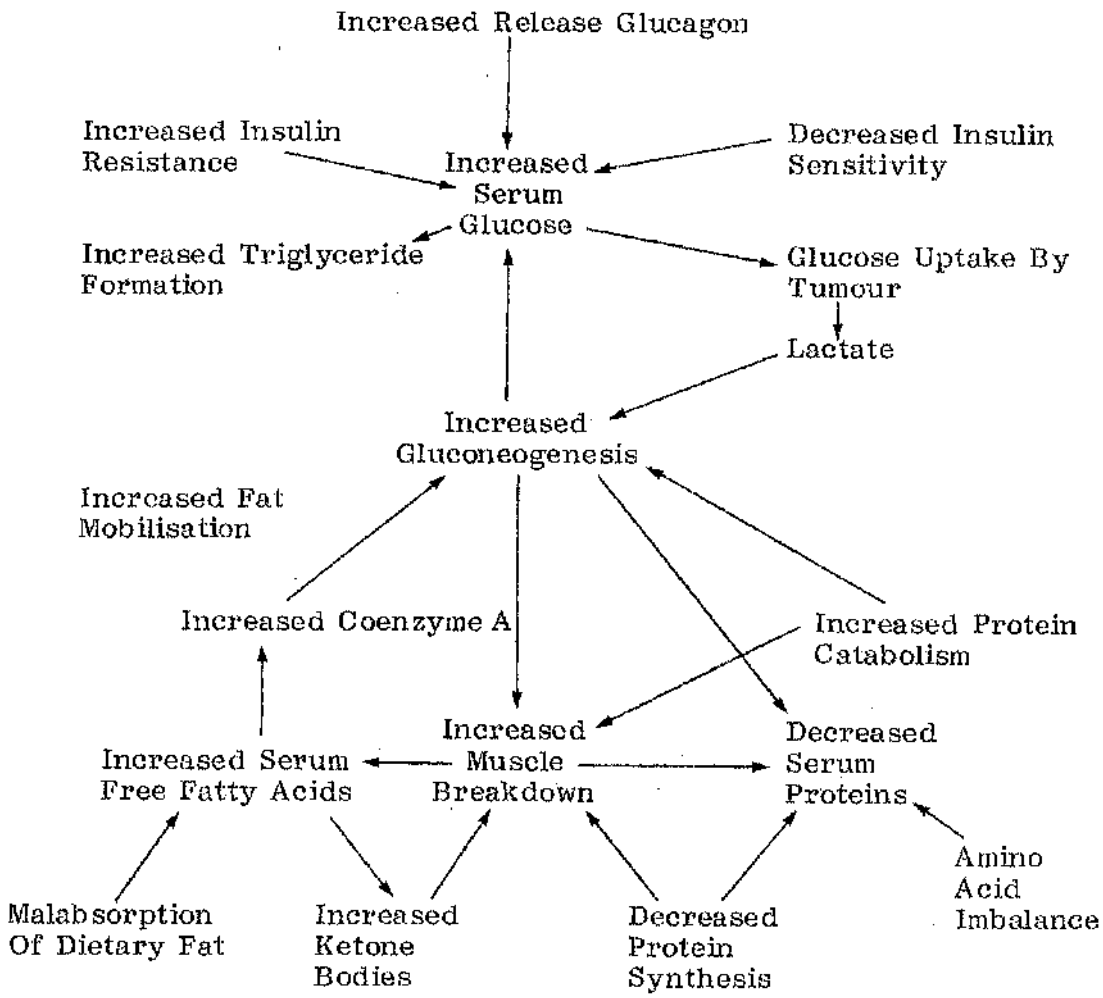

FIGURE 7: SUMMARY OF METABOLIC ALTERATIONS IN CANCER PATIENTS

Potassium levels vary in cancer patients. Adenocarcinomas of the colon cause increased losses of potassium into the gastrointestinal tract and result in low serum levels; insulin-secreting tumours will also produce hypokalaemia, and hypoglycaemia (Blackburn et al., 1977). There is some evidence that tumours store potassium thus causing host depletion (Warnold et al., 1978).

Calcium levels are increased when there is increased mobilisation of calcium from bone with tumour metastases causing bone destruction, and in parathyroid or other hormone producing tumours. Hypercalcaemia is associated with thirst, polyuria, anorexia and dehydration, and may go on to produce renal and cardiac damage due to calcium deposits in these organs. Low serum calcium levels are associated with hypoalbuminaemia and decreased intake; ionised calcium levels are usually normal in these cases (Blackburn et al., 1977; Theologides, 1979).

Magnesium has an uncertain role in cancer. It is an important intracellular cation and is intimately involved in mitochondrial function. Deficiency leads to anorexia, nausea, general weakness, and disruption of mitochondrial respiration, and may cause decreased potassium and calcium levels with tetany and potentially life-threatening cardiac arrhythmias. Cameron and Hunter (1983) found no particular change in magnesium levels of intracellular or extracellular fluids in cancer bearing hosts compared to controls. High levels of magnesium have been found in some specimens of breast cancer

(Santoliquido, Southwick & Olwin, 1976) and Parsons et al. (1974) reported regression of tumour growth in a number of patients depleted of magnesium and potassium by dialysis and diet. The evidence for a connection between magnesium levels in the host and tumour growth is limited, and requires further elucidation (Blackburn et al., 1977). This will be discussed more fully in Chapter 6.

Non-specific iron deficiency anaemia may be found in many cachectic cancer patients. Iron deficiency may be related to hypopharyngeal cancer - following the Brown-Kelly-Patersonn or Plummer-Vinson pharyngeal web syndrome - and to gastric carcinoma. The incidence of gastric carcinoma is five times greater in areas where iron deficiency is common, than in a generally well nourished population (Blackburn et al., 1977). There may be a connection between iron deficiency and immune deficiency and these factors have both been linked to carcinogenesis (Vitale, 1975).

Trace metal changes vary in cancer patients and depend on intake and losses, as well as tumour effects. The importance of the trace metals is in promoting enzyme activity in the body and deficiency may profoundly alter host cellular activity, and may predispose to cancer (Blackburn et al., 1977).

Zinc and copper have been most extensively studied. Zinc is a co-enzyme for more than eighty enzymes and is necessary for DNA and RNA synthesis and repair. Zinc deficiency has been found in a number of human and animal studies on tumour-bearing

hosts. Increased levels of zinc have been found in the urine of cancer patients (Schwartz, 1975), and Askari, Long & Blackemore (1980) maintain that tumours require zinc for growth. Not every tumour causes zinc deficiency, and patients with tumours of colon and lung and advanced disease have been recorded as having increased plasma zinc levels (Blackburn et al., 1977).

Copper is a zinc antagonist, in addition to being involved in enzyme actions in its own right. Copper levels are known to be increased in the serum of patients with leukaemias and lymphomas and in some solid tumours, notably osteosarcomas and carcinomas of breast, cervix, bladder, liver, lung and gastrointestinal tract (Askari et al., 1980). The ratio of serum copper to serum zinc has been used as a prognostic sign in leukaemias and osteosarcomas and has been proposed as a useful marker of successful treatment in the majority of cancers. The higher the copper: zinc ratio, the poorer the prognosis and the more widespread the disease (Askari et al., 1980).

Selenium levels in patients with breast cancer have been found to be lower than in normal controls, and populations living in areas with high selenium content of soil and crops, have less risk of dying from cancer (Buzby & Steinberg, 1981; Schwartz, 1975).

Manganese is required for synthesis of connective tissue and has been found to be increased in malignant breast tissue and in osteosarcoma tissue (Schwartz, 1975).

Several studies have shown multiple vitamin deficiencies in patients with advanced cancers, but the link between vitamin deficiency and the onset of cachexia is not clear (Theologides, 1979). Shils (1979) maintains that the deficiencies found are due to decreased nutrient intake, malabsorption and excessive losses from the gastrointestinal and urinary tracts, and that these contribute to the continuing vicious circle of malnutrition.

Ascorbic acid levels have been found to be decreased in patients with advanced disease, despite normal food intake (Basu et al., 1974). The lowest levels have been found in patients with metastatic breast cancer and skeletal involvement (Dickerson, 1981; Soukop & Calman, 1979). Vitamin C is important in maintaining cell and mucous membrane integrity and in promoting tissue repair, and deficiency of this vitamin has been shown to increase the susceptibility of animals to chemically-induced tumours (Gori, 1979; Cameron & Pauling, 1973).

Atukorala et al. (1979) found reduced levels of vitamin A in patients with carcinomas of lung, and Ibrahim, Jafarey & Zuberi (1977) found similar decreases in patients with squamous cancers of the mouth and pharynx. Dickerson (1981) suggests that low levels of vitamin A correlate with low levels both of retinal binding protein and of zinc - which is required for protein synthesis. In this case the deficient plasma vitamin A is partly due to deficiency of zinc rather than solely to decreased intake. Vitamin A has an important role in maintaining epithelial integrity and deficiency may play a part in the occurrence

and growth of many different cancers (Sporn, 1977).

Abnormalities of folate metabolism have been reported, with low levels of plasma folic acid found in patients with metastatic carcinoma and in leukaemias and lymphomas (Magnus, 1967). Some tumours have been found to have high folate requirements (Rosen & Nichol, 1962) and will cause depletion in the host. Folic acid is involved in cell replication, and deficiency causes toxic effects on bone marrow and gastrointestinal tract - both tissues which have rapid cell turnover. This has obvious consequences for host nutritional status and defences against infection (Bertino, 1979). Serum vitamin B_{12} levels have been found to be raised in some leukaemias and in metastatic liver disease (Shils, 1979; Barry, 1974). The precise reasons for this, and effects on the host are not clear.

Basu and Dickerson (1976) report a high incidence of thiamine deficiency in patients with both early and advanced malignancy. This may be exacerbated by administration of 5-fluorouracil. Thiamine deficiency may cause confusion and contributes to generalised malnutrition.

Pyridoxine (vitamin B_6) is involved in many enzyme pathways for metabolism and is important in cell proliferation. Deficiency of this vitamin has been found in cancer patients (Basu, 1976).

Other vitamin deficiencies may occur and Dickerson (1981) contends

that the vitamins and trace elements are interrelated, with deficiency of one affecting the requirement of the host for the others. He points out that ascorbic acid has been shown to affect the requirement for and the metabolism of vitamin A, folic acid, vitamin B_{12}, thiamine and some of the other B-complex vitamins.

There appear to be no changes in vitamin, mineral and trace metal status of patients which are specific to cancer. It seems likely that the changes seen reflect the nutritional and metabolic state of the host; and that when they occur they may have major effects on the deteriorating metabolism and nutrition of the host.

Anorexia

Anorexia is a major contributing factor to cachexia; decreased appetite causes diminished intake leading to continued malnutrition and impaired host defences to infection, tumour growth and spread (Garattini et al., 1980). Anorexia may be an early or late feature in the growth of the tumour and affects 40-43% of all cancer patients (Theologides, 1976). A survey of 110 outpatients attending Department of Clinical Oncology, Gartnavel General Hospital, Glasgow, found an incidence of 43% patients with this problem (Willox et al., 1984). The loss of appetite may be part of the cachexia syndrome; or it may be produced by chemotherapy or radiotherapy or their associated nausea and vomiting (Garattini et al., 1980); or it may be an isolated phenomenon occurring, like weight loss, in cancer patients at an early stage of disease when there is no

obvious clinical cause for the anorexia. Patients and relatives often find this a most distressing problem (Theologides, 1976). It is, like weight loss, an obvious sign, appreciated by the layman, that all is not well with internal body function. It becomes a reflection of the state of the disease for both the patient and relatives; if the patient is eating well he feels better and is optimistic about his progress; if his appetite is poor, he feels weak and becomes depressed about the future.

The satiety centre and feeding centre are located in the ventromedial and lateral hypothalamus, respectively (Morley & Levine, 1983). They are influenced by stimuli from within the brain and from the rest of the body. Serotonin is the neurotransmitter which acts via the satiety centre to cause anorexia; dopamine initiates feeding via the feeding centre; the alpha-adrenergic system acts on the satiety centre to stimulate appetite; the beta-adrenergic system acts on the feeding centre to cause anorexia (Morley & Levine, 1983). An imbalance of serotonin and dopamine have been postulated as a cause of anorexia in cancer (Krause, Greep & Fischer, 1979; Theologides, 1981; DeWys 1979).

Hormones may directly influence the feeding and satiety centres. Calcitonin and thyroid releasing hormone act to suppress appetite (Morley & Levine, 1983). The action of insulin is the subject of some debate. Grossman, Cummins and Ivy (1947) found that increased levels of circulating insulin in the blood caused increased appetite; Porte &

Woods (1981) however showed that long-term insulin infusion into the cerebral fluid of baboons caused decreasing food intake and decreasing weight with increasing doses of insulin. Blood glucose levels influence appetite, although it is probably the rate of glucose utilisation rather than the actual level of blood glucose which promotes or depresses appetite (Mayer, 1955). The cancer patient has raised blood glucose levels and a relatively slow rate of utilisation of glucose due to delayed insulin secretion, and this must contribute to the anorexia (DeWys, 1979).

Glucagon, adrenaline, enterogastrone, bombesin, endorphin and cholecystokinin all act to produce anorexia. The last four are also found in the gastrointestinal tract and are involved in regulation of intake and absorption of food (Theologides, 1981; Morley & Levine, 1983). In view of the metabolic upsets seen in cancer patients, alterations in hormone levels are likely to cause anorexia, and some hormone-secreting tumours may cause an imbalance leading to depressed appetite (Theologides, 1981).

Corticotrophin-releasing factor, produced in times of stress, may be important in producing anorexia in cancer patients. The stresses from the cancer itself and its demands on the host resources, from pain, and from the various forms of treatment whether surgery, radiotherapy or chemotherapy act to increase the release of corticosteroids and of corticotrophin releasing factor, and produce anorexia (Morley & Levine, 1983). Stress may induce the production of

endogenous opiates in the brain and these tend to increase appetite (Morley & Levine, 1980; Vaswani, Tejwani & Mousa, 1983). However this may not be so marked in cancer patients where production of these opiates may be diminished.

Metabolic abnormalities can cause anorexia. The presence of liver metastases or abnormal liver function tests have been associated with anorexia (Theologides, 1977).

High levels of lactate act on the hypothalamus to produce anorexia, and this may be relevant in the cancer patient (Pitts & MacClure, 1967; Baile et al., 1970; Deykin & Waterhouse, 1972). The onset of fat depletion has been associated with the appearance of anorexia and is due to the increased levels of free fatty acids and ketone bodies circulating at that time (Garattini et al., 1980). Amino acid imbalances produce anorexia and Morley & Levine (1983) propose that the effect is mediated through the role of amino acids as neurotransmitters, and their known influence on feeding (Leung & Rodgers, 1969; Garattini et al., 1980). Zinc and copper imbalances in cancer patients may contribute to the anorexia (Garattini et al., 1980; Trant, Serin & Douglas, 1982; Blackburn et al., 1977).

Theologides (1976) proposes that small molecular weight peptides are produced by the tumour itself or by its effect on the host, and these cause anorexia. They may act via peripheral or central neuroreceptors to produce their effect. Peptides have been isolated

from the urine of fasted rats which cause anorexia in hungry rats (Lee & Lichton, 1973); and Barai and DeWys (1980) found that when urine from anorectic cancer patients was injected intraperitoneally into mice, appetite was suppressed. Trotter et al. (1981) showed improved appetite following plasma exchange which removed circulating factors. Further evidence for circulating factors affecting appetite comes from Davis, Gallacher & Ladore (1969) who showed that the intake of food in hungry rats decreased by 50% when their blood was mixed with that of fed rats; and Myers (1969) took cerebrospinal fluid from fasted donors and reported increased eating and drinking in satieted monkeys when the fluid was injected into the lateral hypothalamus.

Other theories of appetite regulation include the theory of thermostatic regulation proposed by Brobeck (1948) where body temperature and the heat generated by metabolism regulate feeding. This mechanism may have little part to play in cancer patients except where there is a great increase in basal metabolic rate, or pyrexia associated with infection or tumour. Osmoreceptors in the body monitor shift of water from intracellular to extracellular compartments and thus signal satiety. This may have a role in cancer patients with increased extracellular fluid volume which will produce "satiety" (Theologides, 1976).

Cachectic cancer patients often complain of early satiety: a meal eaten early in the day fills them up for the rest of the day (Strain, 1979; DeWys, 1979). This may be due to diminished muscle tone in the

stomach and intestines from the muscle wasting which parellels the loss of skeletal muscle, which therefore causes sluggish or delayed passage of food along the gastrointestinal tract (DeWys, 1979). Signals produced by the neuroreceptors, baroreceptors, osmoreceptors and chemoreceptors in the gastrointestinal tract indicate satiety to the appetite centres. Hyperglycaemia delays gastric emptying and this will contribute to the problem (DeWys, 1980). Decreased or delayed absorption of food may also account for the early satiety of patients and it is well-documented that cachectic patients have pathological changes in the small intestine similar to those found in starvation (Girdwood, 1964; Barry, 1974). There are stunted microvilli and a greatly reduced area for absorption of nutrients. A decreased production of mucosal cells is found rather than an increased turnover of cells, and this resembles other wasting illnesses being a result of decreased intake and weight loss rather than their cause, and contributing to their continuation (DeWys, 1979; Creamer, 1964; Fischer et al., 1965). Chemotherapy and radiotherapy may contribute to the intestinal pathology by acting on the rapidly dividing cells of the gastrointestinal mucosa; and some types of chemotherapy cause neuropathies which interrupt normal bowel action producing delayed passage of food (Hall, 1979).

Abnormalities of taste and smell have been reported in some cancer patients and these may contribute to the anorexia by diminishing the pleasure of eating , decreasing the secretion of digestive enzymes and decreasing the stimulation of the gastrointestinal tract (DeWys,

1979; Theologides, 1976). Not every patient with cancer develops abnormal taste thresholds although the abnormality has been correlated with increased tumour burden and decreased energy intake (DeWys, 1978). There may be abnormalities in the taste buds similar to the intestinal mucosal abnormalities in some cachectic patients (Russ & DeWys, 1978). Trant, Serin & Douglas (1982) found no abnormalities of taste perception in patients grouped by tumour site, treatment, or appetite. They reported that anorectic patients preferred lower levels of sweetness compared to controls; and that patients on chemotherapy showed no particular preference for any of five concentrations of sucrose. DeWys (1978), however, analysed several studies involving a total of 133 patients and found increased recognition thresholds for sweetness (sucrose) in 30-100% patients; and decreased recognition thresholds for bitter (urea) in 10-20% patients with a wide range of tumours and at various stages of disease. The alterations were particularly striking in the patients who complained of decreased sensation and in those who had developed an aversion to meat. Other taste changes for sour and salt tastes were not statistically different for the group as a whole, but thresholds were increased in the patients with active disease. Response to treatment restored taste to normal; progression of tumour increased the frequency of taste abnormalities with 15 of 20 patients who had advanced disease showing altered thresholds for sucrose and urea (DeWys, 1978). Taste abnormalities are present in some patients with cancer, although there is no common specific change found. These changes contribute to the anorexia of patients by producing decreased sensation and decreased

pleasure in eating, and may even lead to food aversions.

Learned aversions to certain foods may be produced by the effects of the tumour or its treatment, causing discomfort, vomiting, nausea or malaise, which become psychologically associated with the food eaten just prior to the unpleasant event. It may be a particularly difficult symptom to treat and the patient can become quite anorexic during a course of treatment (Holland, Rowland & Plumb, 1977; DeWys, 1980; Bernstein, 1982). Some food aversions and cravings found in a number of patients have no identifiable cause. These appear to resemble those occurring during pregnancy. Brewin (1980) found 22/24 women with tumours had specific taste changes with either the same craving or aversion as occurred during pregnancy or the opposite feeling for the same substance. The changes began before diagnosis or were triggered by treatment or tumour recurrence.

Psychological factors have a major role in anorexia in cancer patients. The sight of food produces excitatory stimuli to the gastrointestinal tract and to the hypothalamus, causing hunger and readiness to digest food. The ability of man to eat when he is not hungry, however, demonstrates the power of the higher brain centres on the appetite and feeding centres (Theologides, 1979).

Holland et al. (1977) propose that psychological factors contribute to the anorexia of cancer patients at various stages of the

disease. At the time of initial diagnosis, the patient is in a state of emotional turmoil with uncertainty about the cause and effects of the tumour, depression about the diagnosis, and anxiety about the treatment and outcome. This stress, with its increase in corticosteroid, corticotrophin and adrenaline production, produces anorexia, and weight loss of 5-10 lb., due solely to the psychological upset is not uncommon. Once a plan of action is formulated for the patient and commenced, the initial anxiety and depression subsides and the anorexia disappears, often with gain of the original amount of weight lost. Should there be relapse, treatment failure or periods of pain and discouragement, anxiety and anorexia may reappear. This time the anorexia is more difficult to resolve and depends both on an alternative treatment plan or relief of pain and positive psychological support to alleviate anxiety and restore appetite, and on improvement in the metabolic state which may be abnormal at this stage of disease.

There is some debate as to the relative importance of the psychological component in causing loss of appetite in cancer patients, however, it is recognised that it plays a part together with the metabolic factors in the genesis of the anorexia, which is a major contributing cause of cancer cachexia (Theologides, 1976; Holland et al., 1977; DeWys, 1979; Trant et al., 1982) (Fig. 8).

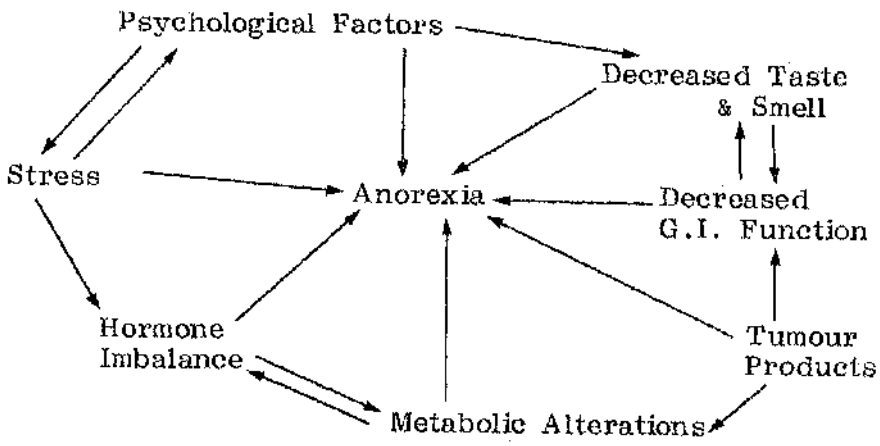

FIGURE 8: FACTORS PRODUCING ANOREXIA IN CANCER PATIENTS

Effects of Treatment on Nutritional and Metabolic State

Surgery, radiotherapy and chemotherapy have major effects on the nutritional and metabolic state of the tumour bearing host (Ohnuma & Holland, 1977; Costa & Donaldson, 1979).

Surgery

The acute effects of surgery are to produce an increase in basal metabolic rate and in protein turnover, with increased circulating levels of adrenaline, corticosteroids, fatty acids and glucose (Brennan, 1979). After the initial post-operative period metabolism returns to its pre-operative state - and the long term effects of the surgery become evident (Fig. 9).

Following surgery of the head and neck, there may be difficulties in chewing and swallowing and taste is often impaired with obvious consequencies for nutrition. Anorexia is a common complaint due to the decreased enjoyment of food and the difficulties and discomfort of eating (Brennan, 1977).

Resection of the oesophagus can cause gastric stasis, with fistulae, diarrhoea, malabsorption of fat and consequent weight loss. Gastrectomy leads to problems of early satiety with anorexia, dumping syndrome, hypoglycaemia, steatorrhoea and deficiency of gastric acid, pepsin and intrinsic factor. These may cause the later development of

SITE OF SURGERY	ACUTE EFFECTS	CHRONIC EFFECTS
General	Metabolic Upset Anorexia, Nausea, Vomiting Ileus	Depends on Site
Upper GI Tract	Anorexia Dysphagia Loss of Taste Sensation	Malabsorption of Fat Fistulae Diarrhoea
Stomach	Anorexia Hypoglycaemia	Deficiencies: Vitamins A, D, B_{12} Minerals Fe, Ca Early Satiety Low Intake Diarrhoea Low Gastric Acid
Intestine	Ileus Anorexia	Vitamin B_{12} Malabsorption Diarrhoea Malabsorption Steatorrhoea
Pancreas	Malabsorption Diabetes Mellitus	Malabsorption Diabetes Mellitus
Liver	Hypoglycaemia Hypoalbuminaemia	Very Few

FIGURE 9: EFFECTS OF SURGERY ON NUTRITIONAL STATE

vitamin deficiencies, particularly of vitamin B_{12} and of vitamins A and D and mineral deficiencies of iron and of calcium (Shils, 1979; Dionigi & Campani, 1981).

Removal of the small intestine causes little upset apart from ileus and anorexia immediately post-operatively (Buzby & Steinberg, 1981). Loss of the terminal ileum may result in decreased absorption of vitamin B_{12} and of bile salts leading to megaloblastic anaemia and neuropathies (in the long term) and to watery diarrhoea and steatorrhoea. Massive bowel resection causes malabsorption and there may be hyperoxaluria with the formation of renal oxalate stones. Removal of the colon has few nutritional sequele for the patient apart from the occasional problem of excess water and electrolyte loss (Buzby & Steinberg, 1981).

Pancreatectomy, with loss of digestive enzymes, leads to malabsorption and excessive losses of fat, protein, vitamins and minerals. Diabetes mellitus may be induced by removal of the tail of the pancreas.

Hepatic resection is usually followed by almost complete regeneration of liver tissue and restoration of liver function to normal (Shils,1979). However, there are often severe metabolic abnormalities with hypoglycaemia and hypoalbuminaemia in the immediate post-operative period (Costa & Donaldson, 1979).

Following surgery, patients who have periods of intravenous or nasogastric feeding may become psychologically dependent on their "lifeline" and unable to cope with eating normally. In these cases it is necessary to 'wean' the patient from the tubes (Holland et al., 1977).

Radiotherapy

Radiotherapy is often complicated by malnutrition in the patient prior to treatment, and by its effects on the patient (Fig. 10). Any extensive or prolonged radiotherapy treatment will cause nausea, vomiting, anorexia and consequent weight loss (Butler, 1980). Irradiation to the brain causes nausea and anorexia due to cerebral oedema, an unavoidable side effect (Donaldson & Lenon, 1979).

Head and neck irradiation may cause both acute and chronic sequele. Acute problems include dysphagia, dry mouth, anorexia and loss of taste - the so-called "mouth blindness" described in 1959 by McCarthy-Leventhal. There may be loss of smell and mucositis leading to oral ulceration (Donaldson, 1977). The loss of taste may persist as an altered taste perception and has far-reaching effects on the patient both psychologically and nutritionally by predisposing to long term anorexia (Shils, 1979; Donaldson, 1977; Donaldson & Lenon, 1979). Salivary gland irradiation leaves a persistently dry mouth with decrease in the quantity and quality of the saliva produced, which becomes thick and viscous allowing an alteration of the bacterial flora

SITE OF RADIOTHERAPY	ACUTE EFFECTS	CHRONIC EFFECTS
General	Nausea, Vomiting Anorexia	Depends on Site
CNS	Nausea Anorexia	
Head & Neck	Dysphagia Dry Mouth Anorexia Loss of Taste & Smell Mucositis	Anorexia Loss of Taste Dry Mouth Dental Caries Weight Loss
Chest	Dysphagia	Fibrosis of Oesophagus Stenosis Fistula
Upper Gastro-intestinal Tract	Nausea Vomiting Anorexia Diarrhoea	Malabsorption Fistula Stricture Ulceration
Pelvis	Weight Loss	Weight Loss

FIGURE 10: EFFECTS OF RADIOTHERAPY ON NUTRITIONAL STATE

of the mouth and leading to dental caries (Donaldson, 1977). The changes in saliva, in taste and smell and the increase in dental caries makes chewing and swallowing difficult and contributes to decreased intake of food and deranged nutritional status, in addition to the effects of the tumour itself. Weight loss was reported in 93% patients receiving even a short course of radiotherapy to the head and neck, and in 8.7% patients, weight loss was greater than 10% body weight (Donaldson & Lenon, 1979). In an already nutritionally compromised patient this represents a major nutritional upset.

Radiation to the chest causes, acutely, dysphagia by its effects on the mucosa of the pharynx and oesophagus. In the long term, there may be fibrosis, stenosis or fistula formation in the oesophagus, with obvious consequencies for nutrition (Donaldson, 1977).

Gastric, small and large bowel irradiation is usually accompanied by nausea, anorexia, vomiting and diarrhoea. In the stomach, there may be decreased acid and pepsin secretion and chronic ulcer formation in the long term. These may contribute to anorexia, malabsorption and weight loss (Donaldson & Lenon, 1979).

Small and large bowel irradiation results in variable degrees of malabsorption of glucose, protein, electrolytes and fat. Fistula formation can occur, and there may be ulceration or strictures and bacterial overgrowth due to altered gastrointestinal flora (Donaldson, 1977). 88% patients undergoing abdominal or pelvic irradiation had

weight loss during therapy; in 13% this weight loss was greater than 10% body weight. This reflects the poor nutritional state of many of these patients (Donaldson, 1977).

Chemotherapy

Chemotherapy and its effects are potentially damaging to the nutritional state of the patient; and the nutritional status affects the effectiveness and toxicity of the chemotherapy (Donaldson & Lenon, 1979) (Fig. 11). Chemotherapy unavoidably affects host cells as well as tumour cells and causes a variety of side effects and damage to organs in the body resulting in major nutritional problems (Ohnuma & Holland, 1977). Combination chemotherapy intensifies the toxicity of each of the single agents used (Costa & Donaldson, 1979).

Nausea and vomiting occur with almost every major class of chemotherapeutic agent (Ohnuma & Holland, 1977). This action is mediated by an effect on the chemoreceptor trigger zone located in the floor of the fourth ventricle (Borison, 1974; Cockel, 1971). There are a few chemotherapeutic agents which do not cause nausea and vomiting and these include some of the alkylating agents such as Chlorambucil and Busulphan, the vinca alkaloids and steroids. Nausea and vomiting and the anorexia which frequently accompanies them cause diminished food intake, electrolyte imbalance, dehydration, general weakness and weight loss.

Altered taste sensations are found with Cyclophosphamide, which

SYSTEM AFFECTED	ACUTE EFFECTS	CHRONIC EFFECTS
General	Nausea, Vomiting	Weight Loss
	Anorexia	
	Vitamin Deficiencies	
	Infection	
Haemopoeitic	Anaemia	Infections
	Low WBC/Platelets	
Gastrointestinal	Oral Ulceration	
	Increased Bacterial Over-growth	
	Anorexia	Anorexia
	Electrolyte Imbalance	Malabsorption
	Malabsorption	Constipation
	Diarrhoea	
	Constipation	
	Ileus	
Liver, Pancreas	Anorexia, Hypoalbuminaemia	
Genitourinary	Hyperglycaemia	
	Impaired Renal Function	Impaired Renal Function
	Increased Excretion Mg^{2+}/K^{+}	Anorexia
	Urea	Electrolyte Imbalance
CNS	Neuropathy	Neuropathy
	Confusion	Anorexia
	Lethargy	
Respiratory	Fibrosis	Fibrosis (Lung)
Cardiovascular	Cardiac Failure	Water Retention
		Electrolyte Imbalance

FIGURE 11: EFFECTS OF CHEMOTHERAPY ON NUTRITIONAL STATE

may produce a metallic taste in the mouth, and 5-Fluorouracil which causes decreased sensitivity for salt and sweetness. These contribute to anorexia as previously discussed (Carson & Gormican, 1977).

Stomatitis, mucositis, glossitis and pharyngitis occur with many chemotherapeutic agents. The rapid turnover of cells in the gastro-intestinal tract leave it vulnerable to the effects of the drugs. Dose-limiting and severe oral mucosal toxicity has been described following treatment with Actinomycin D, Adriamycin, Azaserine, Daunorubicin, 5 Fluorouracil, Methotrexate and Methylglyoxal Bisguanyl-hydrazone. Cyclophosphamide and Phenylalanine mustard may produce ulceration in the mouth (Ohnuma & Holland, 1977). These effects cause decreased uptake of food and fluids and, if prolonged, lead to nutritional problems.

The effects of chemotherapeutic drugs on mucus membranes are a likely cause for the malabsorption syndrome seen in cancer patients receiving chemotherapy. Diarrhoea is another manifestation of this toxicity. Actinomycin D, 5 Fluourouracil and Methylglyoxal Bisquanyl-hydrazone may cause severe diarrhoea with abdominal pain. Methotrexate, Hydroxyurea, Nitrosoureas and 5-Azacytidine frequently cause diarrhoea, while 6-Mercaptopurine, Cyclophosphamide, Procarbazine and Levamisole are less frequent causes. In severe cases there is proctitis, mucosal ulceration, bleeding, and even perforation with the drug - induced diarrhoea; and prolonged diarrhoea results in dehydration, electrolyte imbalance, malabsorption, general weakness and

malnutrition (Ohnuma & Holland, 1977). Constipation and ileus may follow vinca alkaloid administration; the constipation at times alternating with diarrhoea. Jaw pain is a feature of Vincristine use (Ohnuma & Holland, 1977; Holland et al., 1973).

Liver damage can be induced by a number of chemotherapeutic agents, and this leads to anorexia, hypoalbuminaemia, deranged liver function and even jaundice. Asparaginase, Azaserine, Duazomycin and 6 Mercaptopurine commonly cause liver damage. Methotrexate, nitrosourea compounds, Mithramycin and 5-Azacytidine also cause liver dysfunction (Einhorn & Davidsohn,1964; Ohnuma & Holland, 1977).

Pancreatic dysfunction occurs with asparaginase. Streptozotocin causes hyperglycaemia and abnormal glucose tolerance tests due to its effects on the islet of Langerhans cells in the pancreas (Sadoff, 1972). Hyperglycaemia has been found with Methylglyoxal Bisguanyl-hydrazone (Ohnuma & Holland, 1977).

Cardiac damage leading to cardiac failure with water retention and electrolyte imbalance may follow treatment with Daunorubicin or Adriamycin (Blum & Carter, 1973).

A large number of chemotherapeutic agents, apart from the vinca alkaloids, Bleomycin, Asparaginase and steroids, cause bone marrow suppression with consequent immune depression, infection, fever, increased energy consumption and anorexia which contribute to the

increasing deterioration of the nutritional state.

The central nervous system is affected by many drugs which cause confusion, drowsiness, disorientation and lethargy with their consequent nutritional problems. Drugs most commonly implicated in these problems include Methotrexate, Procarbazine, Vincristine, Asparaginase, Cycloleucine, steroids and Cis-dichlorodiammine platinum (II) which has been associated with confusion, coma, increasing cerebrospinal fluid pressure and death. Azoserine, 5 Fluorouracil and Levamisole rarely cause central nervous system effects (Ohnuma & Holland, 1977). Narcotics given to cancer patients to relieve pain affect the central nervous system causing sleepiness and constipation leading to missed meals and anorexia (Ohnuma & Holland, 1977).

Renal problems may be encountered after treatment with Cis-dichlorodiammine platinum (II), Methotrexate and Streptozotocin. The increasing levels of urea and creatinine which may follow administration of these drugs leads to anorexia and metabolic upsets. Cisdichlorodiammine platinum (II) induces renal tubular damage with losses of magnesium and potassium in the urine (see Chapter 6). Streptozotocin toxicity involves proteinuria with increasing uraemia. Other drugs which cause electrolyte imbalance through effects on the kidney include Cyclophosphamide which may induce inappropriate anti-diuretic hormone secretion from the pituitary and produce low plasma sodium levels. Mithramycin, Methotrexate and Actinomycin D can produce low serum calcium levels (Ohnuma & Holland, 1977).

Protein synthesis may be impaired by Asparaginase, and 5 Fluorouracil has been particularly implicated in thiamine deficiency (Dickerson, 1981).

Pulse chemotherapy allows time for nutritional recovery between courses (DeWys, 1982) although the time interval between courses determines the extent of improvement.

Surgery, radiotherapy and chemotherapy all influence nutritional status and contribute to cachexia directly by causing weight loss, decreased intake and deranged metabolism; and indirectly by effects on the appetite and on taste sensations. In patients who are not successfully treated, these therapies may exacerbate the nutritional problems and promote the continued nutritional and metabolic decline to cachexia.

In summary, therefore, there are many factors influencing the nutritional and metabolic state of the cancer patient (Fig. 12).

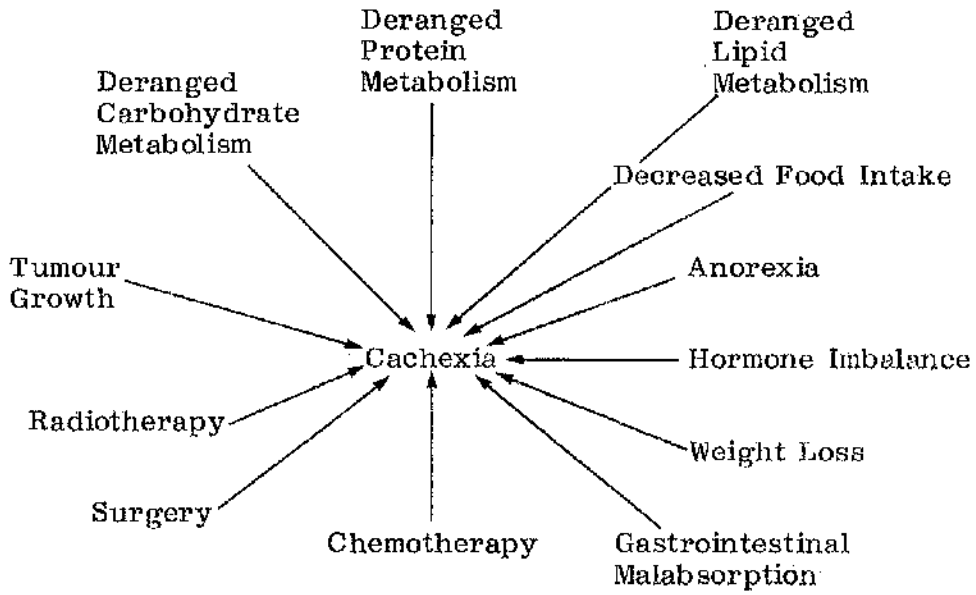

FIGURE 12: SUMMARY OF FACTORS PRODUCING CACHEXIA IN CANCER PATIENTS

B. AIMS OF THESIS

The Introduction to this thesis outlines some of the numerous metabolic and nutritional problems encountered in the cancer patient, many of which are unresolved. The aims of the thesis are to investigate in more detail several of the metabolic and nutritional implications of cancer.

Three main areas will be considered. Section one will examine methods of assessing the nutritional status of cancer patients and will compare the reliability of clinical evaluation, dietary intake histories with computer analysis of diet, and biochemical estimations of nutritional deficiencies. This section will also evaluate a fast, easy and reliable method of anticipating potential nutritional problems, which will allow their early correction.

Section two will examine some of the nutritional and metabolic problems caused by cancer and its treatment. The extreme effects of cancer and chemotherapy are seen in the cachetic cancer patient who has major nutritional and metabolic alterations. The effects of cachexia on muscle composition will be investigated in a preliminary study using cachectic cancer patients.

The effects of cancer and chemotherapy on saliva production and composition are monitored over a 3 month period, in patients receiving

chemotherapy for a variety of tumours. Saliva production is important in enjoyment and mastication of food, and changes in saliva composition may be reflected in the anorexia and abnormalities of taste seen in cancer patients. A second study will follow saliva production and composition over a 3 month period with assessments before, after one month, and after three months of chemotherapy.

The effects on metabolism of two cytotoxic drugs in common use: Cis-dichlorodiammine platinum (II) and Cyclophosphamide will be examined in animal studies. Wistar rats with and without tumour and with and without one of the drugs will have measurements of weight, ketone body production and intermediary metabolism made.

Further animal and clinical studies will evaluate the effects of Cis-dichlorodiammine platinum (II). The animal studies will examine the effects of the drugs on heart, liver, muscle and kidney tissues, looking at the metabolic results of treatment at the subcellular level. Clinical studies will use teratoma patients - a group of cancer patients who are young and in a good nutritional state prior to the onset of disease - and will look at the nutritional and metabolic consequencies of the tumour and of treatment with Cis-dichlorodiammine platinum (II). Trace metal and magnesium, potassium and calcium status, dietary intake, weight loss and other nutritional parameters will be considered. The use of magnesium supplements and their effects on tumour growth, final outcome, renal function and magnesium and potassium levels in urine and serum will be examined. The problems of

magnesium supplementation, of finding effective ways of supplementation, and of checking compliance in taking supplements will also be discussed.

Section three is concerned with the ways of improving nutritional status of cancer patients and will examine the problem of anorexia. The incidence of the problem in cancer patients will be discussed and a double-blind crossover study using prednisolone and placebo tablets in an attempt to find a useful appetite stimulant will be reported.

SECTION 1:

THE ASSESSMENT OF NUTRITIONAL STATUS IN CANCER PATIENTS

CHAPTER 2: NUTRITIONAL ASSESSMENT OF CANCER PATIENTS

Introduction

Considerable controversy has raged over the simplest and most effective methods of assessing nutritional status of patients, and over the most acceptable compromises in assessing patients quickly and easily using labour-saving methods. It seems, however, as Baker et al. (1982) point out, that there is no one definitive test of nutritional status available at the present time.

Clinical examination is the oldest method of nutritional assessment and Baker et al. (1982) propose that a careful history and physical examination is sufficient for the nutritional assessment of most patients and will allow predictions of morbidity. Baker, et al. (1982) found in 81% patients good correlation between clinical assessment of nutritional state and anthropometric and laboratory measurements on the same patients. Grant, Custer & Thurlow (1981), however, warn that clinical evidence of nutritional deficiencies develops late in the deficiency state, and usually reflects gross deficiencies of longstanding. They regard history and clinical examination simply as useful pointers to the presence of nutritional abnormalities.

Dietary histories may give a reasonable guide to the likely nutritional state of a patient, as they reflect the food intake over

varying periods of time. Shapiro (1979) has compared the "in depth" 3 day dietary history - which assesses usual food intake, portion size and takes a three-day record of food eaten - to a 7- day record of food consumed and a 24-hour recall history, which assesses food intake in the previous 24 hours. Dietary histories were also compared to weighed food intakes over longer periods of time. She concludes that the 24 hour recall dietary history is useful when used with other information gathered about a patient. It is not a good indicator of long-term intake of an individual, although when used on several occasions it may reflect the pattern of eating of the patient. It may also be used when assessing a group of individuals on one or two occasions only (Shapiro 1979; Woods et al., 1981). Problems with this method of assessment have increased with the variety of foods and methods of preparation and presentation now available, and variations in daily and weekly food intake may be considerable. Recommended daily allowances of food intake apply to groups rather than to individuals, and intake of any nutrient which is below the recommended daily intake is not, in itself, diagnostic of malnutrition (Shapiro, 1979).

Anthropometric tests use weight, height, muscle bulk and estimates of body fat to give an assessment of nutritional status. Weight loss has been cited by Shenkin (1979) as the single most important factor available in assessing nutritional status. Body weight gives an indication of energy reserves and may be compared to tables of normal ranges (Jelliffe, 1966). Rate of weight loss is important too;

with 5% weight loss over one month and 10% of normal weight lost over six months indicating significant weight loss, which will be associated with poor energy reserves and increasing morbidity (Blackburn & Harvey, 1982). Serial measurements of weight are useful in monitoring the progress of patients. Among the problems of measuring weight is in finding accurate weighing machines and tables which correspond to the population group being observed. Changes in body weight do not indicate which body compartment has been affected, and do not take account of changes in fluid balance, as in oedema or dehydration. Changes also in the amount of body fat or muscle may cause marked alterations in body weight, causing tables to be unreliable (Goode, 1981).

Measurements of midarm circumference give a reasonably accurate index of lean body mass and are useful in following progress over the longterm (Blackburn & Harvey, 1982).

Triceps skinfold thickness gives an estimate of total body fat, and hence of the major energy stores in the body (Shenkin, 1979). Durnin & Womersley (1974) recommend measuring skinfolds at four sites (triceps, biceps, scapula and suprailiac) for good correlation with body fat; however Burgert & Anderson (1979) maintain that for clinical purposes, measuring triceps skinfold thickness is adequate.

These methods are useful in hospital practice where they can be

standardised with a single observer and inexpensive equipment. Good reproducibility can be achieved, and as objective measurements on repeated occasions, anthropometric data are as accurate as other methods of estimating body composition (Hooley, 1980; Woods et al., 1981). Anthropometric measurements do not however indicate the degree of malnutrition, and not every patient who is nutritionally deficient shows decreased anthropometric data (Blackburn & Harvey, 1982). Skinfold thickness results indicate total body fat and energy reserves. Changes in subcutaneous fat, however, occur slowly in starvation and refeeding and do not reflect acute nutritional changes (Grant et al., 1981). Some patients become hypoproteinaemic, with attendant oedema, which masks the state of severe malnutrition underlying the apparently well-nourished patient who shows no change in weight, arm muscle circumference or triceps skinfold thickness (Blackburn & Harvey, 1982).

Laboratory assessment of nutritional status is useful but results often require careful interpretation. The state of visceral protein stores in the body and the ability of the liver to synthesise proteins can be assessed by measuring serum levels of total protein, albumin, transferrin, prealbumin and retinol-binding protein (Jeejeebhoy, 1981). The former three are easiest to measure; however the prolonged half lives of albumin (20 days) and transferrin (5-7 days), makes them less useful for assessing early malnutrition or in monitoring periods of nutritional depletion and repletion. The shorter half lives of prealbumin (2-3 days) and

retinol-binding protein (12 hours) give them a decided advantage in monitoring (Wright, 1980).

Protein loss may be exacerbated by diseases of the gastro-intestinal tract; and production may be decreased in liver disease. Both of these may cause misleading assessments of nutritional state if protein levels alone are used for estimation (Baker et al., 1982). Serum albumin levels are influenced by a number of factors including infection, oedema, surgery, decreased lymphatic return, and sodium retention, so interpretation of serum albumin levels must take these factors into account in estimating nutritional depletion (Blackburn & Harvey, 1982).

Serum transferrin levels may be affected by deficiency of serum iron and will be increased in cases of chronic bleeding (Goode, 1981; Shenkin, 1979).

The excretion of creatinine has been used to assess muscle breakdown, creatinine being a measure of skeletal muscle mass (Wright, 1980). Various indices have been proposed using creatinine - such as creatinine/height index to assess nutritional state, however measurement of creatinine requires normal kidneys, accurate urine collections over 24 hours, and there is a wide range of normal values depending on age, sex and muscle mass (Grant et al., 1981).

Nitrogen balance studies are not particularly useful in assessing

nutritional status as the results vary with intake and metabolic rate;, however, they provide a useful check on whether nitrogen intake is meeting losses of nitrogen (Shenkin, 1979).

Other tests of protein status are less relevant for general assessment of patients. Total body nitrogen may be estimated using neutron activation analysis, requiring specialised equipment, not readily available in a general hospital. Measurements of protein synthesis and catabolism may be useful also, but are time-consuming requiring intravenous infusions, repeated blood and urine sampling, and complicated calculations. Amino acid levels may indicate protein turnover. Interpretation of the pattern of amino acids in the blood is difficult since chronic protein depletion gives a general reduction in amino acid levels; while in the earlier stages of muscle breakdown, there is a high urinary nitrogen with increases in the serum levels of the branched chain amino acids leucine, isoleucine and valine. Amino acid analyser facilities are not present in every hospital; and a quantitative indication of protein loss is not possible from the amino acid pattern (Goode, 1981). 3 methyl histidine is produced where actin and myosin in muscle breaks down. It is excreted, unchanged, in the urine and is not re-cycled. It has been used as a measure of protein catabolism; however errors arise where there is active synthesis of muscle, and if there has been recent intake of meat in the diet. There is controversy over whether 3 methyl histidine is really representative of the behaviour of muscle protein as a whole, as it is present in only 65% muscle protein; and

age, sex, diet, trauma, stress and infection all influence 3 methyl histidine levels. An amino acid analyser is required for analysis (Grant et al., 1981).

Ketone bodies are produced by the body when fat is broken down and used as an energy source, and their presence in the serum indicates insufficient energy intake (Shenkin, 1979). Some patients do not produce ketone bodies, despite decreased intake, and in these cases there is no suppression of gluconeogenesis; with rapid and continued protein breakdown to supply precursors for glucose. These patients have increased morbidity and mortality (Goode, 1981).

Total body potassium measurements have been used to estimate body cell mass. However this is difficult to measure routinely (Jeejeebhoy, 1981).

Biochemical estimations of mineral deficiencies are very difficult to interpret, as serum levels of trace metals such as zinc or copper may bear no relationship to body stores of the element (Hall, 1982). In some cases, urine levels together with serum levels may be helpful, such as when low urinary levels of magnesium or phosphorus indicate dietary deficiencies of these elements. Zinc excretion in the urine is markedly increased in catabolism, and monitoring urinary levels of zinc will allow the metabolic switch to anabolism to be identified, and supplements of zinc and other elements commenced accordingly. The picture may be further complicated in

cases with renal damage where inappropriate losses of zinc or magnesium are occurring. The other problem in identifying mineral deficiencies is the difficulty of measuring trace elements in the blood (Shenkin, 1979).

Vitamin levels in serum may also be misleading. Plasma levels of vitamins A, B, C and folic acid often reflect recent dietary intake rather than body status. Shenkin (1979) maintains that a good dietary history is important in assessing vitamin status. Most vitamins have large body stores, and the most reliable method of determining deficiency is by loading tests which require serum and urine estimations of vitamin levels before and after a loading dose of vitamin. These tests are time consuming and are rarely performed. Intracellular measurements of vitamins, such as leucocyte ascorbic acid and red cell folate estimations may be taken to indicate whole body status (Shenkin, 1979; Goode, 1981).

Other laboratory measurements used to assess nutritional status include haemoglobin and packed cell volume, both of which are decreased in simple starvation, and tests of immune status. Total lymphocyte counts have been used to indicate protein depletion and malnutrition (Wright, 1980).

There has been some controversy over the usefulness of tests of cell-mediated immunity to assess nutritional status. Blackburn & Harvey (1982) and Daly, Dudrick & Copeland (1978) consider that

cell-mediated immunity reflects protein-energy malnutrition and can be used to predict surgical morbidity in patients. Jeejeebhoy (1981) and Bancewicz et al. (1981) contend that although associated with malnutrition, cell mediated immunity is an unreliable index of protein-energy malnutrition in ill patients, and does not predict surgical morbidity. Tests of cell mediated immunity are difficult to standardise, reproduce and interpret, and it is not known at what stage of nutritional depletion that immune status declines (Woods et al., 1981). Patients with cancer may be anergic due to the tumour or its treatment, and there may be a circulating suppressor factor for cell-mediated immunity in addition to the other problems (Blackburn & Harvey, 1982; Daly et al.,1978). These factors make cell mediated immunity an unreliable method of assessing nutritional state in cancer patients.

A number of authors have proposed combinations of several tests to give an index of nutritional status. Smale et al. (1981) propose a prognostic nutritional index using serum albumin, transferin, triceps skinfold thickness and delayed hypersensitivity in surgical patients to predict the chances of post operative complications. Baker et al. (1982), however, contend that as individual tests of nutritional status are of low predictive value, combining several tests into a statistically derived index will not result in improved identification of high-risk patients.

On balance, it appears that the most consistently reliable tests

of nutritional status are weight loss, with assessment of rate of weight change; an estimate of dietary intake to allow prediction of present and future nutritional state; biochemical assessment of protein status; and general clinical examination. A combination of these will give the best assessment of nutritional status at present available.

Aims

The aims of this study were to look for a reliable, reproducible, fast and easy way of assessing the nutritional status and the nutritional requirements of cancer patients. Preliminary studies using 24 hour recall dietary histories with computer analysis to give accurate information about dietary intake, showed this to be a quick and easy way of identifying dietary deficiencies (Trotter et al., 1981). Correlation with clinical and biochemical evidence of deficiency, however, was not carried out. This study aimed to examine the reliability of, and correlation between, clinical evaluation, dietary intake assessment and biochemical measurements of nutritional status in a random group of oncology in-patients.

Methods

42 patients were randomly selected from in-patients admitted to the oncology unit at Gartnavel General Hospital, Glasgow over a six week period. Patients were admitted for investigation, cytotoxic

treatment or pain control. Each patient's nutritional status was assessed by clinical examination, dietary intake analysis and biochemical and haematological estimations.

Clinical evaluation

A general history was taken from the patients with specific questions to highlight any nutritional problems. A detailed clinical examination was carried out, looking particularly for signs of nutritional deficiencies. Figure 13 illustrates the type of form used to record findings and Table 1 lists the signs and symptoms of the major nutritional deficiencies. Weight loss was assessed as moderate loss (3 Kg - 6 Kg.) or severe loss (> 6 Kg.).

Dietary evaluation

A 24 hour dietary recall history was taken from the patient at the time of clinical examination, taking account of all food and drink consumed in the previous 24 hours (see Figure 14). This was coded using the McCance and Widdowson Tables of Food Composition (1978) into food groups and portion size (Table 2). Computer analysis of the data, using a programme supplied by Tayside Health Centre gave a comprehensive account of the amounts of nutrients consumed (Table 3). Recommended daily allowances issued by the Department of Health and Social Security (1979) were used as standards; and a value of 80% of the recommended daily intake was taken as the lower limit of normal, thus allowing for the wide variation in "normal" dietary intakes (Table 4).

NUTRITIONAL ASSESSMENT FORM

Name _____ Age/DOB _____

Diagnosis _____ Date of Admission _____

Treatment _____

Weight _____ Weight Loss _____ Height _____

Known or probable metabolic problems _____

Impaired food intake _____

Bowel habit _____

Physical Strength _____ Activity (ECOG) _____

1. Skin disease _____

2. Hair _____

3. Eyes External _____

Fundi _____

4. Mouth _____

5. Nails _____

6. GIT Dysphagia _____

Ascites _____

7. CNS Cranial nerves _____

Power _____

Tone _____

Reflexes _____

Cerebellar _____

Peripheral Sensation _____

FIGURE 13: NUTRITIONAL ASSESSMENT FORM

SITE	SIGN	DEFICIENCY
Skin	Dry Skin	General Undernutrition Vitamin C
	Depigmentation	General Undernutrition
	Bruising, Petechiae	Vitamin K
	Clinical Anaemia	Iron; B_{12} Folic Acid
	Nasolabial Seborrhoea	Riboflavin
	Squamous Metaplasia	Vitamin A
	Follicular Keratosis	Vitamin A
	Dermatitis	Nicotinic Acid
	Perifollicular Haemorrhages	Vitamin C
	Poor Wound Healing	Vitamin C, Zinc
Hair	Thin, Depigmented	General Undernutrition Vitamin C
	Follicular Keratosis	Vitamin C
	"Corkscrew Hair"	Vitamin C
Eyes	Dry Eyes (Xerophthalmia)	Vitamin A
	Night Blindness	Vitamin A
	Keratomalacia	Vitamin A
	Amblyopia	Vitamin B_{12}
	Fundal Haemorrhages	Vitamin K
Mouth	Apthous Ulceration	General Undernutrition
	Angular Stomatitis	Riboflavin
	Angular Cheilosis	Riboflavin
	Atrophic Glossitis	Iron; Folic Acid
	Gingival Haemorrhages	Vitamin C
Nails	Brittle, Striated	General Undernutrition Calcium
	Koinychia	Iron
	Leuconychia	Iron
CVS	Low Blood Pressure	General Undernutrition
	Oedema	General Undernutrition
	Congestive Cardiac Failure	Thiamine

TABLE 1: SIGNS OF NUTRITIONAL DEFICIENCIES

GIT...../

SITE	SIGN	DEFICIENCY
GIT	Ascites	General Undernutrition
	Diarrhoea	General Undernutrition
	Diarrhoea, Dermatitis, Dementia	Nicotinic Acid
	Dysphagia	Iron
	Atrophic Bowel	Folic Acid
Musculo-skeletal	Decreased Power	General
CNS	Peripheral Neuropathies	General, Thiamine, B_{12}
	Subacute Combined Degeneration Spinal Cord	B_{12}
	Encephalopathy	General, Thiamine

TABLE 1 (CONTD): SIGNS OF NUTRITIONAL DEFICIENCIES

MENU

Breakfast	Porridge + milk Cup of tea + milk + 2 sugar
	**********
Mid Morning	Cup of milk
	**********
Lunch	Soup Cup of tea + milk + 2 sugar
	**********
Mid Afternoon	Nil
	**********
Dinner	1 Boiled potato Custard Cup of tea + milk + 2 sugar
	**********
Supper	Cheese + tomato sandwich Cup of tea + milk + 2 sugar
	**********
Extras	1 Glass of lemonade 1 Glass of orange squash
	**********

FIGURE 14: SAMPLE MENU FOR COMPUTER CODING

DIET HISTORY SHEET

CARD TYPE 2

No.	Food	C/T	Food Group	Ref. No.	Weight (g)	Factor
	Cols.	1	2	3/6	7/11	12/16
1	Porridge	2	A	0018	120	1
2	Milk	2	B	0124	400	1
3	Sugar	2	K	0843	40	1
4	Soup	2	N	0955	150	1
5	Boiled potatoes	2	G	0640	60	1
6	Custard	2	A	0102	120	1
7	Cheese	2	B	0152	30	1
8	Tomato	2	G	0666	60	1
9	Bread	2	A	0033	40	1
10	Butter	2	B	0140	10	1
11	Lemonade	2	L	0881	150	1
12	Orange squash	2	L	0884	30	1
13		2				
14		2				

TABLE 2: COMPUTER CODING OF SAMPLE MENU

COMPUTER ANALYSIS

k cals = 1078

TOTAL ENERGY

k joules = 4539

NUTRIENTS	g
Water	972.40
Protein	34.03
Fat	41.60
Carbohydrate	151.18
Total nitrogen	5.46
	(389.81 mmol)

CARBOHYDRATES	g
Sugars	79.14
Lactose	18.80
Other sugars	0.00
Starch	11.58
Starch + Dextrose	41.66

NUTRIENTS	g
Fibre	3.54
Edible Matter	1.12
Solids	0.00
Alcohol	0.00
Cholesterol	63.20 mg

MINERALS	mg	mmol
Sodium	2243.60	97.59
Potassium	1521.30	38.91
Calcium	983.10	24.53
Magnesium	130.00	5.35
Phosphate	831.90	26.86
Iron	3.09	0.06
Copper	0.48	0.01
Zinc	4.47	0.07
Sulphur	304.90	9.51
Chloride	3605.40	101.70

VITAMINS	mg
Thiamine	0.50
P. Nic	7.59
B6	0.53
Riboflavin	1.25
Vitamin C	23.40
Pan	2.53

VITAMINS	mg
Nic	2.65
Vite	1.74
Ret	356.00
B12	1.65
B10	14.61
Car	580.50

VITAMINS	mg
F. Folate	38.20
Total Folate	87.80
Vit D	0.32

TABLE 3: COMPUTER ANALYSIS OF SAMPLE MENU

	Recommended Daily Intake	80% Recommended Daily Intake
Energy (Kcal)		
Men	2500	2000
Women	2000	1600
Protein (g)		
Men	60	48
Women	50	40
Calcium (mg)	800	640
Iron (mg) men	10	8
women	18	14.4
Zinc (mg)	10	8
Magnesium (mg)	250	200
Thiamine (mg)	1.0	0.8
Vitamin C (mg)	30	25
Vitamin B_{12} (µg)	3.5	2.8
Folic acid (µg)	300	240
Retinol (µg)	750	600

TABLE 4: REFERENCE VALUES FOR DIETARY INTAKE

Biochemical Evaluation

Venous blood samples were taken from each patient at 9 a.m. on the day of examination to eliminate any diurnal variation which might influence results. Aliquots of whole blood, serum and plasma were sent for full blood count and platelet estimation and for vitamin B_{12} and folic acid assay to the Department of Haematology, Gartnavel General Hospital, Glasgow. Further samples were sent to the Department of Biochemistry, Gartnavel General Hospital, Glasgow, for urea and electrolye, total protein, albumin, iron and calcium estimation using the SMAC autoanalyser (Standard Technicon Methodology). Magnesium and zinc levels were measured by atomic absorption spectrophotometry. Miss Jean Bell at Department of Biochemistry, Western Infirmary, Glasgow undertook analysis of samples for vitamin A (retinol) using a High Pressure Liquid Chromatography method.

The remainder of the blood from the patients was sent to the Clinical Oncology Research Laboratories, Glasgow University, and analysed for ketone bodies and for thiamine and vitamin C levels. The ketone bodies, acetoacetate and D-beta hydroxybutyrate were measured by enzymatic analysis using the method of Mellanby and Williamson (1975) and Williamson and Mellanby (1975) respectively. Thiamine (vitamin B_1) levels were measured by assessing erythrocyte transketolase activity using the method of Bayoumi & Rosalki (1976). This gave some indication of tissue levels of the vitamin. Levels of leucocyte ascorbic acid were measured using Denson & Bower's (1961) colometric

method. This gives a good assessment of tissue levels of vitamin C. There were, however, some technical problems with the spectrophotometer, and a number of the samples were discarded, or gave readings which were unreliable.

Table 5 shows the reference biochemical values used in assessing the results.

Results

Of the 42 in-patients participating in the study, the majority had solid tumours, with teratoma forming the largest group (Table 6). Ages ranged from 15 to 79 years (mean age 49 years) and male:female ratio was 22:20. Thirty two patients were receiving chemotherapy, two were receiving radiotherapy, and eight received no cytotoxic treatment and had been admitted to the ward for investigation or pain control.

Results of the clinical, dietary and biochemical evaluations of the patients are shown in tables 7, 9, 11 and 13.

Clinical Evaluation (Table 7)

Weight loss (> 3 Kg) and brittle nails were found in 63% patients, these being the most common clinical signs of nutritional deficiency found in the group of patients studied. Patients receiving

		Normal Range	Deficient
Total Protein		62 - 82 g/l	< 62 g/l
Albumin		35 - 53 g/l	< 35 g/l
Haemoglobin	Male	14 - 18 g/dl	< 14 g/dl
	Female	12 - 16 g/dl	< 12 g/dl
WBC		4 - 10 x 10^9/l	< 4 x 10^9/l
Platelets		140 - 440 x 10^9/l	< 140 x 10^9/l
Calcium		2.20 - 2.65mmol/l	< 2.20mmol/l
Iron	Male	18 - 45 µmol/l	< 18 µmol/l
	Female	14 - 32 µmol/l	< 14 µmol/l
Zinc		14 - 18 µmol/l	< 14 µmol/l
Magnesium		0.7 - 1.0mmol/l	< 0.7mmol/l
Thiamine		15 - 24% marginal	> 25%
Vitamin C		1.1 - 2.8 fmol/wbc	< 1.1 fmol/wbc
Vitamin B_{12}		140 - 900 pg/ml	< 140 pg/ml
Folic Acid		75 - 400 pg/ml	< 75 pg/ml
Retinol		0.7 - 1.7 µmol/l	< 0.7 µmol/l
B-Hydroxybutyrate		0	> 0
AcetoAcetate		0	> 0

TABLE 5: REFERENCE VALUES FOR BIOCHEMICAL RESULTS

Site	Number of Patients
Teratoma (Testis)	8
Breast	6
Ovary	5
Gastrointestinal	5
Lung	3
Bladder	2
Prostate	2
Seminoma (Testis)	2
Melanoma	2
Others	7

TABLE 6: TUMOUR TYPES OF PATIENTS PARTICIPATING IN NUTRITIONAL ASSESSMENTS

Sign	Patients					
	Chemotherapy (31)		Non-Chemotherapy (9)		Total (40)	
Weight Loss ≥ 3Kg	21	(68%)	4	(44%)	25	(63%)
Brittle Nails	19	(61%)	6	(67%)	25	(63%)
Apthous Ulceration	15	(48%)	3	(33%)	18	(45%)
	*12	(39%)			*15	(38%)
Dry Skin < 60 years	9/23	(39%)	2/5	(40%)	11/28	(39%)
> 60 years	6/8	(75%)	3/4	(75%)	9/12	(75%)
Glossitis	11	(35%)	3	(33%)	14	(35%)
Bruising	10	(35%)	3	(33%)	13	(33%)
	* 3	(10%)			* 6	(15%)
Peripheral Neuropathy	12	(39%)	1	(11%)	13	(33%)
	* 6	(19%)			* 7	(18%)
Dry Eyes	9	(29%)	3	(33%)	12	(30%)
	* 8	(26%)			*11	(28%)
Dry Hair	9	(29%)	1	(11%)	10	(25%)
Generalised Weakness (Decreased Power & Tone)	6	(19%)	1	(11%)	7	(18%)
Koilonychia	3	(6%)	0		3	(8%)
Nasolabial Seborrhoea	2	(6%)	1	(11%)	3	(8%)
Dysphagia	2	(6%)	1	(11%)	3	(8%)
Depigmentation	2	(6%)	0		2	(5%)

* Corrected values to exclude side effects of chemotherapy - see text

TABLE 7: CLINICAL SIGNS OF MALNUTRITION IN FORTY CANCER PATIENTS

chemotherapy had more weight loss than the non chemotherapy group (Table 8), presumably due to the increased nausea and vomiting, and decreased appetite and dietary intake in these patients. Brittle nails correlated with weight loss in all cases, and showed no difference in incidence between chemotherapy and non chemotherapy groups.

Patients with aphthous ulceration included 3 patients receiving methotrexate chemotherapy, which may cause this symptom, and when these patients are excluded from the results, there is no difference in the incidence of this problem between chemotherapy and non chemotherapy groups. All of the patients with aphthous ulcers had weight loss, and most complained of glossitis also.

Dry skin, a common and normal finding in those over 60 years of age, is also a sign of general malnutrition and especially, of vitamin C deficiency. It occurs in this study in association with weight loss in 39% patients under 60 years of age, and 75% over 60 years. Chemotherapy does not seem to influence its incidence.

Other signs of specific or generalised nutritional deficiencies may be misleading, and the influence on clinical signs of the cytotoxic treatment received by the patient may also be important. Bruising has many causes other than general malnutrition or vitamin K deficiency, and of the 13 patients with this problem, 7 were thrombocytopenic due to cytotoxic drugs. The vinca alkaloids

Weight Loss	Patients					
	Chemotherapy (32)		Non-Chemotherapy (10)		Total (42)	
Nil	5	(16%)	2	(20%)	7	(17%)
Moderate						
0 - 3 Kg	5	(16%)	3	(30%)	8	(19%)
Severe						
3 - 6 Kg	13	(41%)	4	(40%)	17	(40%)
6 -12 Kg	6	(19%)	1	(10%)	7	(17%)
> 12 Kg	3	(9%)	0		3	(7%)

TABLE 8: ANALYSIS OF WEIGHT LOSS IN 42 CANCER PATIENTS

are well known to produce peripheral neuropathies as side effects of treatment, and of the 12 patients found to have neuropathies, 6 were receiving these drugs as part of their treatment. For both of these signs, the true incidence of deficiency states producing clinical signs is much lower than it at first appears.

Dry hair is another difficult sign to interpret, as many patients who receive chemotherapy will experience hair loss and this may progress to alopecia in some cases. On regrowth, hair texture may be altered and feel dry, despite good nutritional state; and this reflects either a previous period of poor nutrition or drug-induced damage. This was the case in all patients with this complaint.

Chemotherapy, however, does not account for all signs of nutritional deficiency. Dry eyes are often ascribed to methotrexate chemotherapy, as mucositis is a well known side effect of this drug. However, of the 9 patients who complained of this symptom and who were receiving chemotherapy, only 1 had been given methotrexate. Thus there is a 28% incidence of this problem, with 91% of the patients with dry eyes having deficient intakes of vitamin A. Only 28% of those with dry eyes, however, had also decreased serum retinol levels.

Dysphagia was caused by mechanical compression of the oesophagus in all cases reported; and depigmentation was induced by chemotherapy rather than malnutrition, in the 2 patients who noticed it.

Koilonychia and nasolabial seborrhoea occurred in patients who were clinically severely malnourished, and who had grossly deficient dietary intakes and multiple biochemical nutritional abnormalities.

Dietary evaluation (Table 9)

73% patients were eating less than 80% recommended daily allowances of energy and 59% were eating less than 80% daily protein requirements. There were more patients in the chemotherapy group (81%) who were not meeting the recommended daily requirements, than in the non-chemotherapy group (50%). This difference reflects the effects of rigorous cytotoxic treatment on appetite causing nausea, vomiting and anorexia.

Dietary deficiences of the trace metals iron, calcium and zinc and of magnesium were common, ranging from 68-80%. Vitamin intakes were particularly low for folic acid (98%) and for thiamine (80%) and vitamin A (78%). The majority of patients had multiple dietary deficiences.

Three patients were reassessed for dietary intake after 3 weeks, and similar dietary compositions were obtained on both occasions.

Comparing the results for patients in this study with results obtained for 59 oncology out-patients in a study by Trotter et al., (1981), there are broad similarities. Table 10 summarises the two

Nutrient	Patients (41)					
	Chemotherapy (31)		Non-Chemotherapy (10)		Total	
Energy	25	(81%)	5	(50%)	30	(73%)
Protein	19	(61%)	5	(50%)	24	(59%)
Calcium	23	(74%)	5	(50%)	28	(68%)
Iron	25	(81%)	9	(90%)	34	(83%)
Zinc	26	(84%)	6	(60%)	32	(78%)
Magnesium	26	(84%)	7	(70%)	33	(80%)
Thiamine	26	(84%)	7	(70%)	33	(80%)
Vitamin C	21	(68%)	5	(50%)	26	(63%)
Vitamin B_{12}	20	(65%)	7	(70%)	27	(66%)
Folic Acid	30	(97%)	10	(100%)	40	(98%)
Retinol	27	(87%)	5	(50%)	32	(78%)

TABLE 9: DIETARY DEFICIENCIES IN 41 CANCER PATIENTS EATING < 80% RDI

Nutrient	% Patients Deficient Intake	
	Outpatient Study (59)	Inpatient Study (41)
Energy	64	73
Protein	31	59
Iron	68	83
Zinc	53	78
Magnesium	78	80
Thiamine	58	80
Vitamin C	66	63
Folic Acid	98	98
Retinol	53	78

TABLE 10: COMPARISON OF DIETARY DEFICIENCIES IN CANCER OUTPATIENTS AND INPATIENTS

studies which show similar numbers of patients having reduced intakes of folic acid, vitamin C and magnesium; although there are more patents in the inpatient group with deficient intakes of most of the other nutrients assessed. This difference between the studies is accounted for by the fact that Trotter et al. (1981) used out-patients of whom more than 50% had no complaints regarding diet or appetite; while the present study used in-patients, the majority of whom were receiving chemotherapy which required hospital admission for control of nausea and vomiting, and which produced anorexia of variable duration in most patients. Of the patients in the present study not on chemotherapy, most had been admitted for investigation of some deterioration in their condition, or for relief of pain or some other symptom. Both studies, however, demonstrate the pattern of multiple dietary deficiencies present in the cancer patient.

Biochemical evaluation (Table 11)

Total protein levels were reduced in 56% patients; and 44% had albumin levels below 35 g/l. 27% showed severe protein depletion with albumin levels below 30 g/l.

All patients had ketone bodies detectable in serum, indicating fat breakdown for energy.

70% patients receiving chemotherapy, and 44% patients not on chemotherapy were anaemic. Cytotoxic drugs are known to cause

	Patients Studied					
	Chemotherapy (30)		Non-Chemotherapy (9)		Total	
↓Total Protein	18	(60%)	4	(44%)	22	(56%)
Albumin < 35g/l	14	(47%)	3	(33%)	17	(44%)
< 30g/l	9	(30%)	1	(11%)	10	(27%)
↓Haemoglobin	21	(70%)	4	(44%)	25	(64%)
↓White Cell Count	6	(20%)	1	(11%)	7	(18%)
↓Platelets	7	(23%)	0		7	(18%)
↓Calcium	12	(40%)	2	(22%)	14	(36%)
↓Iron	13/24	(54%)	6/7	(86%)	19/31	(61%)
↓Zinc	19/22	(86%)	7/7	(100%)	26/29	(90%)
↓Magnesium	10/23	(43%)	1/7	(14%)	11/30	(37%)
↓Thiamine	8/14	(57%)	4/7	(57%)	12/21	(57%)
↓Vitamin C	4/20	(20%)	2/10	(20%)	6/3	(20%)
↓Vitamin B_{12}	1/20	(5%)	1/5	(20%)	2/25	(8%)
↓Folic Acid	1/20	(5%)	0		1/25	(4%)
↓Retinol	2/12	(17%)	0		2/16	(13%)
B Hydroxybutyrate	28/28	(100%)	8/8	(100%)	36/36	(100%)
Acetoacetate	29/29	(100%)	9/9	(100%)	38/38	(100%)

TABLE 11: BIOCHEMICAL ABNORMALITIES IN 39 CANCER PATIENTS

anaemia and failure of iron utilisation, due to their effects on the haemopoietic system, and this is reflected in the results obtained with a smaller percentage of the chemotherapy group (54%) showing serum iron deficiency than the non-chemotherapy group (86%). Both groups had similar intakes of iron.

Zinc levels were markedly reduced in 90% patients, and calcium levels were reduced in 36%, with only one patient, who had bony metastases, showing evidence of raised serum calcium. Chemotherapy influences the levels of magnesium found, with 43% of the chemotherapy group showing depletion compared to 14% of the non-chemotherapy group. This difference is caused by the excessive urinary magnesium losses induced by Cisplatin chemotherapy (see Chapter 6).

Vitamin levels are also reduced, with thiamine showing the most depletion, this deficiency occurring in 57% patients overall.

The results obtained for the in-patients compare well with results published by Soukop & Calman (1979) from a study of 120 patients with malignant disease. Table 12 summarises the results of both studies, which show good correlation. Differences in the results for vitamin C and folic acid are accounted for by technical problems encountered in these assays in the present study. Some of the samples collected for vitamin and mineral estimations went astray and the results were never received. By the time this problem came to light, as some results took up to a month to be reported, most.

	Soukop & Calman (120 Patients)	Present (39 Patients)
Serum Albumin < 35g/ℓ	47%	44%
< 30g/ℓ	20%	27%
Anaemia	49%	64% (44% untreated)
Thiamine	37%	57%
Vitamin C	71%	20%
Folic Acid	23%	4%
Vitamin A	15%	13%

TABLE 12: COMPARISON OF BIOCHEMICAL DEFICIENCIES IN TWO STUDIES OF CANCER PATIENTS

patients had been discharged from the ward, and some had by then shown marked changes in nutritional state. These gaps in the results collected make the biochemical results obtained less statistically significant when comparing them to the dietary and clinical evaluations of the patients' nutritional status.

Discussion and Conclusions

The aim of the study was to look for a method of simply and quickly evaluating the nutritional status of oncology patients, which would allow early identification and treatment of nutritional problems. The study looked at the three main areas of nutritional assessment: clinical evaluation, dietary-history taking, and biochemical estimation of serum proteins, vitamins and minerals, and assessed the value of each.

Table 13 shows the frequency of clinical signs of deficiency and biochemical nutrient deficiencies in the oncology patients with dietary deficiencies. Table 14 shows the frequency of these signs in the patients who were not diet-deficient.

Statistical analysis of the results was performed with the help of Mr. D. Hole, Chief Statistician, Cancer Surveillance Unit, Ruchill Hospital, Glasgow, to look at the accuracy of 24 hour dietary intake histories in predicting specific clinical and biochemical deficiencies. It was shown that deficient energy intake accurately

Dietary Deficiency	Clinical Signs		Biochemical Deficencies	
Energy	Weight Loss	80%	Total Protein	59%
	Brittle Nails	67%		
	Apthous Ulcers	40%	Albumin	48%
	Dry Skin (<60yrs)	43%		
Protein	Weight Loss	72%	Total Protein	61%
	Brittle Nails	63%		
	Apthous Ulcers	42%	Albumin	56%
	Dry Skin (<60yrs)	62%		
Calcium	Brittle Nails	71%	Calcium	42%
Iron	Koilonychia	3%	Haemoglobin	67%
	Glossitis	31%	Serum Iron	48%
Zinc	No Specific Sign		Zinc	95%
Magnesium	No Specific Sign		Magnesium	43%
Thiamine	CNS Signs	33%	Thiamine	53%
Vitamin C	Dry Skin (<60yrs)	35%	Vitamin C	27%
Vitamin B_{12}	Neuropathy	22%	Vitamin B_{12}	55%
Folic Acid	Glossitis	33%	Anaemia	66%
			Folate	4%
Vitamin A	*Dry Eyes	34%	Retinol	67%

*Patients receiving methotrexate excluded

TABLE 13: CLINICAL AND BIOCHEMICAL EVIDENCE OF MALNUTRITION IN CANCER PATIENTS WITH DIETARY DEFICIENCIES

№ Dietary Deficiency	Clinical Signs		Biochemical Deficiencies	
Energy	Weight Loss	10%	Total Protein	23%
	Brittle Nails	50%		
	Apthous Ulcers	30%	Albumin	15%
	Dry Skin (<60yrs)	20%		
Protein	Weight Loss	50%	Total Protein	40%
	Brittle Nails	63%		
	Apthous Ulcers	31%	Albumin	20%
	Dry Skin	27%		
Calcium	Brittle Nails	42%	Calcium	27%
Iron	Koilonychia	40%	Haemoglobin	60%
	Glossitis	100%	Iron	20%
Zinc	No specific sign		Zinc	71%
Magnesium	No specific sign		Magnesium	14%
Thiamine	CNS signs	57%	Thiamine	50%
Vitamin C	Dry Skin (<60yrs)	21%	Vitamin C	0
Vitamin B_{12}	Neuropathy	8%	Vitamin B_{12}	17%
Folic Acid	Glossitis	0	Folic Acid	-
			Haemoglobin	-
Vitamin A	*Dry Eyes	0	Retinol	0

* Patients receiving methotrexate excluded

TABLE 14: CLINICAL AND BIOCHEMICAL EVIDENCE OF MALNUTRITION IN CANCER PATIENTS NOT DIETARY DEFICIENT

identified those patients who had lost weight ($p < 0.001$), and using a non-parametric t-test, was significantly correlated with serum total protein ($p < 0.05$) and albumin levels ($p < 0.05$).

Decreased protein intake showed a trend to correlation with decreased serum total protein levels, and significant correlation with serum albumin levels also ($p < 0.05$). Some patients with low serum total protein and albumin levels had normal intakes of both energy and protein, and these patients had tumours which had responded to aggressive treatment. This treatment had induced anorexia, nausea, vomiting and weight loss over several months prior to the study, but at the time of study appetite and intake had returned to normal. The serum protein levels in these patients had not yet reflected this change in dietary intake.

Dietary protein deficiency corresponded with dry skin in those patients under 60 years, and was weakly significant ($p < 0.08$).

Dietary calcium deficiency was reflected clinically by brittle nails ($p < 0.06$), and biochemically showed a trend towards decreased serum calcium levels.

Decreased intake of vitamin A corresponded to complaints of dry eyes in patients not receiving methotrexate chemotherapy ($p < 0.06$), and appeared to be reflected in a decrease in retinol levels, although there were too few biochemical results to allow statistical analysis.

Other clinical signs such as glossitis, aphthous ulcers, neuropathies and central nervous system signs are not correlated to dietary intake, and are probably produced by other factors such as chemotherapy and tumour effects, as well as by dietary deficiency. These signs are too non-specific to be of value in assessing nutritional status of oncology patients.

Comparing dietary and biochemical results, deficient iron intake shows a trend to correlation with decreased serum iron levels. Serum zinc and magnesium levels show correlations, approaching statistical significance, with decreased dietary intakes. The lack of results returned for many patients hindered statistical analysis for vitamin B_{12} and thiamine. Vitamin C results reflect this problem also, but do show a trend to correlation with dietary intake. Folic acid intake is deficient in all cases and makes statistical analysis, comparing dietary deficient patients to those meeting dietary requirements, impossible.

Three patients showed gross dietary deficiencies of most nutrients and these patients showed the greatest weight loss, with dry skin, brittle nails, dry eyes, dry hair, koilonychia and multiple biochemical deficiencies.

Each of the methods used for nutritional evaluation has its limitations. Clinical evaluation is easy to perform with the minimum of upset to the patient, and with an accurate set of weighing

scales being the most important piece of equipment. Weight loss and rate of weight loss is particularly useful in assessing nutritional deficiency. Clinical signs may, however, be misleading, and may be produced by factors other than nutritional deficiencies, such as cytotoxic therapy or tumour growth. Where nutritional deficiencies are present, clinical signs are a late feature, hence clinical evaluation alone would be of little use in early identification of patients with nutritional problems.

Biochemical analyses require blood samples from the patient and the facilities of a hospital laboratory, with equipment to process the blood. There may be difficulties in establishing reference values for the particular nutrient assay, and interpretation of results may be complicated. In the present study, there were problems with samples going astray and equipment breaking down during processing, and there is always a time-lag between taking samples and receiving results. There are often large body stores of vitamins and minerals, and, since these are difficult to assess, this makes evaluation of the results obtained difficult. Cytotoxic drugs may also influence the biochemical picture by producing specific deficiencies or interfering with assays. Due to the presence of body stores, biochemical abnormalities of nutritional status are probably also a late reflection of deficient intake, and indicate an established nutrient deficiency.

Dietary histories are easy to take and cause minimum upset to patients. Taking a 24 hour recall history is straightforward, providing the patient can remember his intake in the previous 24 hours.

However, a computer is required to allow speedy analysis of diet composition within 24 hours of taking the history. Without a computer, analysis is tedious and laborious. Cytotoxic drugs may interfere with a patient's dietary intake, and thus with the assessment of nutritional status, by inducing anorexia, nausea, vomiting and abnormalities of taste. It is therefore important to take dietary histories from a patient on a number of occasions particularly when chemotherapy may cause several days of complete anorexia, to gain a true picture of nutritional intake.

Dietary histories with computer analysis have advantages over the other methods in allowing the anticipation of nutritional problems, rather than simply reflecting their results; and may decrease expense in the laboratory by pinpointing specific nutrients to be assayed rather than have routine screening of every patient. However, each of the methods - clinical, dietary and biochemical - contributes to the picture of nutritional status of the patient, and ideally all should be used together. From this study, clinical assessment of weight loss, dry skin, brittle nails and dry eyes, dietary intake assessment, and serum protein and albumin levels are the most useful markers of nutritional status. Other information such as tumour type and chemotherapy and its timing, will allow rational interpretation of the data obtained for the patient and must be included in the overall assessment.

In conclusion, therefore, all three methods of evaluation of

nutritional status are useful; however dietary history and analysis is singly the most useful way of predicting which patients will require nutritional monitoring and possible nutritional support.

Future studies using dietary assessments to pinpoint potential deficiencies should evaluate the effectiveness of early nutritional support in preventing or slowing the decline of nutritional status to cachexia. The effectiveness of early nutritional support on the tolerance of patients to cancer treatment and its sequele, and the effects of the nutritional support on tumour growth itself, could then be properly assessed.

SECTION 2:

THE EFFECTS OF CANCER AND CHEMOTHERAPY ON NUTRITIONAL AND METABOLIC STATUS OF CANCER PATIENTS AND TUMOUR-BEARING ANIMALS

CHAPTER 3: EFFECTS OF CACHEXIA ON MUSCLE COMPOSITION

Introduction & Aims

The metabolic disturbances associated with cancer and its treatment have been discussed in the Introduction to this thesis. The syndrome of cachexia, with weight loss and anorexia, represents extreme metabolic disturbance and is associated with progressive tumour growth. The effects of cachexia on muscle composition in cancer patients have not previously been distinguished from the effects of protein-energy malnutrition or from the effects of disuse or acute infection (Jennekens, 1982).

A preliminary study was devised to examine the changes in the muscles of cachectic patients and to compare these to the documented changes seen in starvation and acute illness.

Methods

Four patients took part in the study and were selected on the basis of weight loss and progressive tumour growth (Table 15). Each patient gave informed consent for the procedure of muscle biopsy which was performed by Dr. D. Doyle, Consultant Neuropathologist, Southern General Hospital, Glasgow.

The technique involved infiltrating 2-4 ml of 1% lignocaine subcutaneously over the vastus medialis muscle of the quadriceps femoris group in the mid-thigh. A small skin incision allowed the biopsy needle to be introduced, and this was advanced until the tip was 3-5 mm below the surface of the skin. A small piece of muscle was guillotined and secured within the barrel of the needle which was then withdrawn and the incision sutured. The muscle biopsy was examined using light microscopy, enzyme histochemical techniques and electron microscopy. All processing was undertaken in the Department of Neuropathology, Southern General Hospital, Glasgow.

Table 15 summarizes the patients and their characteristics.

E.S., a 68 year old female had a left ovarian carcinoma diagnosed by biopsy a year before the muscle biopsy. During the original operation, tumour spread to liver, omentum and colon was noted. Treatment, comprising monthly intravenous injections of Thiotepa was commenced after operation, and continued until 2 weeks prior to biopsy. Six months prior to muscle biopsy, E.S. developed ascites which required to be tapped regularly. Over the two months before the procedure, she lost weight and became nauseated and anorexic, with vomiting at times and feeling generally "weak". Examination at the time of biopsy revealed a palpable liver, a left-sided lower abdominal mass and palpable inguinal lymph nodes. Assessment showed tumour progression, despite the treatment. At the time of muscle biopsy haemoglobin was 8.3 g%/dl and had been gradually falling during

Patient	Age	Sex	Tumour	Treatment	Weight Loss	Hb g/dl	T Prot (normal 68-82g/l)	Alb (normal 35-53g/l)
ES	68	F	Ovarian Carcinoma	Thiotepa IV	7 Kg over 2 months (10% body weight)	8.8	58	26
TR	78	M	Renal Carcinoma	Provera	7 Kg over 5 months (13% body weight)	7.7	52	23
JF	60	M	Gastric Carcinoma and metastases	5 Fluorouracil Adriamycin Mitomycin C until 1/12 before biopsy	11 Kg over 4 months (16% body weight)	11.3	59	28
JB	78	M	Prostatic Carcinoma and metastases	Aminoglutethimide Hydrocortisone	6 Kg over 4 months (9% body weight)	9.5	65	36

TABLE 15: CHARACTERISTICS OF CANCER PATIENTS FOR MUSCLE BIOPSY

the previous 3 months; and serum biochemistry showed reductions in total protein, albumin, iron, sodium and chloride. There were increases in serum levels of the liver enzyme glutamine oxaloacetate transaminase, glucose and bicarbonate. E.S. continued to deteriorate physically and metabolically, and died 1 month after muscle biopsy.

T.R. was a 73 year old man who had metastatic left renal carcinoma first diagnosed 6 months prior to muscle biopsy. Metastases involved liver, lungs and abdominal lymph nodes. Initial treatment with Provera tablets, 100 mg. daily, gave, at first, tumour regression; however after four months of treatment there was evidence of tumour progression and Provera was stopped. Over 5 months prior to muscle biopsy he lost 7 Kg weight (13% original body weight) and he became nauseated, anorexic, weak, and had episodes of vomiting at times. He had required repeated blood transfusions, at monthly intervals for 4 months prior to muscle biopsy; and at fortnightly intervals in the month preceding biopsy. On examination at the time of biopsy, hepatomegaly and a left-sided abdominal mass were noted. Haemoglobin was 8.0 g%/dl; serum biochemistry showed decreased total protein and albumin, iron, sodium and chloride; alkaline phosphatase and gamma glutamyltransferase were raised. T.R. continued to deteriorate and died 2 months following muscle biopsy.

J.F. was a 60 year old man with inoperable metastatic carcinoma of the stomach diagnosed at operation 7 months prior to muscle biopsy. The tumour was noted to be locally invasive, and involved the liver and

coeliac axis. Treatment with intravenous 5-Fluorouracil, Adriamycin and Mitomycin-C at four-weekly intervals was given for the first 6 months after diagnosis. Treatment was discontinued after tumour progression was noted, with increasing numbers and size of liver metastases and further infiltration of the stomach by tumour. Over the four months prior to biopsy he had lost 11 Kg in weight (16% of original body weight) and complained of nausea, anorexia and epigastric pain, and felt tired and weak. His haemoglobin fluctuated between 9 g/dl and 12 g/dl in the 5 months prior to muscle biopsy. He did not require blood transfusion. Examination at the time of biopsy revealed hepatomegaly. Haemoglobin was 11.3 g/dl; serum biochemistry showed decreased levels of total protein and albumin, iron and sodium. J.F. continued to deteriorate physically, with tumour progression, and died 2 months following muscle biopsy.

J.B. was a 73 year old man with metastatic carcinoma of the prostate diagnosed two and a half years prior to muscle biopsy. Bony metastases were present at the time of diagnosis. He was treated with Stilboestrol, radiotherapy, Tamoxifen, Estracyt and Aminoglutethimide, each for varying intervals prior to the biopsy. The bony metastases however, were becoming more widespread despite treatment. Six years prior to biopsy, polymyalgia rheumatica was diagnosed. Over the 4 months prior to muscle biopsy he had lost 6 Kg in weight (9% original body weight) and felt nauseated, anorexic, tired and weak. His haemoglobin dropped slowly from 12 g/dl to 9.5 g/dl in the 5 months prior to biopsy. At the time of biopsy haemoglobin was 9.5 g/dl;

serum biochemistry showed normal total protein and albumin, low levels of sodium, chloride and iron, and increased levels of gamma glutamyl transferase, alkaline phosphatase and bicarbonate. Following muscle biopsy J.B. continued to deteriorate slowly and died 4 months later.

None of the patients experienced any side effects from the muscle biopsies and had no physical sequele.

Results

All of the muscle biopsies examined showed similar changes, although the features in the biopsies of J.F. and J.B. were particularly striking. All patients showed variation in muscle fibre size with nuclear aggregates in some fibres and necrosis of peripheral fibres on light microscopy.

Light microscopy of the biopsy from E.S. showed atrophy of type 2 ("fast") muscle fibres, with increased peripheral enzyme activity seen in the mitochondrial enzyme preparations. These appearances suggested metabolic disturbance rather than denervation.

Biopsy from T.R. showed general reduction in fibre size, with low mitochondrial activity in type 2 fibres. This also was consistent with a metabolic disturbance.

The muscle from J.F. showed few changes in fibre size or type on light microscopy, and no specific reduction in mitochondrial activity was seen with enzyme histochemical studies. Electron microscopy, however, revealed considerable disruption of the mitochondria which showed circumferential crystals and numerous intra-mitochondrial crystals (so-called "Parking-lot" bodies). These changes are seen with severe disturbance of mitochondrial function, and reflect metabolic abnormalities.

The features of the muscle biopsy from J.B. showed changes due to polymyalgia rheumatica, as well as metabolic disturbance. Light microscopy showed necrosis of some muscle fibres and a "moth-eaten" appearance of some of the fibres - a characteristic feature of polymyalgia rheumatica. There was atrophy of both muscle fibre types. Mitochondrial enzyme preparations showed disturbed internal architecture of the muscle fibres. Electron microscopy showed disorganisation of some muscle fibres which had decreased amounts of contractile protein which was in disarray, and present both focally and in larger portions in the muscle fibres. There were numerous large mitochondria present in these fibres, and excess lipid was seen. The "moth-eaten" appearance of some fibres, the presence of lipid and of type 2 fibre atrophy are associated with denervation and reinervation and with polymyalgia rheumatica. Superimposed on this are mitochondrial changes reflecting severe metabolic disturbance.

Discussion and Conclusions

All of the patients studied had advanced and progressive tumours which had failed to respond to treatment. All were cachectic with weight loss, anorexia, weakness and anaemia.

All of the muscle biopsies showed abnormalities, and the presence of electron microscopic changes confirmed the cellular disruption. Morgan-Hughes (1982) states that changes in ultrastructure of muscle cells (including mitochondrial changes) are a response to metabolic disturbances both inside and outside the cell.

Starvation results in generalised reduction in fibre size with large groups of atrophic fibres. Type 2 fibre atrophy predominates. In disuse, there is decreased size of both fibre types. There are few abnormalities specific to ageing until after 70 years, when there may be variation in fibres size with, particularly, type 2 fibre loss. Necrosis of muscle fibres and "ragged" fibres, with internal nuclei, cytoplasmic inclusion bodies and decreased numbers of mitochondria are seen with ageing and these are the changes of denervation and reinnervation. In sepsis, there is fibre necrosis in isolated fibres throughout the muscle (Jennekens, 1982).

The changes found in the cancer patients form a distinct entity. There is some overlap with the features of starvation, disuse and ageing, with type 2 fibre atrophy, variation in fibre size, nuclear

aggregates and peripheral fibre necrosis. However, the internal and mitochondrial disruption of the muscle of the cachectic cancer patients are more prominent than in these other states (Plate 1). The mitochondrial disfunction, with increased size and numbers of mitochondria, inclusion bodies and variable enzyme activity, reflects metabolic changes in the body (Morgan-Hughes, 1982). The mitochondrial crystals are thought by Land and Clark (1979) to be produced by impaired biosynthesis of mitochondrial protein subunits coded for by mitochondrial DNA and causing an accumulation of nuclear-coded protein subunits as inter- membrane crystals. They suggest, alternatively, that there may be impaired nuclear protein subunit biosynthesis, with normal mitochondrial biosynthesis, producing excess mitochondrial subunits. The crystals' composition is still the subject of debate - however they are known to be enzymatically inert, and may be proteins. Other theories consider that the crystals represent greatly increased in- foldings of the inner mitochondrial membrane which, in cross section, appear as "crystals" within the mitochondria (Morgan-Hughes, 1982).

The increased nuclear and nucleolar activity in the muscle cells of the cancer patients indicates increased protein turnover. This would be consistent with mobilisation of muscle protein to compensate for low serum protein levels, and to provide precursors for gluconeogenesis to provide energy for further tumour growth (Norton et al., 1980). Lundholm et al. (1976) confirm the increased breakdown of protein of muscle fibres in cancer patients; and Bozzetti et al. (1982) regard decreased protein content of muscle as the first sign of malnutrition in cancer patients.

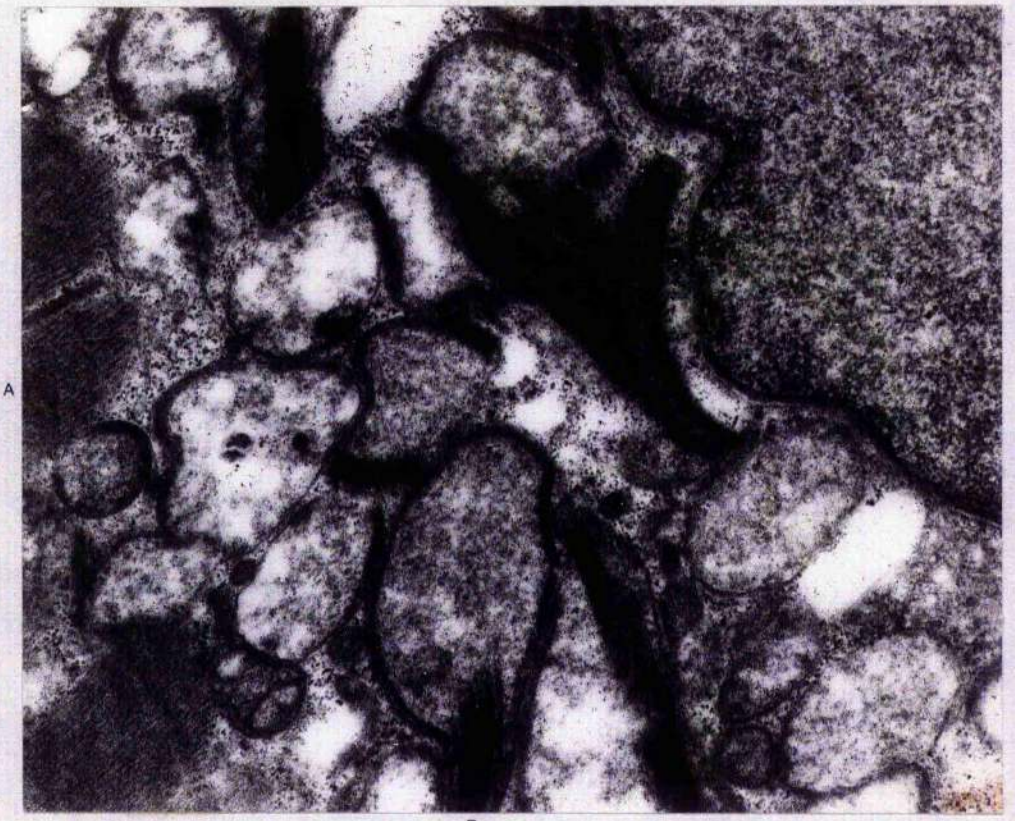

PLATE 1: ELECTRON MICROSCOPIC EXAMINATION OF MUSCLE CELL FROM CACHECTIC CANCER PATIENT SHOWING FIBRILLAR PROTEIN[A] AND MITOCHONDRIA WITH INTRAMITOCHONDRIAL CRYSTALS[B] ("PARKING LOT" BODIES)
(MAGNIFICATION x 33, 330)

None of the patients biopsied showed any improvement metabolically, and no response to further treatment. In these patients it is impossible to distinguish the relative contributions of chemotherapy and tumour growth to the muscle picture. Tumour progression, however, is a major contributary factor in the metabolic disturbances of cachexia.

In summary, muscle biopsy reflects the metabolic changes seen in cachexia. The changes seen in cancer patients are a distinct entity. Future studies should biopsy patients prior to chemotherapy, and at early stages of disease, to identify changes due to tumour alone; and correlate the earliest changes seen in muscle with the metabolic state at that time. A further study in untreated patients with advanced tumours, such as lung tumours would allow the separate effects of chemotherapy and tumour growth on muscle changes to be determined. It would be interesting to look at biopsies from patients who respond to treatment, and to show whether the muscle changes are reversible or not. These studies would contribute to the information on metabolic and nutritional changes in the cancer patients, which in turn may be used to improve nutritional state.

CHAPTER 4: SALIVA PRODUCTION, COMPOSITION AND MICROORGANISM CONTENT IN CANCER PATIENTS: IMPLICATIONS FOR NUTRITION

Introduction and Aims

Cancer and chemotherapy are known to affect appetite and taste sensations, as outlined in the Introduction to this thesis. Further effects may be to alter the production of saliva and to change the microflora of the mouth, which will contribute to the anorexia, abnormalities of taste, dry mouth and other oral problems encountered in the cancer patient and will promote a decline in nutritional state by decreasing food intake and enjoyment.

Sonis, Sonis and Lieberman (1978) found that 40% patients receiving chemotherapy for tumours developed oral complications as a direct result of the drugs. There are several mechanisms suggested for the effects of the drugs on the mouth. Some cytotoxic drugs act on rapidly dividing basal cells of the oral epithelium causing ulceration and necrosis of the buccal mucosa. Methotrexate, in particular, has been implicated as a cause of this problem. Both tumour and chemotherapy may impair host defence mechanisms and exacerbate chronic oral infections, such as periodontitis and pulpitis or allow secondary infection of ulcerated mucosa by bacteria, fungi and viruses (Lockhart & Sonis, 1979). Drug or tumour-induced thrombocytopenia could produce gingival bleeding and mucosal purpura.

A common complaint of patients receiving cytotoxic drugs is of a dry mouth, which causes problems in chewing, tasting and swallowing food (Dreizen, 1981). Both this problem, and the alteration in microflora may exacerbate the nausea and anorexia of some patients, and may produce a further deterioration in nutritional status. The aims of this study were to examine saliva volume and composition, and investigate its microbial content in cancer patients and controls before and during chemotherapy.

Methods

The study was split into two parts: the first, preliminary, study compared saliva volume, alpha amylase, IgA and lysozyme content, and microflora present in 39 oncology out-patients who were receiving cytotoxic drugs, and 20 healthy volunteers. The second study followed these factors in 20 oncology out-patients over a period of three months. The first samples were taken at first attendance at the oncology out-patient clinic at Gartnavel General Hospital, Glasgow, and prior to starting chemotherapy. Further samples were taken after one and three months of treatment.

Saliva was collected using a "forced spitting" method which involved spitting into a container at 10 second intervals for 10 minutes. This gave a reproducible flow rate of whole mixed saliva and included oral microorganisms, epithelial cells and gingival crevicular fluid. The saliva samples were transported immediately

after collection, on ice, to Glasgow Dental Hospital where analysis was performed under the supervision of Dr. M. Ferguson. Bacteria and yeasts were cultured and identified; and saliva volume, alpha- amylase, lysozyme and IgA levels were measured.

Records were made of patients' ages, tumour types, chemotherapy regimens, smoking habits and whether or not they had dental prostheses.

Results

The 39 patients used initially had all received chemotherapy for at least 3 months, and had a variety of tumour types (Tables 16 and 17). M:F ratio was 17:22 and ages ranged from 17-68 years (mean 48 years).

The control group comprised members of Gartnavel General Hospital staff with M:F ratio 8:12 and ages ranged from 19-55 years (mean 30 years). No attempt was made in this preliminary study to match age, sex, or dental status in patients and control groups.

The twenty patients followed for 3 months from the start of treatment had M:F ratio 8:12 and ages ranging from 17-66 years (mean 42 years). Tumour types and chemotherapy used are shown in tables 18 and 19.

In both studies, neither patients nor controls were receiving

Tumour Type	No. Patients
Breast Carcinoma	12
Teratoma	7
Lung carcinoma	3
Ovarian carcinoma	3
Hodgkin's disease	2
Renal carcinoma	1
Colonic carcinoma	1
Pharyngeal carcinoma	1
Oesophageal carcinoma	1
Gastric carcinoma	1
Mesothelioma	1
Rabdomyosarcoma	1
Leiomyoma	1
Lymphoma	1
Chronic granulocytic leukaemia	1
Unknown primary	1

TABLE 16: TUMOUR TYPES OF PATIENTS RECEIVING CHEMOTHERAPY FOR LONGER THAN 3 MONTHS

Drug	No. Patients
Adriamycin	13
Vincristine	11
Cisplatin	9
Vinblastine	8
Methotrexate	7
5-Fluorouracil	7
Cyclophosphamide	7
Bleomycin	6
Prednisolone	6
Mitomycin C	3
Chlorambucil	3
Procarbazine	3
Vindesine	2
Hydroxyurea	1
Iphosphamide	1
D.T.I.C.	1

TABLE 17: CYTOTOXIC DRUGS USED IN PATIENTS FOR LONGER THAN 3 MONTHS

Tumour Type	No. Patients
Breast carcinoma	7
Teratoma	4
Ovarian carcinoma	2
Oesophageal carcinoma	I
Lymphoma	I
Hodgkin's disease	1
Gastric carcinoma	1
Lung carcinoma	1
Leiomyosarcoma	1
Rhabdomyosarcoma	1

TABLE 18: TUMOUR TYPES OF NEW PATIENTS STUDIED

Drug	No. Patients
Adriamycin	8
Vincristine	7
Methotrexate	6
Cyclophosphamide	5
5-Fluorouracil	5
Cisplatin	4
Vinblastine	4
Bleomycin	3
Mitomycin C	2
Chlorambucil	2
Procarbazine	2
Prednisolone	2
DTIC	1
Iphosfamide	1
Tamoxifen	1

TABLE 19: CYTOTOXIC DRUGS USED IN PATIENTS FOLLOWED FOR 3 MONTHS

antibiotic therapy; and no patients were significantly myelosuppressed during the studies.

Table 20 shows the results for the cancer patients and control groups. It can be seen that saliva volume and alpha-amylase activity are significantly decreased, and microbial content of saliva is significantly increased in the patients who have received chemotherapy for more than three months. Lysozyme activity and IgA concentration show no significant difference between the groups.

Table 21 shows the changes occurring in the patients followed for the first three months of their treatment. Over the period of study saliva volume, and hence saliva flow rate, alpha-amylase activity and IgA concentration decreased significantly; candidal colonisation, the number of candida colonies per patient, and the presence of significant numbers of bacteria in the mouth increase with duration of treatment.

In both groups of patients, the most commonly occurring organisms were coliforms, with Escherichia coli the most commonly isolated. Proteus mirabilis, Klebsiella pneumoniae and Pseudomonas aeruginosa were also found. Three patients had Staphylococcus aureus isolated. Of the controls, one volunteer had a coliform isolated and had associated candidal colonisation. All patients with coliforms present also had candidal infection in the mouth.

Smoking had no effect on saliva volume and composition or on

	Controls (20 patients)	Cancer Patients (39 patients)
Saliva volume (ml)	6.94[B]	3.99[B]
Amylase (i.u./l x 10^{-6})	4.57[C]	3.66[C]
Lysozyme (i.u./ml)	705	709
IgA (g/l)	0.16	0.14
Candidal infection rate	40%[A]	76%[A]
Bacterial infection rate	5%[A]	15%[A]

Significance of AA = $p < 0.001$

BB = $p < 0.01$

CC = $p < 0.05$

TABLE 20: SALIVA COMPOSITION OF CONTROLS VERSUS CANCER PATIENTS RECEIVING CHEMOTHERAPY FOR MORE THAN 3 MONTHS

	Duration of Treatment (Months)		
	0	1	3
Saliva Volume (ml)	6.16[A]	5.46	3.83[A]
Amylase (i.u./l x 10^{-6})	4.91[C]	3.87	3.09[C]
Lysozyme (i.u./ml)	682	706	833
IgA (g/l)	0.18[C]	0.13	0.11[C]
Candida infection rate	70%[B]	50%	80%[B]
Bacterial infection rate	5%[A]	10%	15%[A]

Significance of AA = $p < 0.001$

BB = $p < 0.01$

CC = $p < 0.05$

TABLE 21: CHANGES IN SALIVA COMPOSITION DURING 3 MONTHS CHEMOTHERAPY

candidal colonisation. Patients with false teeth, however, showed increased candidal colonisation.

Most patients were receiving combinations of chemotherapeutic drugs so it was not possible to look at the effects of individual drugs. There was a trend however, for patients receiving Cyclophosphamide and Methotrexate to show decreased saliva volumes; while those receiving Cisplatin, Adriamycin and Mitomycin C showed increased incidence of candidal infection, with less effect on saliva volume (Table 22).

Discussion and Conclusions

No patients specifically complained of mucositis or dry mouth during the study, although there is a significant reduction in saliva volume and in saliva flow rate as chemotherapy progresses. It is interesting that some cytotoxic drugs seem to have more effect on saliva flow rate than others: these effects would indicate damage to the acinar secreting cells of the salivary glands, and the two drugs most frequently implicated in this study, Methotrexate and Cyclophosphamide, are both known to cause damage and necrosis to this type of cell. The other drugs cause damage to the glands as a dose-related side effect of treatment: the more toxic drugs showing earlier effects on saliva production.

The significant reduction in alpha-amylase production with continuing cytotoxic treatment reflects the damage to the acinar cells of

Drug	% Cancer Patients	
	Decreased saliva Volume	Increased Infections
Adriamycin	55	85
Cisplatin	20	70
Methotrexate	75	50
Cyclophosphamide	86	57
Mitomycin C	80	100
5-Fluorouracil	50	50

TABLE 22: EFFECTS OF CYTOTOXIC DRUGS ON SALIVA VOLUME AND MICROBIAL CONTENT

the salivary glands,and the, consequent decreased saliva production.

The amount of IgA antibody present in the saliva decreases with duration of treatment, and allows candida infection of the mouth. Epstein et al. (1982) showed that the presence of IgA antibody inhibits adhesion of Candida albicans to the oral epithelium. This is one reason for the significant increase in Candida albicans colonies isolated from the mouths of patients as treatment progresses.

The control group showed 40% incidence of oral candidal colonisation, which agrees with results obtained by Odds et al. (1979) for several different control populations.

The 70% candidal colonisation of cancer patients prior to chemotherapy indicates some decreased resistance to infection, and may be due to nutritional depletion caused by the tumour. Nutritional assessments, however, were not made on these patients. There was a significant ($p < 0.01$) increase in candidal colonisation as chemotherapy continued, and some drugs had more effect on this than others. Adriamycin, Cisplatin and Mitomycin-C were particularly likely to cause candidal growth, and this may be explained by the anorexia, nausea and vomiting induced by these drugs producing dehydration, with decreased saliva flow and poor oral hygiene. The transient myelosuppression caused by the drugs may also contribute to the problem.

Bacterial infections of the mouth are usually transient and

opportunistic (Martin, Al-Tikriti & Bramley, 1981). The increased numbers of organisms isolated from the patients on treatment are significant, and will provide a reservoir for potentially infective organisms to become more widespread, producing septicaemia, bacteraemia, endocarditis and multiple abscesses in immuno-compromised patients. The presence of coliforms in the mouth allow increased oral attachment of candida colonies (Centeno et al.,1983), and all patients with bacterial infection of the mouth had concomitant candida colonisation.

In summary, cancer and chemotherapy produce decreased saliva volume, decreased alpha-amylase production, and decreased IgA antibody in saliva, and cause increased oral candidal colonisation and increased opportunistic infection. The consequences of these alterations are dry mouth, decreased taste sensations, difficulties in chewing and swallowing, increased incidence of mucositis and the establishment of a reservoir for potential acute and subacute bacterial dissemination, all of which will have effects on the nutritial status of patient. Smoking has no effect on these changes; the presence of dental prostheses increases the risk of candida colonisation and bacterial infection.

Oral hygiene and regular inspection of the mouth is therefore extremely important for all patients on chemotherapy and particularly for those with dental prostheses. Those patients who have most reduction in saliva flow and are at risk of dry mouth and mucositis, may benefit from use of saliva substitutes.

This is a preliminary study. Future studies should identify those cytotoxics which produce the most drastic effects on saliva production and composition. The effects of diminished saliva flow and candidal infection on taste sensation, appetite and palatability of food should be studied; and the effects of improved oral hygiene and the use of saliva substitute on these factors should be assessed.

CHAPTER 5: SOME METABOLIC EFFECTS OF TUMOUR GROWTH AND CYTOTOXIC DRUGS IN ANIMALS

Introduction and Aims

The effects of tumours on host metabolism, and the side effects of cytotoxic drug therapy causing nutritional and metabolic upset have been discussed in detail in the Introduction to this thesis.

The aims of these studies were to examine the metabolic changes occurring in the tumour-bearing host; to define the effects of two cytotoxic drugs, Cisdichlorodiammine platinum (II) (Cisplatin) and Cyclophosphamide on host metabolism; and to determine whether tumour-induced metabolic alterations may be improved or exacerbated by the administration of these cytotoxic drugs.

The drugs chosen for study, Cisplatin and Cyclophosphamide, are both alkylating agents: Cisplatin links DNA base pairs in a single strand across the helical turns; Cyclophosphamide cross-links one strand of DNA to the other. Both drugs cause nausea, vomiting and anorexia. Cisplatin may produce electrolyte problems and renal failure, due to an effect on the renal tubules (see Chapter 6 for a fuller discussion on Cisplatin toxicity). Cyclophosphamide may exacerbate liver disease, and may cause a haemorrhagic cystitis with subsequent renal problems. These drugs are often used clinically in combination with other drugs; in these studies they have been examined

as single agents.

Methods

Female Wistar albino rats weighing 150-180 g were used. These animals were bred in the Department of Clinical Oncology, Glasgow University and were maintained on a standard laboratory chow (CRM, Labsure, Rank-Hovis-McDougal Agricultural Division, Dorset, England). Water was supplied ad libitum, and the animals were subjected to alternating 12 hour periods of light and dark.

A fast-growing cachectic Walker 256 carcinosarcoma obtained from the Institute of Cancer Research, Sutton, Surrey, was maintained in Wistar albino rats and was used to make a single-cell suspension of tumour cells for experimental use. This involved excision of a 14 day tumour from a passage animal, the tumour then being immersed in sterile phosphate buffered saline (PBS) containing 50 µg/ml penicillin and 100 µg/ml streptomycin, and dissected in a sterile laminar flow cabinet (Microflow Pathfinder) to remove connective tissue and necrotic debris. The tumour fragments were incubated overnight at 4°C in 10 ml DMEM-F10 medium (Flow Laboratories) containing 2.5% trypsin, and then stirred at 37°C for 25 minutes to disaggregate the trypsinised tumour. Tissue was filtered out using sterile 75 micron metal gauze, and the medium removed by centrifugation at 800 rpm for 5 minutes. The cells were washed three times in sterile phosphate buffered saline, and the viability of the suspension determined by trypan blue exclusion. A

suspension of 2 x 10^6 Walker 256 cells in 0.2 ml sterile phosphate buffered saline was used. Tumour growth in the rats was monitored by caliper measurements of length and breadth of tumour on alternate days. Tumour weight was noted at sacrifice.

The drugs used for the study were Cisplatin (Neoplatin, Bristol Myers Pharmaceuticals, Slough, Bucks.) at the LD_{10} dose of 6.3 mg/kg body weight; and Cyclophosphamide (Endoxana, W.B. Pharmaceuticals Ltd., Bracknell, Berks.) at the LD_{10} dose of 310 mg/kg body weight. Both of these dosages were determined by a previous preliminary experiment.

For each drug, four groups of rats with at least 6 animals in each group were used. Group 1 received tumour only; Group 2 received tumour and drug; Group 3 received drug alone; and Group 4 was the control group. All innoculations and injections were performed under ether anaesthesia; and animals were killed by ether inhalation. Figure 15 indicates the timescale of the experiments. On day 0, Groups 1 and 2 received subcutaneous innoculations of 0.2 ml tumour cell suspension, and Groups 3 and 4 received subcutaneous innoculations of 0.2 ml sterile phosphate buffered saline. When tumour dimensions averaged 30 x 25 mm, usually 12-14 days after innoculation, the animals in Groups 1 and 4 were injected intraperitoneally with phosphate buffered saline and those in Groups 2 and 3 with the LD_{10} dose of Cisplatin or Cyclophosphamide. Six days later, the animals were sacrificed, when the tumour dimensions in Group 1 (tumour alone) averaged 40 mm x 30 mm. Tumour volume was determined using the formula

Group	1	2	3	4
	T	T + D	D	C
	(Tumour alone)	(Tumour + drug)	(Drug alone)	(Control)
Day 0 Subcutaneous innoculation	2×10^6 Walker 256 cells	2×10^6 Walker 256 cells	0.2 ml P.B.S.	0.2 ml P.B.S.
Day 11-14 Intraperitoneal injection	P.B.S.	LD_{10} dose drug	LD_{10} dose drug	P.B.S.
Day 17-20	-	Sacrifice	-	-

P.B.S. = Phosphate buffered saline (pH 7.4, 0.15 M)

LD_{10} dose = amount of drug (mg/kg body weight) required to kill 10% animals in a group

FIGURE 15: TIMESCALE FOR DRUG AND TUMOUR ANIMAL STUDIES

of Daly et al. (1980) for a prolate spheroid, $V = 1/6\ AB^2$ (where A = long diameter and B = short diameter).

After sacrifice, blood was taken from the heart of each animal for biochemical analysis for urea and electrolytes, iron, calcium, albumin, total protein and liver enzymes, and for ketone body estimation. The tumours were excised and weighed. Biochemical analysis was performed at the department of Biochemistry, Gartnavel General Hospital, Glasgow on a SMAC autoanalyser (Technicon methodology). Ketone bodies, beta hydroxybutyrate and acetoacetate, were measured enzymatically using the methods of Williamson and Mellanby (1975) and Mellanby and Williamson (1975) respectively. Determinations of nitrogen and water content of the bodies were performed by autoclaving frozen carcasses and then homogenising them in twice their carcass weight of water. One aliquot was taken for nitrogen estimation by the microkjeldahl method, and an autoanalyser adaptation of the Berthelot reaction (Fleck 1967). A second aliquot was taken, and water content determined by lyophilization.

Statistical significance was computed using a student's t-test for non-paired data, and multiple regression analysis.

Results

Weight changes were similar in both drug studies, and are shown in Figure 16. In each case, the control group, group 4, was the

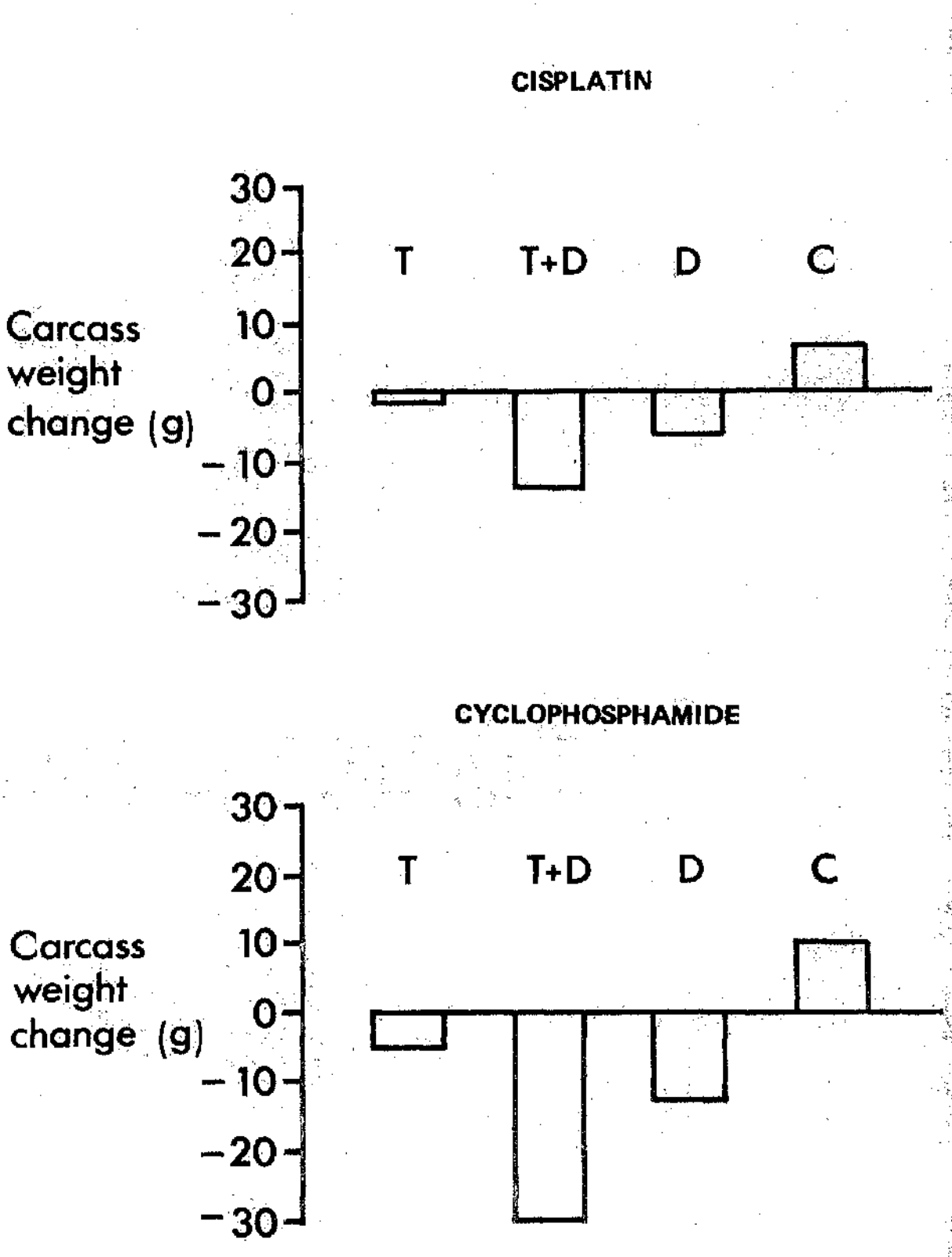

FIGURE 16: COMPARISON OF WEIGHT CHANGES IN TUMOUR (T), DRUG (D), TUMOUR AND DRUG (T+D) AND CONTROL (C) ANIMAL GROUPS

only group to gain weight. This group had a mean weight increase of 7 g in the Cisplatin study and 12 g in the Cyclophosphamide study. Tumour alone (Group 1) produced a small net weight loss; the tumour itself accounting for only 5.6% total body weight. Each drug on its own produced more weight loss than the tumour alone. Tumour and drug caused the greatest weight loss: a mean loss of 13 g in the Cisplatin group and 30 g in the Cyclophosphamide group.

The nitrogen and water content of the carcasses from each group are shown in table 23. Water content shows no statistically significant difference between groups. Nitrogen content is significantly reduced in the tumour alone (Group 1) groups in both studies compared to the controls (Group 4), in keeping with the cachectic nature of the tumour causing protein depletion. Interestingly the tumour and drug (Group 2) and drug alone groups showed no difference in nitrogen content compared to controls.

Figure 17 shows the tumour volumes for groups 1 and 2 in each study. In the Cisplatin study, there is a 75% reduction in tumour volume in the tumour plus Cisplatin group (group 2) compared to the tumour group (group 1); and there is a 98% reduction in tumour volume in the tumour plus drug group (group 2) compared to the tumour alone group (group 1) for Cyclophosphamide, illustrating the cytotoxic effects of the drugs on the tumour.

Table 24 shows the blood ketone results. Ketone bodies are greatly elevated in the tumour alone group (group 1) studies. The drug

GROUP	Cisplatin		Cyclophosphamide	
	PROTEIN N_2(%)	H_2O(%)	PROTEIN N_2(%)	H_2O(%)
1 (T)	19.2^{A}	70.6	19.2^{B}	70.6
2 (T + D)	22.6	70.3	22.2	69.9
3 (D)	21.3	72.7	21.4	70.1
4 (C)	22.0^{A}	72.3	22.0^{B}	72.3

Significance of AA $p < 0.01$

BB $p < 0.01$

TABLE 23: CARCASS NITROGEN AND WATER CONTENT OF TUMOUR-BEARING AND CYTOTOXIC DRUG TREATED ANIMALS

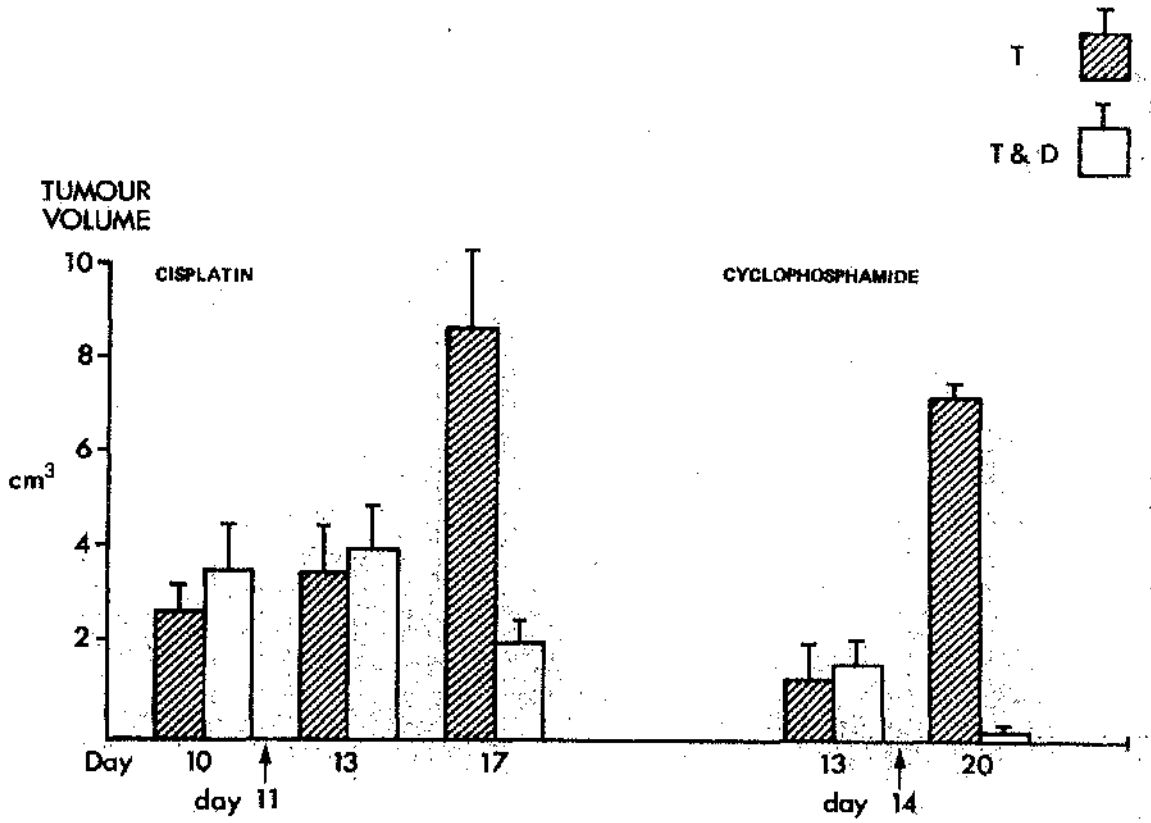

FIGURE 17: COMPARISON OF TUMOUR VOLUMES IN TUMOUR (T), AND TUMOUR AND DRUG (T+D) ANIMAL GROUPS

	Cisplatin		Cyclophosphamide	
GROUP	B-OH (mmol/l)	Aceto(mmol/l)	B-OH(mmol/l)	Aceto(mmol/l)
1 (T)	0.528	0.310	0.990	0.279
2 (T + D)	0.031	0.007	0.042	0.006
3 (D)	0.007	0.012	0.013	0.006
4 (C)	0.010	0.004	0.018	0.005

B-OH = B-hydroxybutyrate

Aceto = Acetoacetate

TABLE 24: BLOOD KETONE LEVELS IN TUMOUR BEARING AND CYTOTOXIC DRUG TREATED ANIMALS

alone and control groups (Groups 3 and 4) show only marginally detectable levels of the ketone bodies. The tumour and drug group (group 2) for both Cisplatin and Cyclophosphamide shows an increased level of ketone bodies, indicating continued fatty acid oxidation, but at levels greatly reduced from the tumour alone (Group 1) results.

Plasma concentrations of urea and electrolytes, bicarbonate, creatinine, alkaline phosphatase, calcium and phosphate were within one standard deviation of the mean control values for all groups. The results for plasma iron, total protein, albumin, and the liver enzymes are shown in Figures 18 and 19.

Plasma iron concentration is reduced in the tumour alone groups (Group 1) reflecting the adverse effects of the tumour on metabolism, and the non-specific iron deficiency found in cancer bearing hosts. The tumour and Cisplatin group (Group 2) and the Cisplatin alone group (Group 3) produced increases in the plasma iron, with the tumour and drug group (group 2) showing the greatest elevation of plasma iron. This increase corresponds with the increased plasma iron concentrations found in patients receiving Cisplatin chemotherapy which is caused by failure of iron utilisation (Von Hoff et al., 1979). Both groups 2 and 3 receiving Cyclophosphamide produced slight decreases in plasma iron concentration.

Total protein and albumin levels are markedly reduced in the tumour alone groups (Group 1). The Cisplatin groups (Groups 2 and 3)

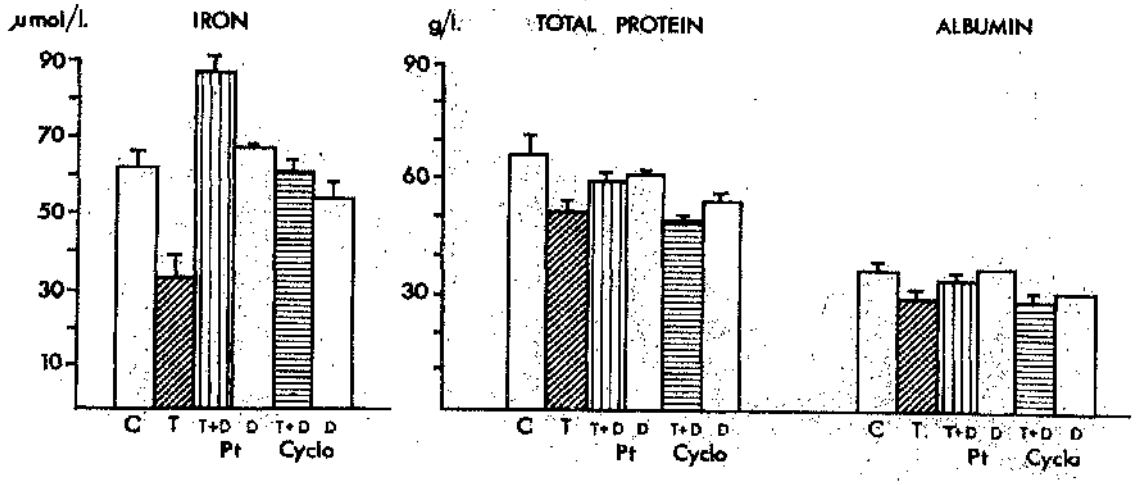

FIGURE 18: COMPARISON OF PLASMA IRON, TOTAL PROTEIN AND ALBUMIN LEVELS IN TUMOUR (T), DRUG (D), TUMOUR AND DRUG (T+D) AND CONTROL (C) ANIMAL GROUPS

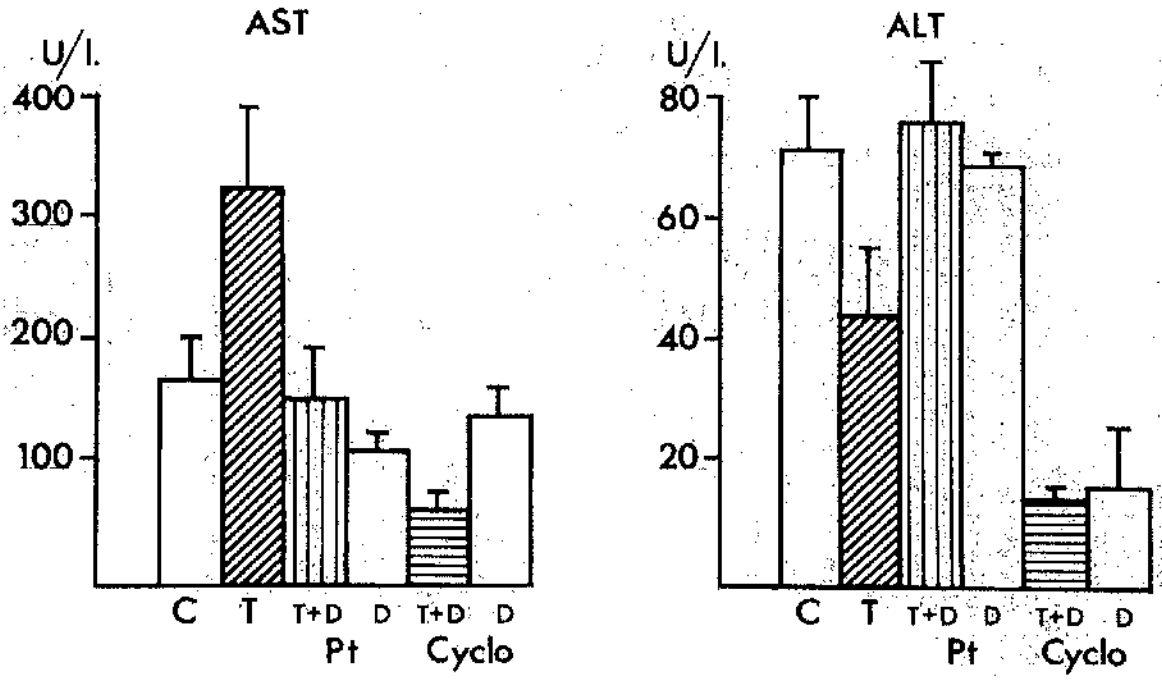

FIGURE 19: COMPARISON OF LIVER ENZYMES ASPARTATE TRANSAMINASE (AST) AND ALANINE TRANSAMINASE (ALT) IN TUMOUR (T), DRUG (D), TUMOUR AND DRUG (T+D) AND CONTROL (C) ANIMAL GROUPS

produced a fall in total protein and albumin compared to control groups. This decrease is less than for the tumour alone group (Group 1) and reflects the modifying effects of the drug on the tumour-induced nutritional changes. Cyclophosphamide alone, and with the tumour (Groups 2 and 3) produces a similar fall in total protein and albumin to the tumour alone (Group 1). There is no significant difference between the drug alone, tumour alone, and drug and tumour groups, showing no additive metabolic injury from drug and tumour.

Figure 19 shows the results obtained for the liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These enzymes also reflect damage to organs other than the liver: skeletal muscle, cardiac muscle and kidney damage producing high plasma levels. Aspartate aminotransferase is a mitochondrial enzyme; alanine aminotransferase is a cytoplasmic enzyme. High plasma levels of these enzymes indicate cellular damage; however low levels may be misleading, reflecting the exhaustion of the enzyme supply from necrotic cells.

The results of the studies show aspartate aminotransferase is elevated up to twice the control value in the tumour alone group (Group 1) indicating tumour-induced cellular damage. Alanine aminotransferase is reduced in this group, due to exhaustion of leakage of cytoplasmic enzymes from the damaged cells. Cisplatin alone (Group 3) produced a fall in both enzymes, indicating some drug-induced cellular damage. The drug and tumour group (Group 2) shows no

significant difference compared to the control group for either enzyme. Cyclophosphamide alone and with tumour caused falls in both AST and ALT, with the tumour and drug group (Group 2) showing the most marked decreases, indicating the cellular injury caused both by the drug and the tumour.

Discussion and Conclusions

The tumour itself produces marked metabolic upsets in the host, with weight loss, decreased nitrogen content, decreased plasma iron and plasma total protein and albumin concentrations. Ketone body levels are increased markedly and liver enzymes are deranged. All of these factors indicate nutritional and metabolic injury to the host, and are similar to metabolic changes produced in cancer patients.

The drugs used, Cisplatin and Cyclophosphamide, both cause weight loss, although the changes in nitrogen content are not so marked as in the tumour alone group. Both drugs produce biochemical upsets in ketone body, iron, protein, albumin and liver enzyme levels in the serum; with Cyclophosphamide producing the greatest metabolic upset at the dose used in this study.

The tumour responded to treatment with both drugs, and there is a marked amelioration of the effects of the tumour on plasma iron, total protein and albumin, ketone bodies, liver enzymes and carcass nitrogen levels by the drugs.

In summary, both tumour and drugs alone produce distinct

metabolic and nutritional changes in the host, similar to those in cancer patients. The tumour tends to produce the greatest metabolic insult; although the drugs, and especially Cyclophosphamide cause significant changes in body weight. When the tumour responds to the drug, as in the tumour and drug groups, there is improvement in the metabolic and nutritional state of the host, and this may be useful clinically. However, if the tumour is not controlled by the cytotoxic drugs administered, there may be superadded metabolic problems for the patient from both the tumour and the drugs.

Since the changes seen in animals with a cachectic tumour are the same as those seen in cachectic human tumours, it will be possible to look at ways of modifying tumour effects on metabolism, and of minimising unwanted drug effects. The study could be extended to look at other cytotoxic drugs which are known to cause nutritional and metabolic upset - for example Adriamycin, 5 Fluorouracil and Methotrexate. Future studies should look at nutritional manipulations such as ketogenic diets or specific inhibitors of some of the metabolic pathways which are "switched on" in cancer patients, and the effects of these substances on tumour growth and host metabolism. This tumour model will also be useful in allowing predictions of likely nutritional and metabolic problems associated with the use of new drugs in cancer patients.

CHAPTER 6: METABOLIC AND NUTRITIONAL EFFECTS OF CISDICHLORODIAMMINE (II) PLATINUM

Introduction

Since platinum was found to inhibit bacterial cell division in a chance observation by Rosenberg, Van Camp and Krigas in 1965, developments and refinements of the metal have produced Cisdichlorodiammine platinum (II) or "Cisplatin", a potent broad-spectrum anticancer agent useful in both animal and human tumours. It is particularly effective in the treatment of teratomas, ovarian carcinomas, some lung tumours, bladder and cervical cancers, tumours of the head and neck, and in a number of childhood cancers; and its range of therapeutic uses is expanding (Williams & Whitehouse, 1979).

With increasing use of Cisplatin, the side effects of treatment have become apparent. Early trials found nephrotoxicity to be the dose-limiting factor in treatment with Cisplatin (Krakoff 1979) and Gonzalez-Vitale et al. (1977) found an acute tubular necrosis, involving particularly the distal tubules and collecting ducts, in the kidneys of patients who had died following Cisplatin administration. The nephrotoxicity, with increasing blood levels of urea and creatinine was found to be irreversible (Krakoff 1979). Preventative measures using vigorous hydration and diuretics, usually mannitol or frusemide, have helped to diminish the incidence of fatal nephrotoxicity, and have allowed the escalation of doses (Madias &

Harrington, 1978; Krakoff, 1979; Blachley & Hill, 1981). However, there is still microscopic renal damage associated with Cisplatin chemotherapy as demonstrated by Kuhn et al. (1980) who monitored the levels of Beta-2-microglobulin in the urine of patients receiving chemotherapy, and found increasing levels after treatment with Cisplatin, which persisted for at least 6 weeks post therapy. Jones, et al. (1980) found increased levels of leucine aminopeptidase, N-acetylglucosamine and Beta-2-microglobulin in urine of patients treated with Cisplatin, indicating renal tubular damage. Whether this damage is reversible or not, is not yet clear.

Renal damage has been found to occur after only one dose of Cisplatin, and there may be accompanying, inappropriate losses of magnesium, calcium, potassium and amino acids in the urine (Bar, Wilson & Mazzaferri, 1975; Bitran et al., 1982). Renal toxicity is increased in patients who show elevated plasma platinum levels early in the course of an infusion, and this sign identifies patients at most risk of developing nephrotoxicity (Campbell, Kalman & Jacobs, 1983). Gentamycin, and other aminoglycosides, produce a similar effect on the kidney, and if given concurrently with Cisplatin, may increase the nephrotoxicity of the drug (Baum et al., 1979). In a patient who has had previous nephrotoxicity with Cisplatin chemotherapy, administration of an aminoglycoside may precipitate renal failure (Winkler, Mahr & De Bandi, 1979). Continued use of Cisplatin produces bilateral small kidneys on x-ray and ultrasound and this sign may precede the onset of renal failure

(Friedman & Lantin, 1980).

Among the other side effects of Cisplatin, gastrointestinal toxicity is seen in the majority of patients. Nausea, in 50-100% patients, begins 1-6 hours following treatment with Cisplatin (Von Hoff et al., 1979). Anorexia and nausea may persist for up to a week following treatment, and anorexia tends to increase with continued courses of Cisplatin (Ohnuma & Holland, 1979). These side effects may be so severe as to cause Cisplatin therapy to be discontinued.

Diarrhoea is an occasional side effect of treatment; and liver enzymes may be mildly, but transiently, elevated (Williams & Whitehouse, 1979).

Myelosuppression occurs, and it is dose related and may be cumulative (Williams & Whitehouse, 1979). Anaemia may be severe, requiring transfusions during treatment. The cause of the anaemia is probably not decreased erythropoietin production due to cytotoxic effects on the kidney, but a direct cytotoxic effect on the erythroid stem cells in the bone marrow, causing decreased production of red blood cells with some haemolysis, also, of the circulating red cells (Rothmann & Weick, 1981). Leucopenia occurs particularly in patients who have been pretreated by cytotoxic drugs or radiotherapy, with a reported incidence of 0-50% (Von Hoff et al., 1979). Thrombocytopenia is similarly dose related and frequency related and occurs in 2-50% patients (Von Hoff et al., 1979).

Ototoxicity with loss of hearing and tinnitus occurs in up to 30% patients and is probably irreversible (Williams & Whitehouse, 1979). Other neurological signs and neuropathies have been reported infrequently (Von Hoff et al., 1979).

Schilsky & Anderson (1979) were the first to report hypomagnesaemia following Cisplatin chemotherapy. Of thirty-seven patients studied they found twenty-two patients became hypomagnesaemic following treatment. Four of these patients had inappropriately high levels of urinary magnesium implicating renal tubular damage as the cause of the hypomagnesaemia. A further study by Schilsky, Barlock & Ozols (1982) found hypomagnesaemia in twenty-two of twenty-four patients treated with Cisplatin. Eleven of the twenty-two were persistently hypomagnesaemic two years after treatment, and eight out of nine patients had persistently high urinary magnesium levels. This hypomagnesaemia was not related to the total dose of Cisplatin administered, or to the serum magnesium nadir during treatment; and there was no evidence of gross renal failure, with serum creatinine levels remaining normal. None of these patients developed hypocalcaemia or hypokalaemia; although a number of authors have found both hypokalcaemia and hypokalaemia in association with the hypomagnesaemia produced by excessive loss of magnesium in the urine (Lyman et al., 1980; Hill & Russo., 1981; Cognetti et al., 1982). The symptoms of hypomagnesaemia may at first be vague and non-specific, similar to the side effects of Cisplatin treatment, with general malaise, anorexia, nausea, depression and irritability. Continued

and severe hypomagnesaemia may cause muscle twitching and induce hypocalcaemia and severe electrolyte disturbances leading to tetany and fits (Stuart-Harris, Ponder and Wrigley, 1980; Hayes et al., 1979). Muscle twitching, and tetany have been reported in 5-10% patients receiving Cisplatin (Williams & Whitehouse, 1979). Magnesium deficiency may also produce electrocardiographic abnormalities, with myocardial arrhythmias, and has been implicated in some cases of myocardial infarction (Dykner, 1980; Shilsky 1982; Speich, Bousquet & Nicolas, 1980).

In summary, therefore, Cisplatin is a good cytotoxic agent but has a number of potentially serious drawbacks. Nephrotoxicity is the major dose-limiting side effect; and hypomagnesaemia induced by the renal damage may exacerbate Cisplatin-induced anorexia, nausea and electrolyte disturbances, may have a role in myocardial arrhythmias, and may cause further renal problems by inducing nephrocalcinosis (Bunce, Saacke & Mullins, 1980).

Aims

The aims of the studies were to examine the effects of Cisplatin on the nutritional state and aspects of metabolism in animals and cancer patients.

A preliminary study examined the effects of escalating doses of Cisplatin on rat tissues, looking particularly at kidney and heart

muscle, for evidence of the reported toxicity of Cisplatin.

Clinical studies were then designed to monitor the effect of Cisplatin treatment on electrolyte, calcium, magnesium and trace metal levels in the plasma of patients receiving Cisplatin in the treatment of teratoma. The acute effects of Cisplatin on these elements were observed during the five day treatment period; the longer term effects were assessed by comparing results obtained during the first course of treatment with those from the fourth course of treatment. Those elements which may require monitoring or supplementation during treatment were identified.

Further clinical studies examined the effects of Cisplatin administration on dietary intake and on renal function. The use of magnesium supplements was monitored to determine their usefulness for the patient by their effects on the tolerance to treatment and outcome of treatment. The optimum method of magnesium supplementation for both patient and hospital staff was also investigated.

A. EFFECTS OF CISPLATIN ON RAT TISSUES

Methods

Female albino Wistar rats, all 10 weeks of age and weighing 160-170 grams were used for this study. Cisplatin doses ranging from 2 mg/Kg, 6 mg/Kg, 20mg/Kg to 30 mg/Kg body weight were administered intraperitoneally. Each group of rats contained two animals. the rats were sacrificed using ether inhalation six days after the administration of Cisplatin.

Following sacrifice, the heart, liver, kidney, soleus and gastrocnemius muscles were removed and a sample of each frozen immediately in liquid nitrogen for electron microscopic examination and histochemical staining. The remaining tissue was fixed in formal saline for histological examination. Processing of the tissues was carried out at Institute of Neurological Sciences, Southern General Hospital, and reporting of the results obtained was undertaken by Dr. David Doyle, Consultant Neuropathologist, Southern General Hospital, Glasgow.

Results

Kidney structure was much more markedly affected than structure of any of the other organs. All organs, however, showed, similar patterns of cellular and subcellular damage with the greatest

disruption present at the highest doses of Cisplatin.

In the kidney, there were few microscopic changes evident at 2 mg/Kg dose of Cisplatin ; at 6 mg/Kg, the LD_{10} dose of Cisplatin, there is evidence of mild tubular atrophy affecting, preferentially, the distal tubules (Plate 2). At 20 mg/Kg and 30 mg/Kg doses there is extensive damage to both proximal and distal renal tubules with mineralised cellular debris, protein casts and red cell casts present, indicating leakage of these materials from the tubular lining cells and failure of reabsorption of filtered protein and minerals. The glomeruli appear relatively normal. In all sections examined there is evidence of regenerative mitotic activity in the tubular cells, following the necrosis caused by the Cisplatin insult. Damage is most widespread in the 30 mg/Kg Cisplatin animals (Plate 3).

The site of intracellular damage was identified by enzyme histochemistry as being in the mitochondrion. In all the tissues examined, kidney, heart, liver and muscle, mitochondria were reduced in numbers and were shown to be least actively functioning at the highest doses of Cisplatin.

Electron microscopy of the tissues showed reduced numbers of mitochondria which were large, with increased numbers of internal cristae; the changes being most evident at the highest doses of Cisplatin.

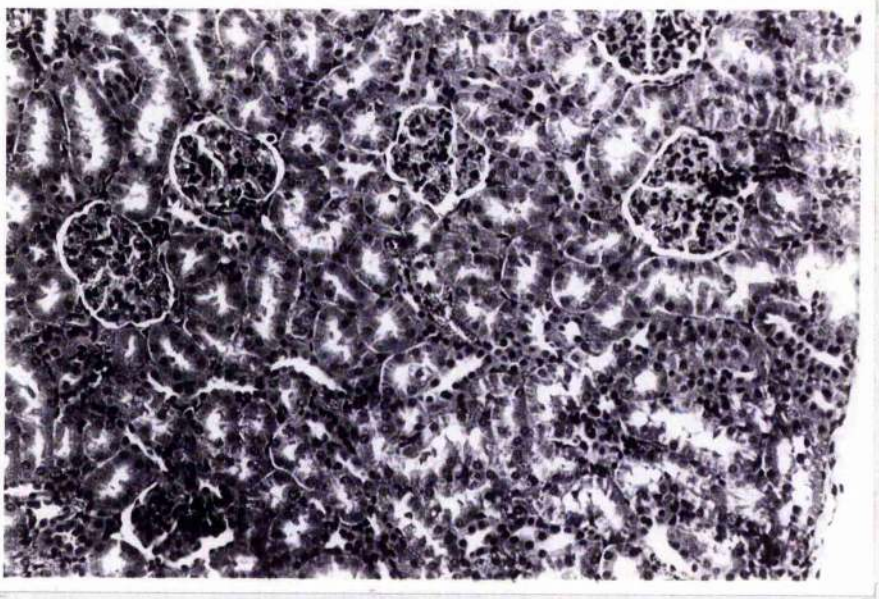

PLATE 2: RAT KIDNEY SHOWING MINIMAL ACUTE DAMAGE FOLLOWING INTRAPERITONEAL ADMINISTRATION OF 6mg/Kg CISPLATIN (MAGNIFICATION x 100)

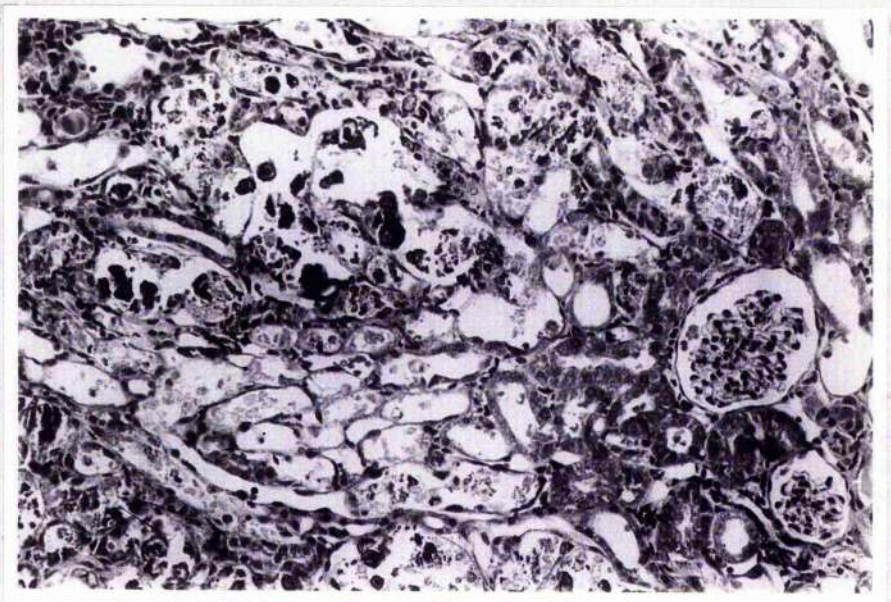

PLATE 3: RAT KIDNEY SHOWING SEVERE, ACUTE TUBULAR DAMAGE WITH RELATIVE SPARING OF GLOMERULI FOLLOWING INTRAPERITONEAL ADMINISTRATION OF 20mg/Kg CISPLATIN (MAGNIFICATION x 100)

Conclusions

These findings confirm the presence of renal damage due to Cisplatin administration, the severity of damage increasing with escalating doses of Cisplatin. The renal tubules are severely affected, particularly the distal tubules, while there is relative sparing of the glomeruli, even at the highest doses of Cisplatin. Magnesium and other minerals are not reabsorbed from the glomerular filtrate due to the tubular damage, and are therefore excreted excessively.

At a cellular level, the increased size of the mitochondria with increased numbers of internal cristae indicate hypertrophy of the remaining mitochondria, to compensate for the reduced numbers of mitochondria produced by the toxic effects of Cisplatin. The role of magnesium deficiency in the mitochondrial changes is uncertain. Magnesium is an essential mitochondrial cation which is necessary for efficient functioning of the mitochondrion. It may be that magnesium loss in the urine is due to mitochondrial damage with consequent release of intramitochondrial constituents. The primary cause of the mitochondrial changes is the Cisplatin administration; the magnesium deficiency produced by this may exacerbate the problem, and further diminish mitochondrial activity. The mitochondrial changes may also be a reason for the inefficient metabolism, weakness, weight loss and anorexia seen in cancer patients.

In summary, there is evidence of cellular and mitochondrial damage in liver, heart, kidney and muscle as a direct result of Cisplatin administration. Further studies should aim to elucidate the role of magnesium in these changes. Studies should examine the effects of a range of serum and tissue magnesium levels on mitochondrial function, looking for similarities in the patterns obtained to the Cisplatin effects. An evaluation of the use of magnesium supplements in reversing or preventing the mitochondrial damage should also be undertaken.

It will be difficult to evaluate the contribution of Cisplatin induced mitochondrial damage to the metabolic changes seen in tumour bearing animals treated with this chemotherapeutic drug (Chapter 5); and it will be interesting to repeat the experiment discussed in Chapter 5 using varying doses of Cisplatin in animals with and without tumour. Measurements of animal weights, tumour growth, liver enzymes, ketone bodies, total protein and albumin levels and plasma iron levels would be compared in the drug alone, drug and tumour and tumour alone groups with escalating doses of the drug, looking for the effects of increasing mitochondrial dysfunction.

Clinical Studies

B. EFFECTS OF CISPLATIN ON TRACE METAL LEVELS IN BLOOD

Methods

Seven patients with histologically proven teratomas were studied in detail during their first five-day course of combination chemotherapy using Cisplatin, Vinblastine and Bleomycin in a modification of the Einhorn regime (Fig. 20) (Einhorn & Donahue,1977). Four patients were studied again during their fourth course of treatment. Patients were hydrated with 4 litres 0.9% saline, daily, to establish a good diuresis, and Cisplatin 20 mg/m^2 was administered on each day for five days. The Cisplatin infusion was timed to start at 6 p.m. each evening, to minimise diurnal variations in the levels of trace metals in the samples.

Blood samples were taken 1 hour prior to the start, and at the end of the 4 hour Cisplatin infusion. Samples were taken on each day of the first and fourth courses of treatment.

The blood was centrifuged immediately and the plasma stored at 4 degrees centigrade. Plasma was analysed for sodium, potassium, calcium, magnesium, zinc, copper, iron, albumin and creatinine. Urine was collected continuously for the five treatment days and was analysed for potassium, calcium, magnesium, zinc, and creatinine. A plastic collection bottle was used for the urine to eliminate contamination from trace metals present in the disposable type of container. All analyses were performed at Department of Biochemistry, Gartnavel General Hospital, Glasgow under the supervision of Mrs. Jean McAllister.

MODIFIED EINHORN REGIME

Cisplatin 20 mg/m^2 4 hr. i.v. infusion	Days 1-5	)	repeated 3 weekly
Vinblastine 0.15-0.20 mg/kg i.v. bolus	Day 2	)	
Bleomycin 30 mg 4 hr. i.v. infusion	Day 2		weekly

4 courses of treatment then patients reassessed

Consolidation treatment - 2 courses given

If partial response to original treatment

Cisplatin 100 mg/m^2 4 hr. i.v. infusion	Days 1 & 2	)	repeated 3 weekly
Vinblastine 0.15 mg/kg i.v. bolus	Days 1 & 2	)	

i.v. = intravenous

4 hr. = over 4 hours

FIGURE 20: MODIFIED EINHORN REGIME FOR CISPLATIN COMBINATION CHEMOTHERAPY

Results

Patients ages ranged from 20-32 years. All had histologically proven teratoma: 6 were testicular; 1 was mediastinal. All patients studied had evidence of metastatic spread of disease in the paraaortic lymph nodes or lungs, or both sites. Three of the patients had had previous radiotherapy. Following initial chemotherapy, four patients had two further courses of consolidation treatment (Cisplatin 100 mg/m^2 on two days, with Vinblastine 0.15 mg/Kg on both days) (Fig. 20) and six of the original seven patients had no evidence of disease or recurrence up to two years after the end of treatment. One patient developed septicaemia and severe electrolyte disturbances following course four, and died from these complications.

All patients experienced considerable nausea and vomiting during treatment. Five of the patients had treatment delays due to low white blood cell counts following the previous course of treatment. Three patients had septicaemic episodes and three required blood transfusions during treatment (Table 25).

Two patients gained weight during treatment (8.5 Kg and 2 Kg respectively); and four patients lost on average 7.5 Kg weight (range 2.5 Kg to 11 Kg) during treatment (4% to 15% body weight).

Plasma levels of sodium, copper and albumin showed no significant change during the 5 days of treatment or between the first and fourth

Side Effects	No. Patients	% Patients
Nausea	7	100%
Vomiting	7	100%
Treatment delays	5	71%
Neutropenia	5	71%
Septicaemia	3	43%
Blood transfusion	3	43%
Weight gain	2	28%
Weight Loss	4	57%

TABLE 25: SIDE EFFECTS OF TREATMENT WITH CISPLATIN

courses. Serum creatinine showed no change over the period of treatment, indicating no significant renal damage in any patient. Plasma calcium, magnesium, zinc and iron results are summarised in Figs. 21,22,23 and 24. During the five days of treatment, plasma calcium levels rose; and plasma iron levels showed a particularly marked rise. Plasma levels of magnesium showed a slight,but not significant,fall over the 5 days of treatment; while zinc levels fell slightly and then returned to pretreatment levels during the treatment period.

Table 26 compares the levels in first and fourth courses. The levels of calcium and zinc in the blood showed no significant difference between the first and fourth courses. Two of the four patients studied during the fourth course of treatment showed elevated levels of plasma iron compared to the first course. Plasma magnesium levels in three out of four patients were markedly reduced in the fourth course compared to the first course. Two of three patients who had pretreatment radiotherapy showed marked falls in magnesium levels.

Over the five-day treatment periods, urinary excretion of sodium increased in keeping with the saline load administered and the saline diuresis produced in these patients. Potassium excretion decreased over the five days. Excretion of calcium, magnesium and zinc remained constant or showed a slight increase in amount. These changes were also seen in the fourth course of treatment, and there was no significant difference in levels between first and fourth courses.

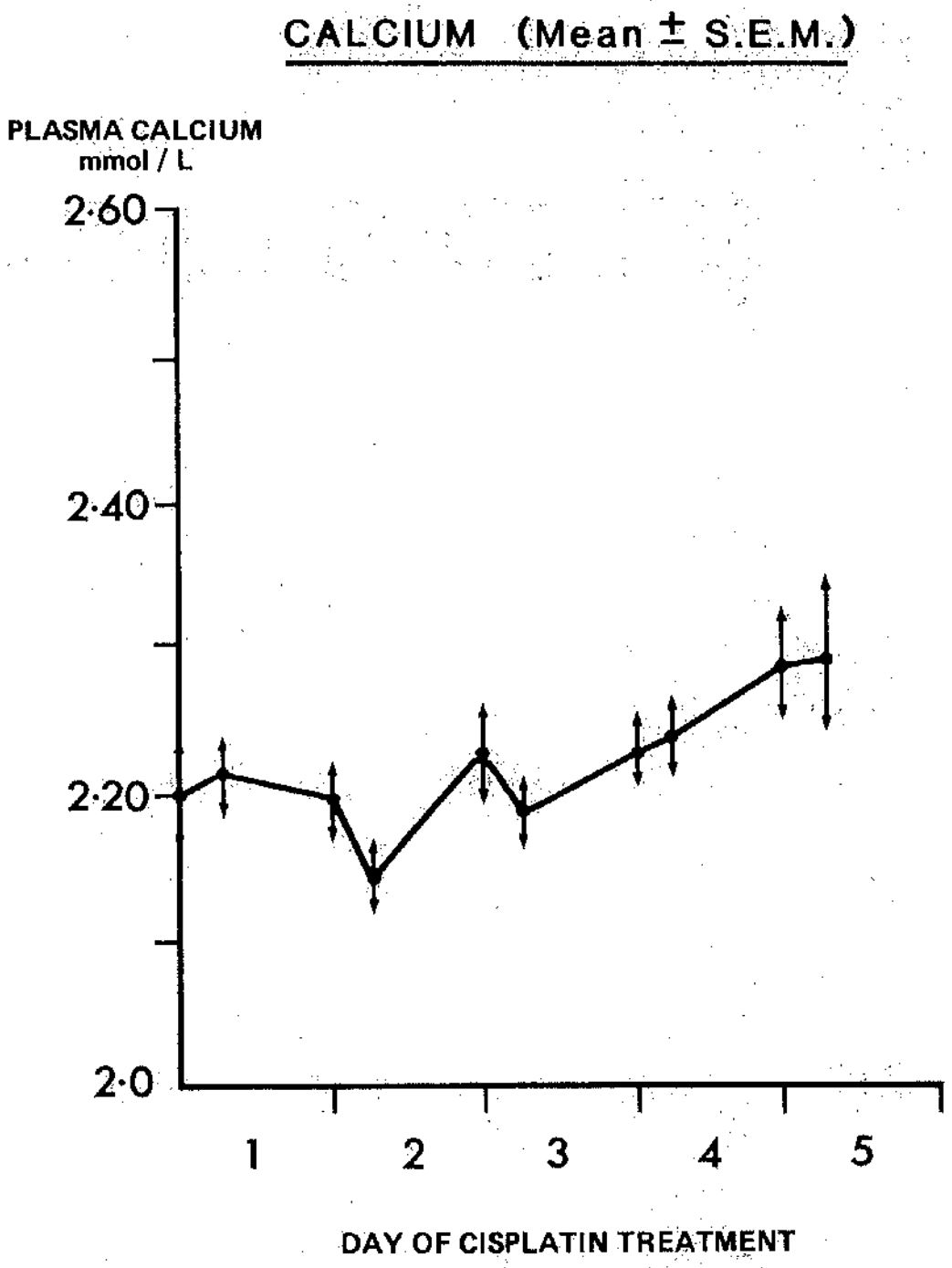

FIGURE 21: PLASMA CALCIUM LEVELS OVER 5 DAYS INPATIENT TREATMENT DURING FIRST COURSE OF CISPLATIN CHEMOTHERAPY

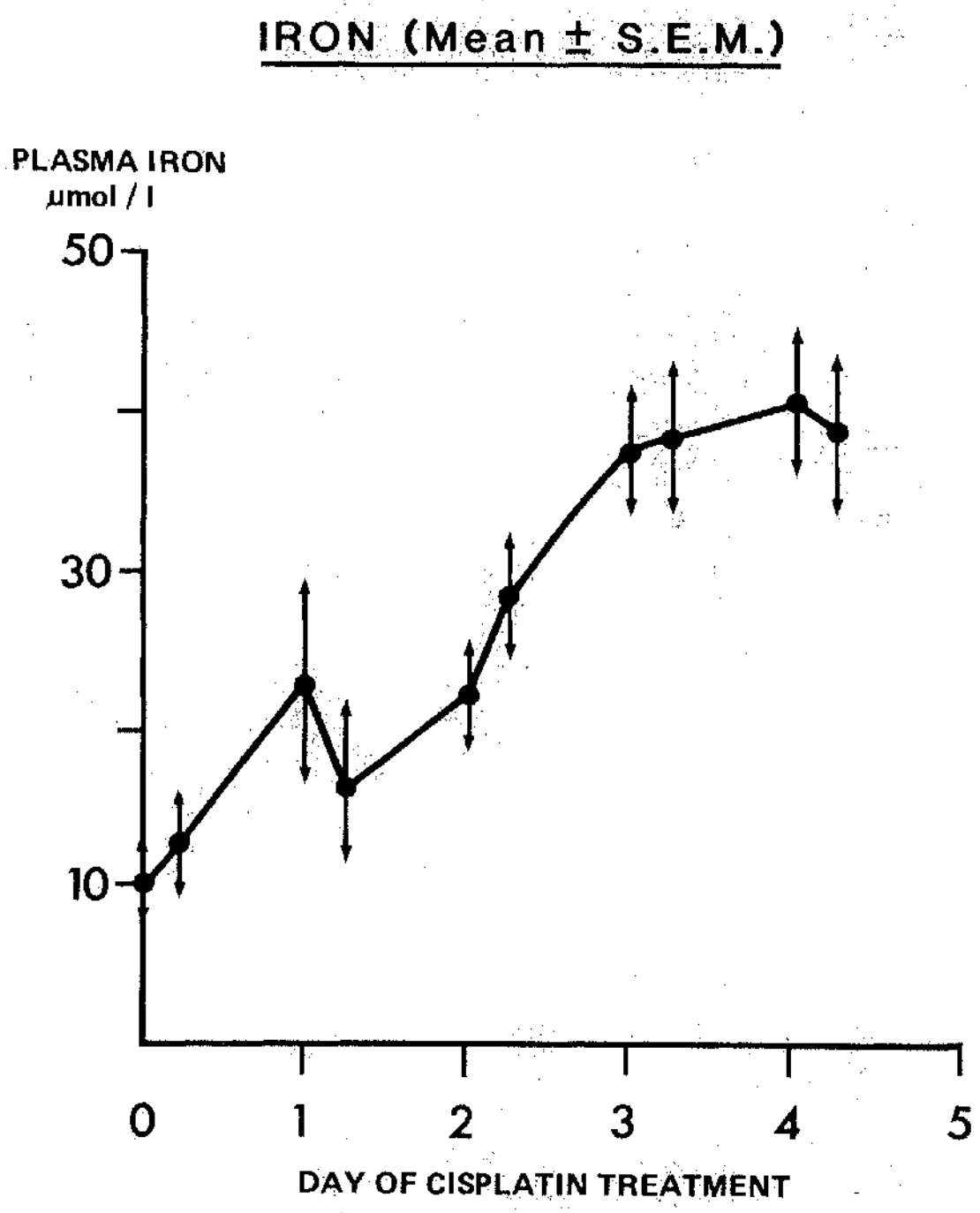

FIGURE 22: PLASMA IRON LEVELS OVER 5 DAYS INPATIENT TREATMENT DURING FIRST COURSE OF CISPLATIN CHEMOTHERAPY

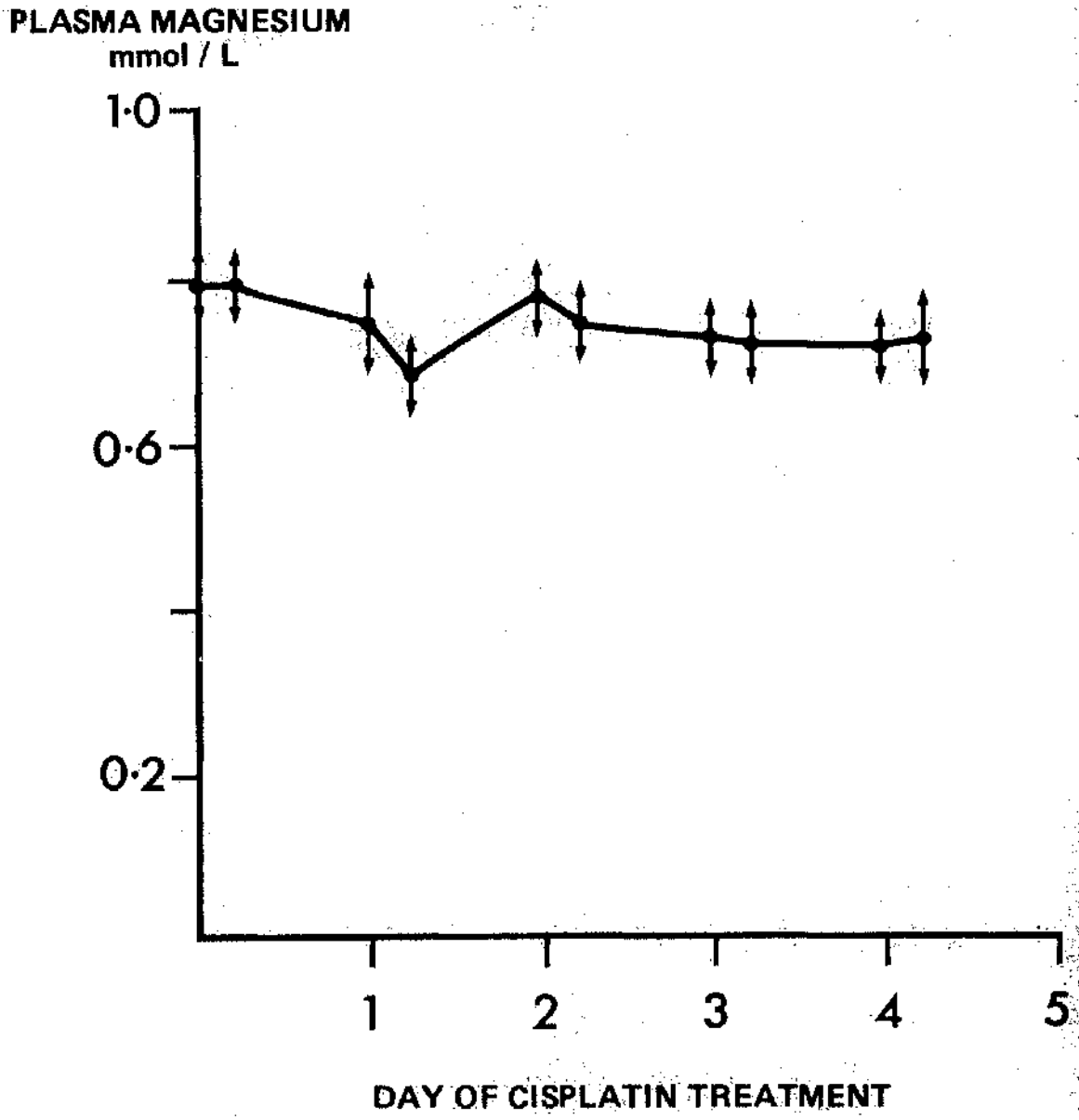

FIGURE 23: PLASMA MAGNESIUM LEVELS OVER 5 DAYS INPATIENT TREATMENT DURING FIRST COURSE OF CISPLATIN CHEMOTHERAPY

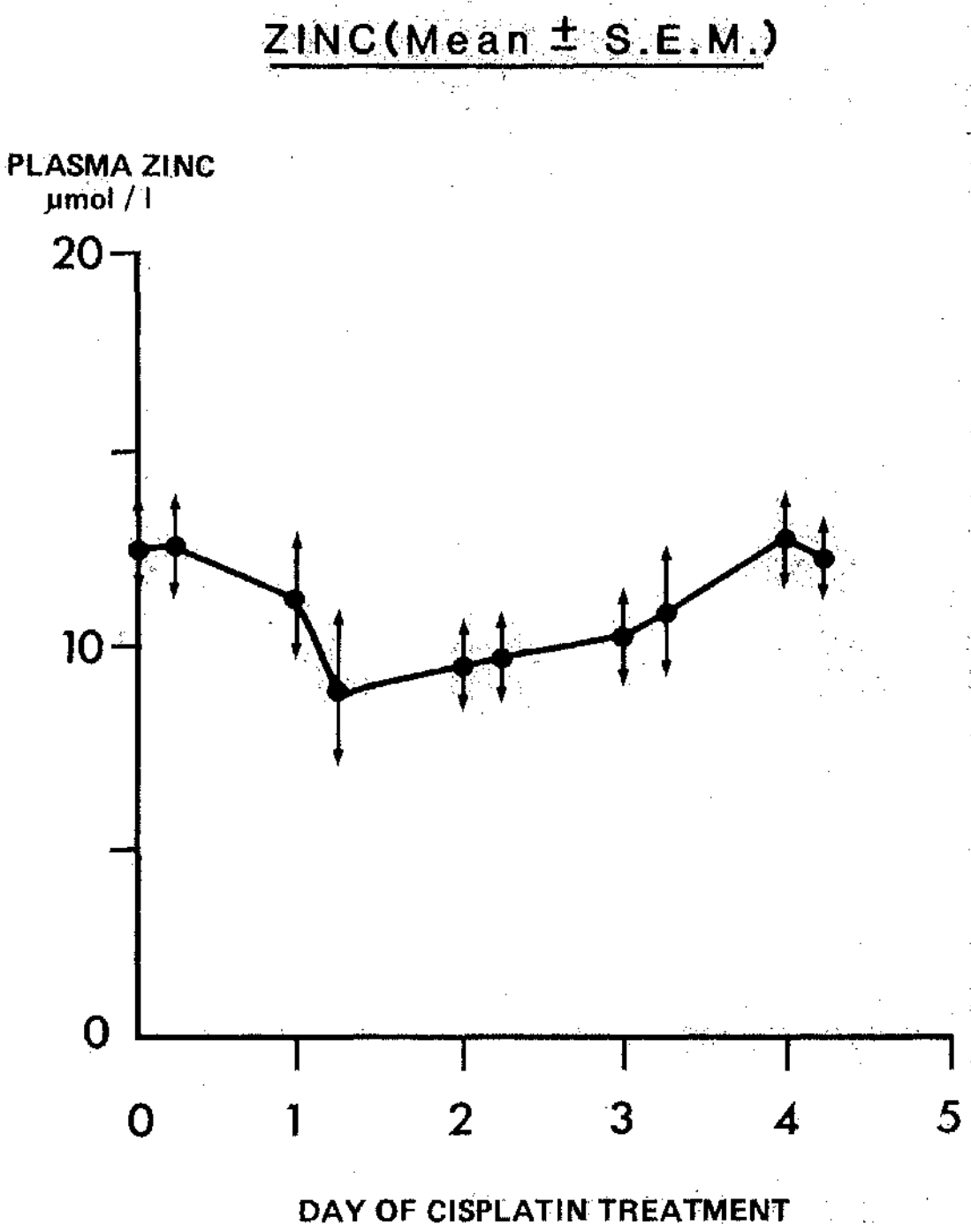

FIGURE 24: PLASMA ZINC LEVELS OVER 5 DAYS INPATIENT TREATMENT DURING FIRST COURSE OF CISPLATIN CHEMOTHERAPY

	Calcium		Magnesium		Zinc		Iron		Copper	
	1st	4th	1st	4th	1st	4th	1st	4th	1st	4th
JM	A 2.25	A 2.14	0.66	0.64	9.7	8.4	14	32	A 23.9	A 13.8
WS	2.18	2.03	A 0.85	A 0.41	14.6	14.7	B 21	B 33	24.4	21.1
GP	B 2.21	B 2.39	A 0.71	A 0.60	9.6	8.9	25	21	13.2	12.5
SG	-		B 0.74	B 0.62	10.6	12.2	29	27	-	

Significant changes Between 1st and 4th courses

AA $p < 0.001$

BB $p < 0.005$

TABLE 26: COMPARISON OF TRACE METAL, MAGNESIUM AND CALCIUM LEVELS BETWEEN 1st AND 4th COURSES OF CISPLATIN TREATMENT

Conclusions

The changes seen in plasma levels of the trace metals and electrolytes are similar to those seen during an acute illness and are not specific to cancer patients or Cisplatin chemotherapy (Kay, 1981). The "stress response" accounts for the changes in plasma zinc seen during treatment (Delves, 1982); and the increased sodium excretion has been explained by the forced saline diuresis. The increased plasma iron levels were most marked in those patients who required blood transfusions during treatment, and would suggest a failure of iron utilisation in these patients, giving rise to anaemia. This would be accounted for by the decreased production of erythrocytes due to Cisplatin effects on the erythoid precursors (Rothman & Weick, 1981). Supplementation of iron would be of no benefit to these patients.

From the results obtained, there is no evidence that routine supplementation of the trace metals in general is necessary in this group of patients. However nutritional support and magnesium supplementation may be beneficial. Nutritional depletion was seen in 50% patients, who had weight loss of greater than 10% body weight; and these patients were most likely to have treatment delays due to neutropenia. Poor nutritional status will contribute to, and prolong Cisplatin-induced myelosuppression, and may influence the eventual outcome of treatment by delays which prevent adequate treatment of the tumour.

Most patients showed a fall in serum magnesium levels and two

patients became symptomatic requiring treatment with magnesium supplements. These were patients who had lost most weight (11 Kg and 9 Kg each), who had delays of treatment due to low white blood cell count, and who required transfusions for anaemia.

The causes of hypomagnesaemia are multifactorial. The most common cause ascribed to Cisplatin treatment, renal magnesium wasting, was seen in only one of the seven patients studied; the others showed a tendency to conserve magnesium by reducing its excretion in the urine.

Anorexia and nausea induced by treatment may play a part in hypomagnesaemia: decreased food intake with only 30% absorption of ingested magnesium (Wacker & Parisi,1968), may exacerbate the deficiency of magnesium. Ohnuma & Holland (1979) state that the anorexic effects of Cisplatin increase with repeated exposure to the drug. There may, in addition, be malabsorption induced by Cisplatin and Vinblastine, with diarrhoea which may compound the problem. Vomiting can account for significant magnesium losses, with up to 25% total body magnesium present in gastric juice (Wacker & Parisi, 1968). The "soft" water in the West of Scotland with its low levels of calcium and magnesium ions will not help to replete a depleted patient between courses of chemotherapy. Shilsky et al. (1982) also contend that the forced saline diuresis, with mannitol infusions, required for the Cisplatin regime of treatment will produce increased and inappropriate losses of magnesium in the urine. Some or all of these factors may be operating in each of the patients receiving Cisplatin.

Table 27 shows the serum magnesium levels over a nine month period in nineteen patients receiving the modified Einhorn regime of Cisplatin, Vinblastine and Bleomycin (Fig. 20) at 3-4 week intervals for teratoma. All nineteen patients became hypomagnesaemic (serum magnesium less than 0.70 mmol/l) by the fourth course of chemotherapy; and eleven patients developed serum magnesium levels below 0.50 mmol/l. These eleven patients had associated abnormalities of serum calcium and potassium levels, and had symptomatic hypomagnesaemia. All responded to intravenous magnesium supplementation which restored levels of magnesium, calcium and potassium to normal in all but three patients, who required potassium supplements in addition.

Six patients receiving "high dose" Cisplatin (50 mg/m^2) over one day at 3-4 weekly intervals for ovarian carcinoma were monitored for changes in serum magnesium levels (Fig. 25). All six patients had serum magnesium levels below 0.70 mmol/l after four courses of treatment. Three of the patients had levels below 0.50 mmol/l and one patient's magnesium level fell below 0.30 mmol/l.

In summary, although the trace metals do not require to be routinely supplemented in patients receiving Cisplatin, there is weight loss, anorexia, general nutritional depletion and hypomagnesaemia which, if severe and prolonged, leads to potassium and calcium depletion. Further studies were performed on teratoma patients receiving Cisplatin to examine the effects of magnesium supplementation on outcome, side effects and toxicity of treatment; and to look at the effects of

Plasma Magnesium (mmol/l) Range	Number of Patients (19) Total	No. with Calcium <2.2mmol/l	No. with Potassium <3.5mmol/l
0.60 - 0.69	4 (21%)	0	0
0.50 - 0.59	4 (21%)	0	0
0.40 - 0.49	3 (16%)	0	1 (33%)
0.30 - 0.39	5 (26%)	1 (10%)	3 (60%)
0.20 - 0.29	3 (16%)	1 (33%)	2 (67%)

TABLE 27: LOWEST RECORDED MAGNESIUM, CALCIUM AND POTASSIUM LEVELS DURING TREATMENT IN ALL PATIENTS RECEIVING CISPLATIN OVER A NINE MONTH PERIOD

Cisplatin 50 mg/m^2 4 hr.intravenous infusion	)	
	)	
Adriamycin 45 mg/m^2 intravenous BOLUS	)	Day 1 and every 4 weeks
	)	
Cyclophosphamide 600 mg/m^2 intravenous BOLUS	)	

4 hr = over 4 hours

FIGURE 25: CHEMOTHERAPY REGIME FOR OVARIAN CANCER

Cisplatin, with and without magnesium supplements, on dietary intake and renal function. The palatability of magnesium supplements was also tested.

C. EFFECTS OF MAGNESIUM SUPPLEMENTATION IN PATIENTS RECEIVING CISPLATIN

Methods

Seventeen patients receiving Cisplatin chemotherapy for the first time were randomised to receive supplements of magnesium or not. Patients received Cisplatin either in doses of 20 mg/m^2 as the modified Einhorn regime (Fig. 20) or in doses of 100 mg/m^2 over one day (Fig. 26). Saline diuresis, with the administration of mannitol as required, was used as in the previous study.

The magnesium status of each patient was assessed prior to therapy by giving a loading dose of magnesium sulphate, 0.25 mmol/Kg body weight intravenously over 30 minutes and collecting all urine for the following 24 hours. Levels of magnesium in the urine which exceeded 80% intravenous dose indicated normal body stores of magnesium. Patients were stratified depending on their magnesium excretion, whether above 80% or below 80% of the intravenous loading dose. Each patient was then randomised to receive magnesium supplements or not. The levels of supplementation depended on the dose of Cisplatin used (Fig. 27), and was based on the recommended daily intake of magnesium (DHSS, 1979). Intravenous

Initially

Cisplatin 100 mg/m^2 4 hr. i.v. infusion	)	
	)	Days
Vincristine 2 mg i.v. bolus	)	1, 10, 21
	)	
Bleomycin 30 mg 4 hr. i.v. infusion 4 hours)	)	

After 3 weeks

Cisplatin 20 mg/m^2 daily 4 hr. i.v. infusion Days 1-5	)	
	)	
Bleomcyin 30 mg. 4 hr. i.v. infusion Day 1	)	3 weekly
	)	
V.P.16 100 mg/m^2 i.v. infusion Days 1-5	)	

i.v. = intravenous

4 hr. = over 4 hours

FIGURE 26: "HIGH RISK" CHEMOTHERAPY FOR TERATOMA

Randomisation depending on dose of Cisplatin:

1. Cisplatin 20mg/m^2 for 5 days (Modified Einhorn Regime)

   All patients randomised to:

   A - Supplements or

   B - No Supplements

A. Magnesium sulphate: 8 mmol in 500 mls 0.9% saline intravenously over four hours following Cisplatin infusion over each five days of treatment.

   Magnesium citrate: 5 mmol t.i.d. orally daily after intravenous infusion is discontinued.

2. Cisplatin 100mg/m^2 for 1 day

   All patients randomised to:

   C - Supplements or

   D - No Supplements

C. Magnesium sulphate: 24 mmol in 500ml 0.9% saline intravenously over 12 hours following Cisplatin infusion.

   Magnesium citrate: 5 mmol t.i.d. orally daily after intravenous infusion is discontinued.

FIGURE 27: RANDOMISATION SCHEDULE FOR MAGNESIUM SUPPLEMENTS

supplementation was given as magnesium sulphate, 8 mmol in 500 ml 0.9% saline over four hours immediately following the Cisplatin infusion. Once the intravenous infusion was discontinued, oral magnesium supplements were given to supply 30 mmol magnesium daily (10 mmol thrice daily). This was estimated to provide each patient with the recommended daily intake of magnesium of at least 8 mmol, allowing for 30% absorption of ingested magnesium (Wacker & Parisi, 1968).

Patients were grouped and compared according to initial prognosis, as determined by tumour volume and extent (Fig. 28); and five day and one day ("High Dose") Cisplatin groups were also compared. Assessments were made for each group of final outcome, rate of fall of tumour markers, treatment delays, weight changes and episodes of neutropenia and septicaemia. Changes in dietary intake and renal function were noted, and palatability of and compliance in taking magnesium supplements were assessed. Tumour growth in each patient was assessed weekly using clinical, biochemical and radiological evaluation.

A magnesium infusion test and a creatinine clearance test to assess renal function were performed prior to the first course of treatment. Creatinine clearance estimations were also made before each course of chemotherapy.

Daily measurements of full blood count and platelets were performed during each course of treatment at Department of Haematology, Western Infirmary, Glasgow. Blood levels of urea and electrolytes and

Patients are assessed clinically, radiologically and by tumour marker (human chorionic gonadotrophin and alphafeto protein) levels. These place them into high volume metastases (High risk) group or low volume metastases (good prognosis) groups. High risk group have 60% complete response rate; good prognosis group have 90% complete response rate.

	High volume metastases	Low volume metastases
Clinical stage	IIC	IIA
	III M3	IIB
	III N3	III M1
	IV L2	III M2
	IV L3	III N1
	Bone	III N2
	Brain	IV L1
	Liver	
Tumour markers		
HCG	> 50,000 ng/ml	< 50,000 ng/ml
AFP	> 500 ng/ml	< 500 ng/ml

FIGURE 28: ASSESSMENT OF PROGNOSIS IN TERATOMA

magnesium were measured daily; and liver function tests, zinc and calcium levels and the tumour markers, human chorionic gonadotrophin and alphafeto-protein were measured weekly.

Urine samples were taken daily during the five day inpatient treatment and were analysed for beta-2-microglobulin, N-acetylglucosamine and magnesium levels. All biochemical estimations were performed at Department of Biochemistry, Gartnavel General Hospital, Glasgow.

During the inpatient treatment period, and at intervals between courses of treatment, each patient had 24-hour dietary recall histories taken, and computer analysis of these gave an estimate of the dietary intake over a course of treatment (see Chapter 2 for method).

Patients who received supplements were assessed for compliance in taking the supplements.

Results

Seventeen patients were studied in detail, M:F ratio being 16:1. Eight patients were randomised to receive supplements of magnesium over the first four cycles of treatment; nine patients received no supplements. No patients were magnesium deficient before treatment. Seven of the supplemented group received Cisplatin over 5 days as in the modified Einhorn regime; six of the non supplemented group received this regime. The other patients, one in the supplemented group and

two in the non-supplemented group received, initially, one day courses of "high dose" Cisplatin at shorter intervals (Fig. 26). The ages of patients in the supplemented group ranged from 18-39 years (mean 29 years); in the nonsupplemented group ages ranged from 22-47 years (mean 33 years). Three of the patients in the supplemented group and four in the non-supplemented group were in the bad prognosis "high risk" group. The cumulative platinum for each group was similar for both supplemented and non-supplemented groups (Table 28). One patient in the supplemented group and two patients in the non-supplemented group had received pretreatment radiotherapy.

Dietary intake

All patients were nauseated during treatment and vomited following Cisplatin administration; there was no difference between supplemented and non-supplemented groups. Anorexia and dietary intake were similar for both groups and the intakes of energy, protein, vitamins, minerals and magnesium followed a similar pattern through each complete treatment cycle. Figure 29 illustrates the effect of Cisplatin treatment on dietary intake, using energy intake to represent all dietary components, and taking a typical cycle from one course of treatment to the next. All patients, including those receiving high dose one-day treatment, and using results from all courses of treatment, have been used in this graph. This shows that dietary intake decreases from day 3 of Cisplatin treatment, and remains low for at least ten to twelve days following Cisplatin. Intake returns to

	Supplemented Patients (8)	Non-Supplemented Patients (9)
Modified Einhorn regime	7	6
High dose Cisplatin	1	3
Ages (mean)	18-39 yrs (29 yrs)	22-47 yrs (33 yrs)
Prognosis - high risk	3	4
- good prognosis	5	5
M:F	8:0	8:1
Cumulative platinum/patient		
- high risk	890 mg	902 mg
- good prognosis	740 mg	719 mg
Pretreatment radiotherapy	1	2

TABLE 28: CHARACTERISTICS OF PATIENTS RECEIVING CISPLATIN WITH AND WITHOUT MAGNESIUM SUPPLEMENTS

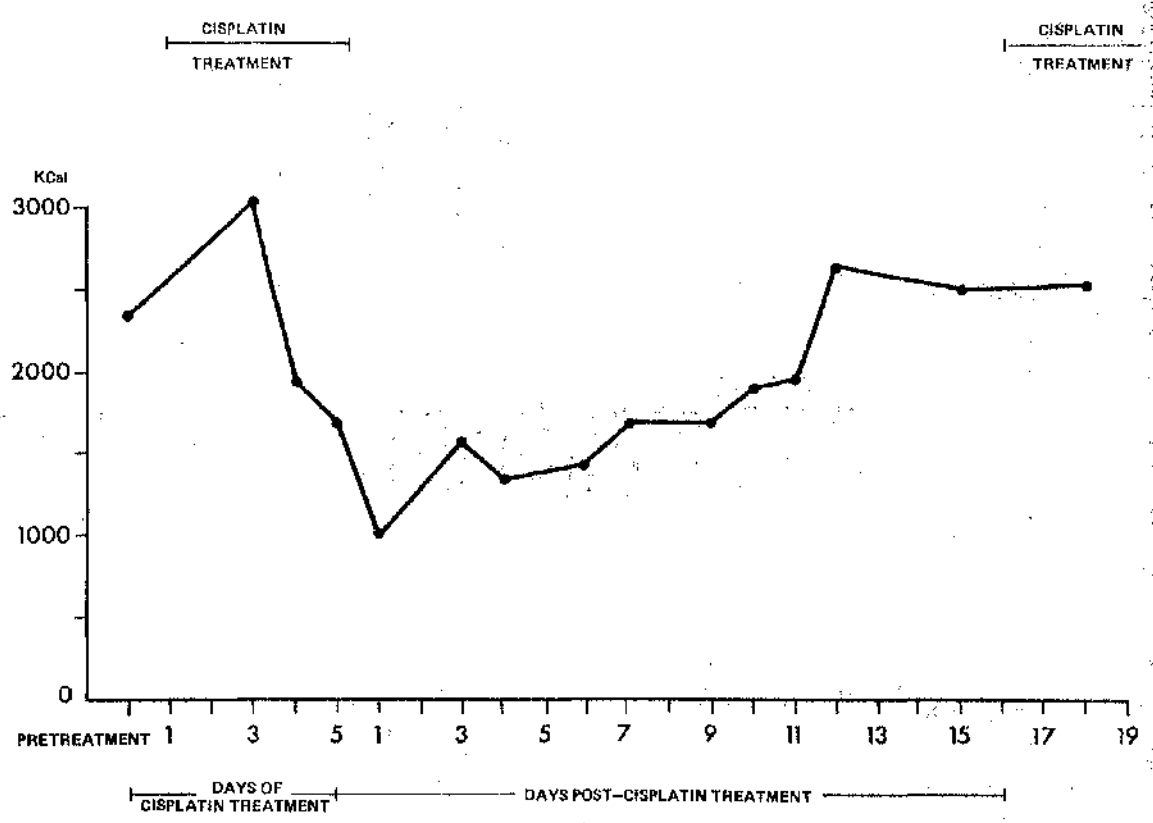

FIGURE 29: EFFECT OF CISPLATIN TREATMENT ON ENERGY INTAKE

normal from day 12; however treatment may restart any day from day 16 onwards, leaving very few days of improved intake to compensate for a fortnight of reduced intake. Intake falls on average to 50% or less of the pretreatment intake.

Figure 30 compares the intake during course one and course four of treatment. Although there is a similar decrease in intake over the first five days of treatment, the patients during course one recover more quickly, with improved intake from day 3 post-Cisplatin. Intake returns to pretreatment levels by day 10. Intakes during course four start at the same mean pretreatment level as in course one, but fall further following Cisplatin, and remain low for longer than in course one. There were too few results of dietary intake analysis for each individual patient to allow statistical analysis of the curves obtained. This agrees with the suggestion by Ohnuma & Holland (1979) that Cisplatin has a cumulative effect on appetite suppression.

Toxicity of treatment

Table 29 gives the results and side effect of treatment for the supplemented and non-supplemented groups; and table 30 compares the effects of treatment of the 5 day Cisplatin regime and the 1 day "High Dose" regime. There is no significant difference in outcome between the supplemented and non-supplemented groups; and the rate of fall of tumour markers, indicating response to treatment, does not differ between the groups. Tumour growth as determined by clinical

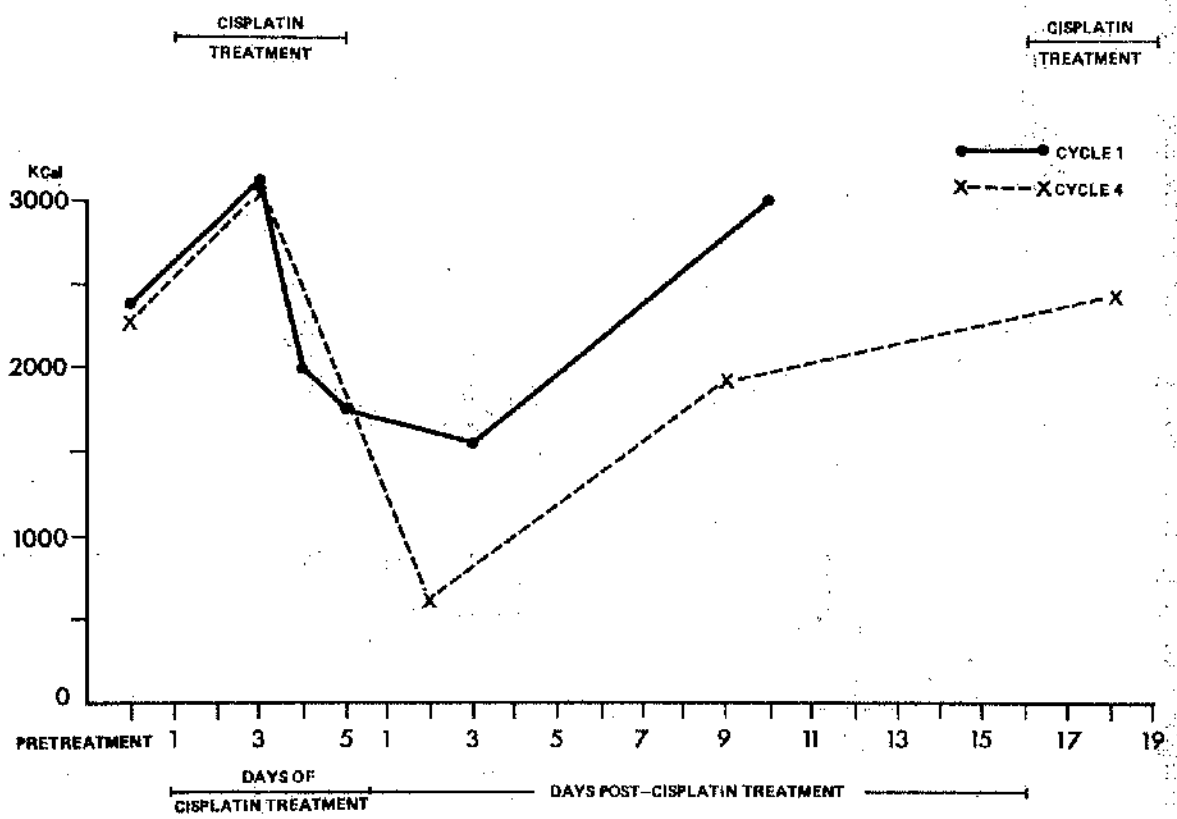

FIGURE 30: COMPARISON OF ENERGY INTAKES BETWEEN CYCLES 1 AND 4 OF CISPLATIN TREATMENT

	Supplemented patients			Non-Supplemented patients		
	Good Prognosis (5)	Bad Prognosis (3)	Total (8)	Good Prognosis (5)	Bad Prognosis (4)	Total (9)
Outcome						
Complete response	5	1	6(75%)	5	1	6(67%)
Partial response	-	2	2(25%)		2	2(22%)
Died	-	-	-		1	1(11%)
Treatment delays	2	1	3(38%)	3	3	6(67%)
Weight changes						
Gain	1	-	1(13%)	-	-	-
Stable	1	1	2(25%)	1	-	1(11%)
Loss	3	2	5(63%)	4	4	8(89%)
Neutropenia	4	2	6(75%)	4	4	8(89%)
Septicaemia	1	1	2(25%)	0	1	1(11%)
Anaemia and transfusions	2	-	2(25%)	1	1	2(22%)
Hypokalaemia (mmol/l)						
Borderline (3.0-3.5)	2	1	3(38%)	4	2	6(67%)
Low (< 3.0)	1	-	1(13%)	1	2	3(33%)
Hypomagnesaemia (mmol/l)						
Borderline (0.70-0.50)	3	2	5(63%)	-	1	1(11%)
Low (< 0.50)	2	-	2(25%)	5	2	7(77%)
Renal failure	0	0	0	0	0	0

TABLE 29: EFFECTS OF TREATMENT WITH CISPLATIN IN MAGNESIUM SUPPLEMENTED AND NON-SUPPLEMENTED GROUPS

	Supplemented patients		Non-Supplemented patients	
	5 Day Course (7)	1 Day Course (1)	5 Day Course (7)	1 Day Course (2)
Outcome				
Complete response	5	1	5	1
Partial response	2	-	1	1
Died	-	-	1	-
Delays in treatment	2	1	4	2
Weight changes				
Gain	1	-	-	-
Stable	1	1	1	-
Loss	5	-	6	2
Neutropenia	5	1	6	2
Septicaemia	2	-	-	-
Anaemia and transfusion	2	-	1	1
Hypokalaemia (mmol/l)				
Borderline (3.0 - 3.5)	3	1	6	1
Low (< 3.0)	1	-	1	1
Hypomagnesaemia (mmol/l)				
Borderline (0.70 - 0.50)	4	1	3	-
Low (< 0.50)	2	-	4	2
Renal failure	0	0	0	0

TABLE 30: EFFECTS OF TREATMENT IN GROUP RECEIVING 5 DAY COURSE CISPLATIN vs GROUP RECEIVING 1 DAY HIGH DOSE CISPLATIN

radiological and biochemical (tumour markers) evaluation was similar for both groups.

Of the side effects of treatment, the supplemented group shows a trend towards fewer treatment delays compared to the non-supplemented group, however this is not statistically significant. There is a similar trend for prolonged neutropenic episodes, which was the main cause of the treatment delays. All patients receiving high dose Cisplatin and all patients who had pretreatment radiotherapy had delays in treatment and neutropenic episodes, whether on supplements or not.

Anaemia requiring blood transfusion occurred with similar frequency in supplemented and non-supplemented groups.

Weight changes showed no signficant differences between supplemented and non-supplemented groups. The patient who gained weight in the supplemented group gained 3 Kg, and showed complete response to treatment. The average weight loss in this group was 10 Kg with the range being 8 Kg to 12.5 Kg. In the non-supplemented group the average weight loss was 11 Kg; the range in this group being from 2 Kg to 25 Kg. Those patients in both groups with the greatest weight loss tended also to be the partial responders to treatment, and had the lowest dietary intakes. In general, weight loss correlated with outcome: those patients, in either group, with the greatest weight loss tended to respond poorly to treatment. Individual weight variations, however, were wide in the complete responder group, so it is probably not a useful predictor of outcome for individual patients. Serum

magnesium levels are significantly higher in the supplemented group compared to the non-supplemented group ($p < 0.01$ using paired t-test) (Fig. 31; Table 31). Serum potasium levels were not significantly different between the groups, although two of the non-supplemented patients required potassium supplements.

Renal function

There is a much higher excretion of magnesium by the supplemented group of patients during the 5 days of intravenous therapy. The non-supplemented group, however, shows an obligatory average daily loss of 3 mmol magnesium. Since the supplemented patients were receiving 8 mmol magnesium daily as supplements, there is retention of between 1 and 3 mmol magnesium in the supplemented group. Urinary potassium levels fall in both groups, with no significant difference between groups. It will be interesting in future to monitor the effect of increased levels of supplements on urinary magnesium levels, which will allow assessment of the body retention of magnesium. It proved impossible in this study to collect urine between courses, and to monitor magnesium excretion over this period.

The results of the renal function tests show that all patients have an increase in levels of N-acetyl glucosamine in the urine as treatment progresses (Table 32). Beta-2-microglobulin levels parallel the changes in N-acetyl glucosamine levels. N-acetyl glucosamine is an enzyme produced by kidney tubular cells and is an indicator of renal

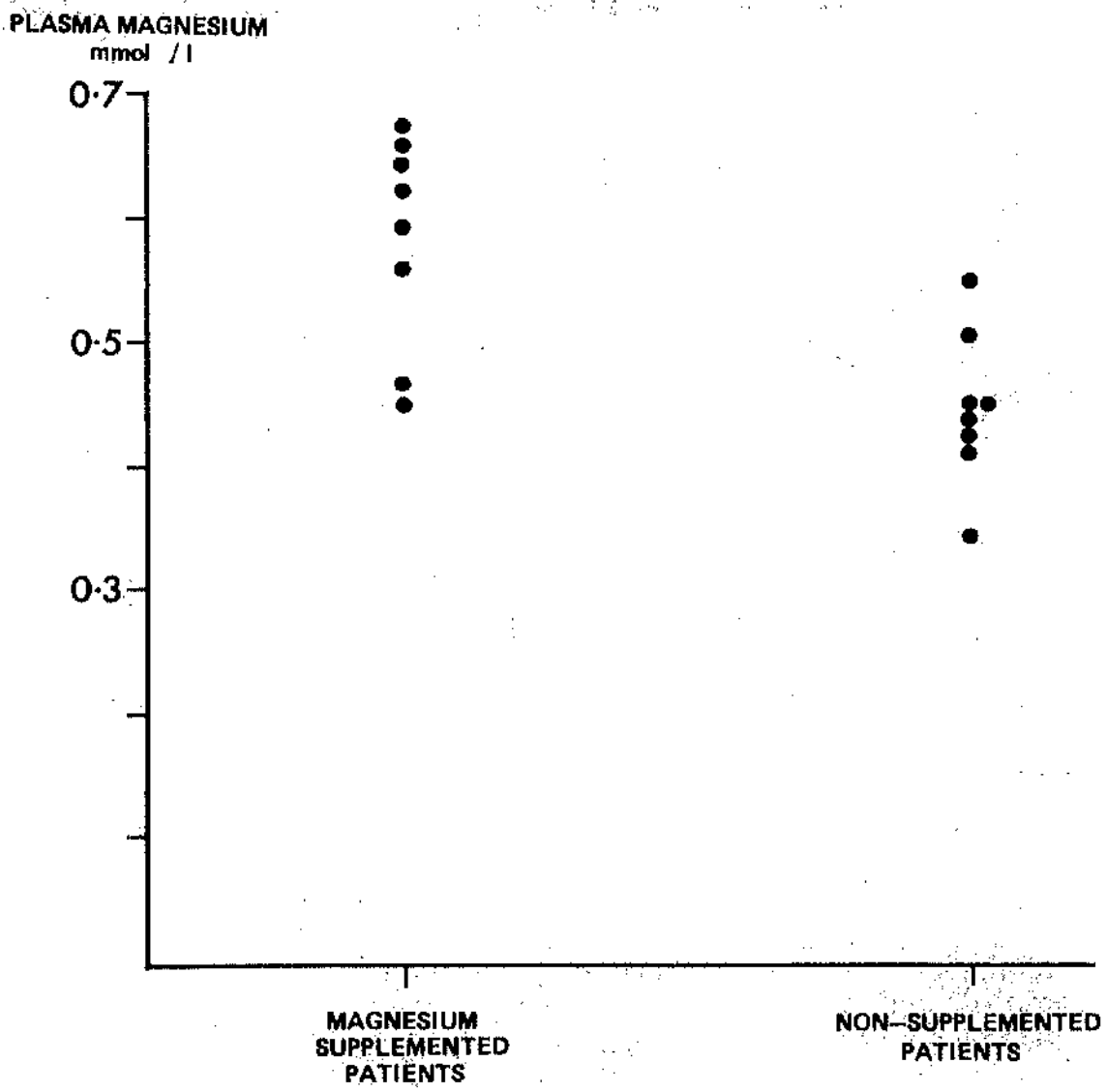

FIGURE 31: LOWEST SERUM MAGNESIUM LEVELS IN MAGNESIUM SUPPLEMENTED AND NON-SUPPLEMENTED GROUPS

	Supplemented Patients	Non-Supplemented Patients
Lowest serum magnesium level (mean) (mmol/l)	0.59 A	0.47 A
Lowest serum potassium level (mean) (mmol/l)	3.19	3.07
Urinary magnesium excretion (mean) (mmol/day)	8-10	3
Overall urinary potassium excretion (compared to normal)	decreased	decreased

Significance AA $p < 0.01$

TABLE 31: COMPARISON OF MEAN MAGNESIUM AND POTASSIUM LEVELS IN SERUM AND URINE OF MAGNESIUM SUPPLEMENTED AND NON-SUPPLEMENTED GROUPS OF PATIENTS RECEIVING CISPLATIN

Patients	Levels of N-acetyl glucosamine (x upper limit normal)			
No Supplements	Course 1	Course 2	Course 3	Course 4
A.B.	1.6	1.8	6.6	5.5
P.W.	1.7	-	2.2	3.8
M.W.	1.6	2.0	2.7	1.5
W.McA.	2.3	2.7	-	3.9
W.D.	0.3	1.6	0.9	1.6
J.H.	1.5	1.4	2.0	2.0
W.M.	1.9	2.2	3.6	3.0
P.McM.	2.5	3.5	4.6	-
K.F.	6.3	3.8	>14	>10
Supplements				
C.P.	1.4	1.9	1.4	2.6
K.McG	5.9	4.0	2.1	2.3
A.A.	0.9	0.9	0.7	0.5
W.M.	-	2.4	1.6	2.0
C.D.	0.9	1.1	1.2	1.5
R.L.	1.6	1.6	1.2	4.1
J.F.	0.3	1.9	1.1	1.4
P.McD.	0.6	0.5	0.9	1.0

Mean levels non-supplemented group to supplemented group comparing magnesium levels course 1 to course 3.

Significance $p < 0.01$

TABLE 32: LEVELS OF N-ACETYL GLUCOSAMINE IN MAGNESIUM SUPPLEMENTED AND NON SUPPLEMENTED GROUPS OVER 4 COURSES OF CISPLATIN

tubular damage. Beta-2-microglobulin is a low molecular weight protein present in the serum, filtered by the glomerulus and reabsorbed in the tubules. Measurement of its levels in serum and urine gives an estimate of overall renal function (Morgan, 1982). The results obtained show that, despite adequate hydration and good diuresis in these patients, there is progressive renal damage with, particularly, renal tubular damage occurring, although this is not gross enough to affect creatinine clearance or serum creatinine and urea levels.

A non-parametric t-test was applied to the figures obtained for N-acetylglucosamine levels, looking at changes for supplemented and non-supplemented groups and comparing the results obtained for courses two, three and four to those obtained for the first course. In general, the increase in N-acetylglucosamine levels above normal were higher in the non-supplemented group than in the supplemented group. A significant difference in N-acetylglucosamine levels between supplemented and non-supplemented groups is found in the third course of treatment when compared to the first course ($p < 0.01$). By the fourth course of treatment there are four patients in the non-supplemented group who are receiving magnesium supplements due to low plasma levels, and there is no statistical significance ($p < 0.11$) found between the groups when comparing N-acetylglucosamine levels in first and fourth courses. These preliminary results suggest that there is less renal damage occurring in the magnesium supplemented group, although progressive damage does occur in both groups.

It seems therefore, that the magnesium-supplemented group do

retain some of the supplements given, and have less microscopic renal damage over the four courses of treatment. Future studies should monitor the magnesium excretion between courses - which will allow assessment of whether or not supplements are being taken, and whether there is body retention of magnesium. Further work looking at N-acetylglucosamine levels in patients on varying doses of magnesium supplements will be important, and may allow evaluation of the effects of increasing the magnesium dose on renal function and treatment delays. The long term follow up of these patients will be of value in assessing the reversibility of the renal damage.

Magnesium Supplements

From the evidence of serum and urine magnesium levels it appears that patients may not be receiving sufficient magnesium supplements to maintain serum levels in the normal range (0.70 - 0.90 mmol/1). There may be several reasons for this which include insufficient supplementation, to meet the increased output of magnesium in urine and vomit; decreased absorption of the oral supplements due to cytotoxic effects on the intestinal mucosa; increased metabolic demands for magnesium; failure of the patients to take the oral supplements; or a combination of these.

There was no evidence of malabsorption in any patient, and there was no excessive loss of magnesium in the urine of the supplemented group. All patients experienced considerable nausea and vomiting during

treatment: the magnesium content of the vomit was not measured. It was not within the scope of this study to measure metabolic demands for magnesium, which may well be increased in the metabolic turmoil following aggressive chemotherapy, as discussed in Chapter 5 and in the first part of this Chapter.

Compliance of the patients in taking the supplements was difficult to assess. All patients received intravenous supplements according to the chemotherapy regime followed (Fig. 27). Many patients, however, did not volunteer or even admit when directly questioned by the doctor (although they might later confess to the dietician) that they were not taking the oral supplements when at home between courses.

There were a number of problems in finding an acceptable oral supplement. An initial trial using magnesium gluconate tablets (2 mmol magnesium/tablet) required five tablets to be taken three times daily to supply the required amount of magnesium. The tablets themselves were of medium size and quite palatable to the patients. The manufacturers, however, discontinued production. A search was made for an acceptable alternative magnesium supplement for use in this study. The Department of Pharmacy, Gartnavel General Hospital, made up a number of different suspensions of magnesium (Fig. 32). The first, a magnesium chloride mixture formulated at Glasgow Royal Infirmary, proved unacceptable to all but the most stoical patients due to its bitter metallic taste. Two further mixtures were tested; a magnesium chloride and a magnesium citrate suspension, both

1. Magnesium chloride mixture (Glasgow Royal Infirmary)

Magnesium chloride		40.6 g
Lemon syrup		60 ml
Raspberry syrup		60 ml
Distilled water	to	200 ml

expiry 2 weeks
provides 5 mmol magnesium in 5 ml

2. Magnesium chloride mixture (Strathclyde University)

Magnesium chloride		40.6 g
Sodium citrate		7.2 g
Orange syrup		120 ml
Distilled water	to	200 ml

expiry 2 weeks
provides 5 mmol magnesium in 5 ml

3. Magnesium citrate suspension (Strathclyde University)

Magnesium citrate		31.18 g
Magnesium chloride 1% w/v solution		12 ml
Orange syrup		40 ml
Chloroform water	to	200 ml

expiry 4 weeks
provides 5 mmol magnesium in 5 ml

Directions to patients

Take two teaspoonfuls three times daily after meals.

FIGURE 32: FORMULATIONS OF ORAL MAGNESIUM SUPPLEMENT MIXTURES USED

formulated at Department of Pharmacy, Strathclyde University, Glasgow. Of these, the second proved to be most palatable to the patients, and most acceptable to both medical and pharmacy staff as its expiry date was 4 weeks following formulation, thus allowing the supply for each patient between inpatient chemotherapy cycles to be given to the patient on discharge from the ward. This helped to avoid problems when patients were seen at outpatient clinics by medical staff other than those directly involved in the study, who might omit to provide a further supply of supplements for them.

A number of patients, however, felt after five days as an in-patient receiving Cisplatin, with the accompanying anorexia, nausea and vomiting, that to take an unpleasant-tasting mixture three times a day, was too difficult to do. In some cases, the taste of the supplements added to the nausea and anorexia experienced; and to many patients the supplements provided no immediately obvious benefits for them.

That some patients did take the supplement is shown by the improved levels of plasma magnesium in the supplemented group. However a priority for the future must be to find a palatable oral supplement for use between treatment cycles.

Discussion and Conclusions

There is no evidence that magnesium supplements have any adverse

effects on final outcome or have any effects on tumour growth. Indeed, although not statistically significant, patients may benefit from magnesium supplementation with fewer treatment delays, fewer neutropenic episodes and with improved electrolyte balance for potassium and magnesium. Renal damage may also be less in patients receiving magnesium supplements. This work contradicts the evidence presented by Parsons et al. (1972) which suggested that magnesium deficiency may benefit the host by reducing tumour growth and causing tumour regression. Following that suggestion, Mills (1974) proposed that the induction of a state of magnesium deficiency in the tumour-bearing host, followed by magnesium repletion with cytotoxic or radioactive drugs linked to magnesium supplements, would result in tumour regression with no deleterious effects on the host.

On the contrary, the results obtained agree more with the views of Blondell (1980) who demonstrates that on a world-wide basis the levels of magnesium present in water, food and air are inversely proportional to the cancer mortality for each region studied. Magnesium supplements would, in his view, be positively beneficial.

The use of magnesium supplements does maintain more normal levels of serum magnesium and potassium during treatment, and despite magnesium losses in the urine there is conservation of some of the magnesium administered. It appears also that there are marginal benefits from magnesium supplements with patients having fewer neutropenic episodes and hence fewer treatment delays, and less

microscopic renal damage, as shown by N-acetylglucosamine and Beta-2-microglobulin levels. The reasons for these beneficial effects are obscure: it may be that the intracellular and intramitochondrial role of magnesium is particularly important in leucocytes and in renal tubular cells; deficiency of magnesium, which is the second most abundant intracellular cation, may affect these cells more than some less metabolically active cells which are slower to reflect changes in intracellular composition. From the animal studies, the kidney is particularly susceptible to Cisplatin damage.

The effects of Cisplatin on appetite, nausea, vomiting, weight loss and anaemia are not improved by magnesium supplements. These effects are most clearly seen in those patients with the narrowest therapeutic margin for the drug: the patients who received "high dose" Cisplatin, and those who had pretreatment radiotherapy. All of these patients had neutropenic episodes and low magnesium levels, and may have benefitted from increased magnesium supplementation.

Those patients with most weight loss had lowest dietary intakes and most anorexia. The effects of Cisplatin on dietary intake have been shown to be prolonged in some patients, with very few days of normal intake between courses of treatment to compensate for the anorexia.

There is general nutritional depletion in most patients receiving Cisplatin for teratoma, most of whom are young men who were fit and

healthy prior to developing tumours. In the past this has been allowed to pass unnoticed, since if there is complete response to treatment patients quickly regain appetite and weight. This was seen in the patient who did gain weight during the study and who had complete response to treatment, and confirms the conclusions of Chapter 5. Nutritional depletion should, however, now be regarded more seriously as many patients lose weight, often more than 10% body weight, and this is significant nutritional depletion, which may contribute to immune suppression, decrease the therapeutic margin for chemotherapy, and may add to the general malaise of the patient.

The decreased magnesium intake together with the nausea and vomiting and increased magnesium excretion - which was found in all patients on this study, will contribute to the hypomagnesaemia which occurs in most patients receiving Cisplatin for teratoma. Supplements of magnesium are necessary and of benefit to patients and it will be important to find an acceptable, palatable oral supplement. MacAuley et al., (1982) suggest routine intravenous supplementation of magnesium of 12 mmol daily during in-patient treatment, for all patients receiving Cisplatin. However, it is difficult to see how this will compensate for the great decrease in dietary intake of all nutrients, including magnesium, during and between courses of treatment, which has been shown in these patients.

It will be important also to look for evidence of myocardial problems in hypomagnesaemic patients. Williams & Whitehouse (1979)

report a 10% incidence of cardiac arrhythmias in patients receiving Cisplatin. However none of the patients studied showed overt evidence of myocardial damage; routine electrocardiographs or cardiac function studies were not undertaken.

In summary, therefore, magnesium supplements are of no harm and may be of benefit to the patients by promoting fewer neutropenic episodes, fewer treatment delays and less damage to renal function. There is no evidence that supplements adversely affect outcome of treatment, rate of fall of tumour markers, or have any positive effects on the incidence of anorexia, nausea and vomiting or of anaemia requiring blood transfusion.

Appetite and dietary intake are depressed by Cisplatin treatment, and lead to weight loss and nutritional depletion.

Further studies should examine the effects of general nutritional supplementation on patients' outcome, side effects of treatment and well-being. Suitable oral magnesium supplements should be investigated and tested, as the supplements in the present study are unsuitable. Future work should also evaluate the effects of increasing levels of magnesium supplements on treatment delays and renal function. The effects of magnesium depletion on cardiac function, bearing in mind the evidence of myocardial damage from the animal experiment in Chapter 5, should be carefully examined. Future work should also look at ways of improving appetite, perhaps using prednisolone to stimulate appetite between courses (see Chapter 7).

All patients receiving Cisplatin should be routinely monitored for serum levels of magnesium and potassium. The trace metals have been shown to remain within normal limits during treatment, and monitoring and supplementing of these is not routinely required for every patient. All patients should receive adequate magnesium supplements and intravenous and oral supplements should be considered, with the level of supplementation titrated against the plasma magnesium levels; and the effects of a normal serum magnesium on outcome, treatment delays and renal function recorded to see if it is beneficial. Some patients should be considered for more general nutritional supplements of calories, protein and vitamins and the effects of these on treatment toxicity and outcome should be monitored. The method of assessment using 24 hour dietary recall histories (as discussed in Chapter 2) would be of value in selecting appropriate nutritional supplements.

Renal function should be monitored using the more sensitive N-acetylglucosamine and Beta-2-microglobulin assays rather than the conventional serum urea and creatinine or creatinine clearance estimates, which do not reflect early, and possibly reversible, renal damage. The reversibility of any renal damage shown by Beta-2-microglobulin and N-acetylglucosamine levels should also be looked at in patients who have successfully completed Cisplatin treatment.

In conclusion, Cisplatin is indeed a useful and successful cytotoxic drug, provided that it is treated with respect, and adequate monitoring and supplementation of patients is performed.

SECTION 3: METHODS OF IMPROVING THE NUTRITIONAL STATUS OF CANCER PATIENTS

CHAPTER 7: ANOREXIA AND APPETITE STIMULATION

Introduction

Anorexia is a major problem in cancer patients and contributes to cachexia, malnutrition, weight loss and general malaise (Chapter 1). A survey in the Department of Clinical Oncology, Gartnavel General Hospital, Glasgow revealed a 43% incidence of this complaint in 110 consecutive oncology outpatients (Willox et al.,1984). This agrees with the 42% incidence of anorexia found in a study of cancer patients by a general practitioner in Southampton (Woodbine, 1982).

Patients and relatives are often extremely worried by the lack of appetite, and are eager to try any measures to improve it (Theologides, 1976). If the cancer persists, improved nutrition will allow more aggressive treatment of it (Wesdorp et al.,1981); and a logical step towards improving nutritional status would be by stimulating appetite.

Appetite stimulants have been in use for many years to treat a variety of conditions; although there have been very few clinical trials of their effectiveness in cancer patients, despite the frequency of anorexia in this group.

Among proposed appetite stimulants are hormones; and thyroid extract and insulin have been shown to increase food intake in

experimental animals (Garattini et al., 1980; Williams, Williams & DeWitt, 1966; Morrison, 1973). The mechanism of action of these hormones on appetite stimulation has not been elucidated. There may be a direct effect on the feeding and satiety centres, or changes in host and tumour metabolism causing appetite alteration. The effectiveness of these hormones on appetite stimulation in man, and particularly in cancer patients with altered metabolic responses, is not known (Garattini et al., 1980).

Some of the anabolic steroids have been used and are effective in anorexia and cachexia. These include methylandrostenolone-enantate and androstanazol; however no controlled trials of their effectivness have been performed. Methyltestosterone increases body weight and stimulates appetite, although side effects such as masculinisation are a problem (Fruehan & Frawley, 1963).

The antiemetic groups of drugs improve appetite by preventing or decreasing nausea and vomiting. Haloperidol, a butyrophenone, relieves radiation-induced vomiting, nausea and anorexia in 75-96% patients when compared to placebo (7.5-20%), and has few side effects (Cole & Duffy, 1974). It may also be effective in relieving D-amphetamine-induced anorexia (Garattini et al.,1980). Phenothiazines prevent vomiting in patients receiving chemotherapy or radiotherapy and increase the rate of eating (Strain, 1981). Their side effects of hypotension and extrapyramidal symptoms make them unsuitable for use purely to stimulate appetite. Metochlopramide which acts via mainly

peripheral mechanisms to prevent nausea and vomiting, has very little effect on appetite (Middleton, 1972).

Delta 9 tetrahydrocannabinol has some antiemetic effects in patients receiving chemotherapy; and has analgesic, euphoric and appetite stimulating effects. Holland et al. (1977) reported that thirty-four patients with advanced cancers had stimulation of appetite, weight gain and mood elevation after receiving delta 9 tetrahydrocannabinol. However 25% found unpleasant side effects such as dizzyness, somnolence and mental dissociation.

Among the antidepressant drugs which produce documented appetite stimulation are lithium and Amitriptyline. Amitriptyline may produce its effect via its role as a serotonin antagonist, serotonin being an important neurotransmitter with effects on the feeding and satiety centres (Morley & Levine, 1983). Both these drugs have produced weight gains in non-cancer patients (Strain, 1981; Garattini et al., 1980). The benzodiazepines increase food intake in experimental animals (Randall et al., 1960) and are known to produce weight gain and increased appetite in man (Strain, 1981). The effect of the major and minor tranquillisers on relief of anxiety and alteration of mood is well known; however there is debate as to whether it is the relief of anxiety or the direct serotonin antagonist effects of these drugs which causes the appetite improvement (Garattini et al., 1980; Strain, 1981). Antihistamine agents are used to prevent nausea and vomiting

associated with cancer treatment. A number of these drugs are also serotonin antagonists. Cyproheptadine, an antihistamine and serotonin antagonist, is effective in stimulating appetite in asthmatic, underweight children and in underweight adults; with most improvement and weight gain seen in the first week of treatment (Silverstone & Schuyler, 1975; Pawlowski, 1975; Toth & Szonyi, 1976). There have been, to date, no clinical trials of cyproheptadine as an appetite stimulant in cancer patients (Garattini et al., 1980).

Pizitofen, a drug used to treat migraine, is also an antihistamine and serotonin antagonist. It was found to be an effective appetite stimulant in patients with cancers of the brain or skull; and has been proposed as an appetite stimulant for all patients with cancer-induced anorexia (Garattini et al., 1980; Krause, Greep & Fisher, 1979).

Aminoguanidine, a histaminase inhibitor, was found to increase appetite in patients with medullary carcinoma of the thyroid. This tumour produces large amounts of histaminase (Baylin et al.,1970). Its value for other forms of cancer would be limited.

Among the compounds found by chance observation to improve appetite are the corticosteroids. These compounds have been used empirically for many years, and with reputedly good effect, in cancer patients receiving radiotherapy,and in those patients approaching the terminal stages of their disease (Oliver, 1983). High dose steroids such as dexamethasone and methylprednisolone have been used as

effective antiemetics in patients receiving Cisplatin chemotherapy and in those receiving chemotherapy for lymphomas (Lee, 1981; Aaprot & Alberts, 1981). However, there have been no controlled trials of the effectiveness of low-dose corticosteroids as appetite stimulants.

The aims of this study were to examine the effectiveness of a corticosteroid (prednisolone) against placebo in appetite stimulation, weight gain, calorie intake and well-being in cancer patients with anorexia.

Methods

Patients were entered into the study if they complained to the doctor or dietician of poor appetite or weight loss. A check was made on each patient that there was no contraindication to steroid therapy.

The study was conducted as a double blind crossover study; the patient being randomised by the pharmacist to receive prednisolone or placebo in the first three week study period, then receiving the alternative treatment in the the second three week study period. Patients randomised to Arm A received prednisolone 5 mg, t.i.d. for 2 weeks; then 5 mg. b.d. for 2 days, 5 mg. daily for 2 days and nil for 3 days. This dose of prednisolone was chosen to minimise side effects; and a fixed dose was used to simplify treatment. After the first study period, patients received placebo tablets in the same way. Patients randomised to Arm B received, first, placebo tablets, 1 tablet

t.i.d. for 2 weeks; then 1 tablet b.d. for 2 days; 1 tablet daily for 2 days and nil for three days. After the first three week study period,these patients received the prednisolone course. The placebo tablets were provided by Roussel Laboratories and were an inert, chalky mixture which were identical in size, shape and markings to the prednisolone tablets. Neither the patients nor the observers (doctor and dietician) knew which course of tablets was being assessed. Patients were asked whether they would try two different types of tablets, and assess the effectiveness in improving appetite. If they consented to the trial, the pharmacist randomised them to Arm A or Arm B. Patients were told to stop taking the tablets, should they notice any side effects or upset while taking them.

Assessment was performed prior to treatment, after two weeks of treatment and after five weeks. The assessments were timed to coincide with clinic visits and were made at the same time of day at each visit. On each occasion anthropometric measurements of weight, midarm circumference and triceps and scapular thickness were performed. Weight was measured using the same set of scales on each occasion, the patients wearing lightweight clothing and footwear. Weight changes of less than 1 kilogram were not considered to be significant. Midarm circumference was measured by finding the midpoint of the upper arm between acromion and olecranon process, with the arm hanging loosely by the side, the elbow bent. From the midpoint, a tape measure was used to determine the circumference of the arm (Plate 4). The non-dominant arm was used in most patients, although Burgert and

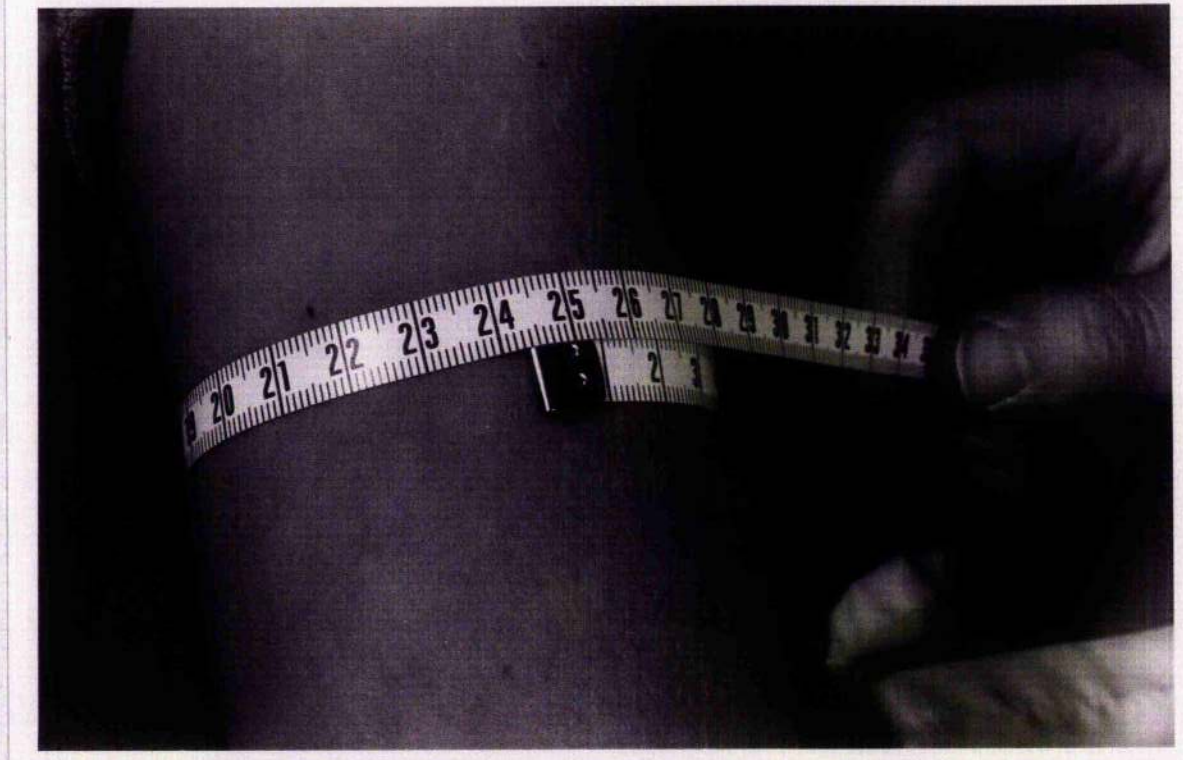

PLATE 4: MEASUREMENT OF MIDARM CIRCUMFERENCE

Anderson (1979) have shown no statistical difference between measurements using dominant and non-dominant arms, except in extreme cases where the dominant arm has been developed at the expense of the other, as in racquet games. From the midarm circumference, the midarm muscle circumference can be calculated.

Triceps skinfold thickness was measured using Harpenden skin calipers. With the patient's arm hanging loosely by his side, the skin 1 cm. above or below the midpoint of the arm was pinched, and the skin calipers placed on the midpoint for 3 seconds and the result then read (Plate 5). An average of at least three readings were used, or, preferably, measurements continued until three identical readings were obtained. Subscapular skinfold thickness was measured in a similar way 1 cm. below the tip of the scapula. Historically, four sites have been used to estimate skinfold thickness: subscapular, triceps, iliac and biceps; and although Durnin & Womersley (1974) recommend the measurement of all four sites with averaging of the result, the triceps and subscapular skinfold thicknesses have been shown by Burgert & Anderson (1979) and Grant et al. (1981) to be sufficient for estimating skinfold thickness. Triceps and subscapular sites were used in this study as it was difficult in some patients to measure all four sites in the time available at the clinic. Two observers took all the measurements in the study; the same observer saw the same patient on each occasion.

A 24 hour dietary recall history was recorded and computer analysis of this gave protein, carbohydrate, fat and calorie content of

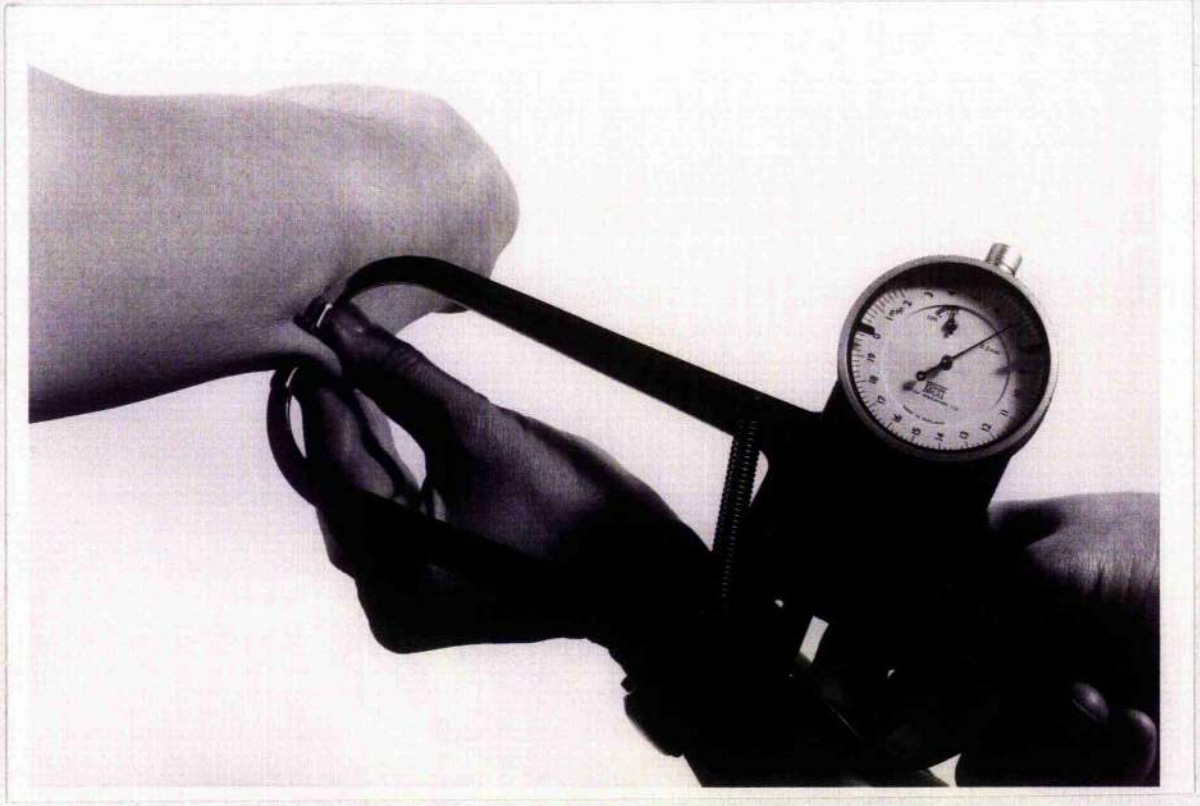

PLATE 5: MEASUREMENT OF TRICEPS SKINFOLD THICKNESS USING HARPENDEN SKIN CALIPERS

the diet (see Chapter 2). Each patient completed a questionnaire and visual analogue scales which assessed appetite, nausea, vomiting, mood and well-being (see Figs. 33 & 34). Intake of calories was assessed in relation to the preceding recorded intake and differences of less than 100 Kcal were not regarded as a significant change in intake. Using the visual analogue scales, changes in each symptom were regarded as significant if the mark was greater than 1.0 cm. from the previous mark on the 10 cm. line.

Results

Of 61 patients complaining of poor appetite and agreeing to participate in the study, 41 were evaluable. Male:female ratio of the patients was 16:25; and ages ranged from 27 years to 80 years with a mean of 60 years. Twenty-three patients received no form of chemotherapy; and 18 patients received regular cycles of chemotherapy, timed to coincide with the study treatment periods. Patients had a variety of solid tumours with the gastrointestinal tumours forming the largest group (Table 33). Within tumour groups, patients were assigned to Arms A and B in similar proportions; although the use of crossover in the study ensured that each patient evaluated both arms of the study in any case. No patient had had recent surgery or was hypercalcaemic.

The 20 patients who were excluded from the study dropped out for a variety of reasons (Table 34). Six patients died while on study; 3 were admitted to hospital; and 4 had irregular cycles of chemotherapy

APPETITE STUDY

CODE: HOSPITAL NO.

NAME:

DATE OF BIRTH:

DIAGNOSIS:

CHEMOTHERAPY:
(Type and duration)

HEIGHT	BEFORE	2/52	5/52
DATA COLLECTED			
WEIGHT			
MID ARM CIRCUMFERENCE			
TRICEPS SKINFOLD			
SCAPULA SKINFOLD			
SYMPTOMS:			
APPETITE (Better Worse, Same)			
PAIN (Site, Type)			
VOMITING			
NAUSEA			
CONSTIPATION			
DIARRHOEA			
"INDIGESTION"			
FLATULENCE			
SIDE EFFECTS OF A or B			
24 HOUR DIETARY RECALL (See attached sheet)			
ANOREXIA ASSESSMENT (See attached sheet)			

FIGURE 33: FORM USED TO COLLECT PATIENT INFORMATION FOR APPETITE STUDY

CODE NAME DATE

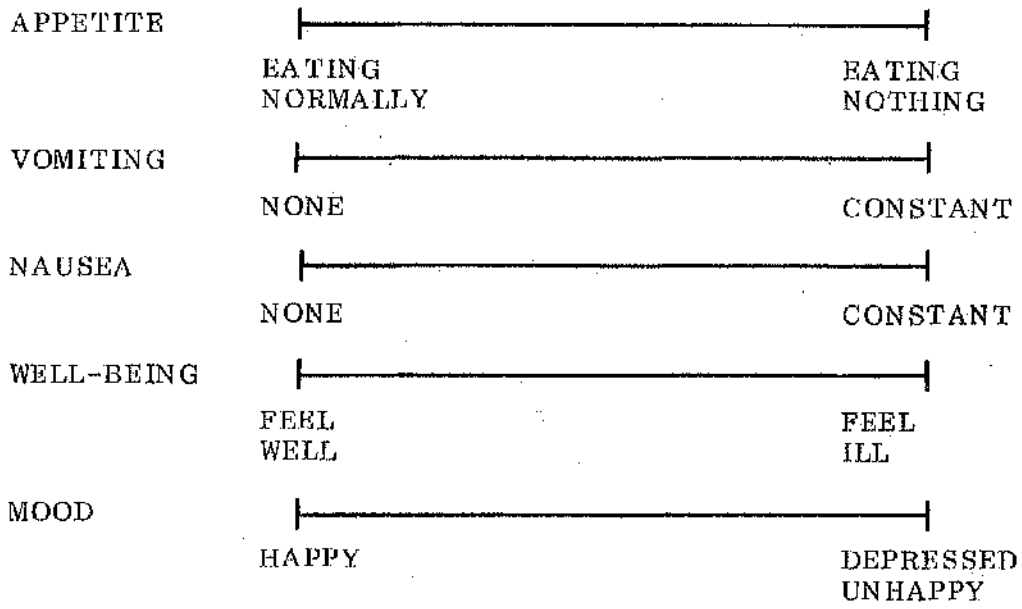

FIGURE 34: VISUAL ANALOGUE SCALE ASSESSMENTS

Tumour Sites	Number of patients
Gastrointestinal	20
Breast	8
Lung	3
Ovary	2
Others	8

TABLE 33: TUMOUR TYPES OF PATIENTS PARTICIPATING IN THE APPETITE STUDY

REASON FOR EXCLUSION FROM STUDY

Stopped tablets	Chemotherapy (11)		No Chemotherapy (9)		Total (20)	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Died	1	2	2	1	3	3
Admitted to hospital	1	0	0	2	1	2
Stopped tablets	1	2	2	2	3	4
Irregular chemotherapy	2	2	-	-	2	2

Of the 7 patients who stopped taking tablets --

1 had no further anorexia

4 found "no change" with tablets
(Arm B - placebo tablets given first)

2 found improvement with prednisolone
(Arm A) but "no change" on placebo when crossed over
- so stopped tablets.

TABLE 34: REASONS FOR STOPPING APPETITE STUDY (20 PATIENTS)

which did not coincide with the study period and hence invalidated the results. Of the 7 patients who stopped taking the tablets, one patient felt better before taking any tablets and so did not start the study; four patients on Arm B had no change in appetite during the first treatment period of the study, and were unwilling to continue. Two patients on Arm A found no continued improvement when changed to placebo tablets, and stopped taking them. In all of these patients, appetite returned to pretreatment levels or became worse.

Response rates within the tumour groups and the chemotherapy and the no-chemotherapy groups reflected the response rates for the entire group of patients (Tables 35, 36, 37). The Chi squared test of statistical significance was applied to the percentages obtained.

In all groups, appetite was significantly ($p < 0.001$) improved in patients receiving prednisolone first, compared to those receiving placebo first (82% and 50% respectively). Patients on Arm A showed decreased appetite when crossed to receive placebo tablets (from 82% to 60%, respectively, with appetite improvement, $p < 0.01$). Patients on Arm B showed improved appetite when crossed over to receive prednisolone (50% to 78% respectively, $p < 0.01$).

Weight did not change significantly during either period of the study. This agrees with the anthropometric data collected, which showed no change over the 6 weeks of study.

Intake did not differ significantly overall; however the

RESULTS

	ARM A (23)		ARM B (18)	
	Prednisolone First	Placebo Second	Placebo First	Prednisolone Second
Appetite improved	19[AB] (82%)	14[B] (60%)	9[AC] (50%)	14[C] (78%)
Weight gain	13 (56%)	10 (43%)	9 (50%)	8 (44%)
Increased intake	16 (69%)	15 (65%)	10 (56%)	12 (67%)
Wellbeing	11[D] (48%)	12 (52%)	4[D] (22%)	6 (33%)

[AA] [CD] $P < 0.001$ [BB] [CC] $P < 0.01$

TABLE 35: RESULTS OF ALL EVALUABLE PATIENTS IN APPETITE STUDY

NON CHEMOTHERAPY RESULTS (23 Patients)

	ARM A (13)		ARM B (10)	
	Prednisolone First	Placebo Second	Placebo First	Prednisolone Second
Appetite improved	10^{AB} (77%)	7^{B} (54%)	4^{AC} (40%)	7^{C} (70%)
Weight gain	8^{D} (62%)	6 (46%)	3^{D} (30%)	4 (40%)
Increased intake	8 (62%)	9 (69%)	6 (60%)	5 (50%)
Wellbeing	7^{E} (54%)	8 (62%)	2^{E} (20%)	3 (30%)

$^{AA}_{DD}_{EE}$ $p < 0.001$ $^{BB}_{CC}$ $p < 0.01$

TABLE 36: RESULTS OF PATIENTS RECEIVING NO CHEMOTHERAPY DURING APPETITE STUDY

CHEMOTHERAPY RESULTS (18 Patients)

	ARM A (10)		ARM B (8)	
	Prednisolone First	Placebo Second	Placebo First	Prednisolone Second
Appetite improved	9^{A} (90%)	7 (70%)	5^{AB} (63%)	7^{B} (88%)
Weight gain	5^{C} (50%)	4 (40%)	6^{C} (75%)	4 (50%)
Increased intake	8^{DE} (80%)	6^{D} (60%)	4^{EF} (50%)	7^{F} (88%)
Wellbeing	4^{G} (40%)	4 (40%)	2^{G} (25%)	3 (38%)

$^{AA}_{EE}_{FF}$ $p < 0.001$ $^{BB}_{CC}_{DD}$ $p < 0.01$

TABLE 37: RESULTS OF PATIENTS RECEIVING REGULAR CHEMOTHERAPY DURING APPETITE STUDY

chemotherapy group showed a significant ($p < 0.01$) difference in intake between prednisolone and placebo groups. The trend for the entire group was towards increased intake when on prednisolone.

Well-being, which assessed whether the patients felt well or ill, and happy or depressed and miserable, was significantly ($p < 0.001$) increased in all of the prednisolone groups, compared to placebo. This feeling was maintained, or increased slightly when patients on Arm A switched to receive placebo; those receiving Arm B increased the feeling of wellbeing when given prednisolone, although the change was not significant.

None of the patients reported any side effects from the treatment.

Discussion and Conclusions

The results show that prednisolone is significantly better than placebo in improving appetite in cancer patients in the short term. There is a major placebo effect (50% overall), and this, together with the trend towards improved well-being when on prednisolone, and the well-known euphoric effects of prednisolone on predisposed patients, suggests there is a psychological component in the anorexia of at least a proportion of cancer patients.

As would be expected, the period of study is too short for any increased protein or fat synthesis to be reflected in changes in anthropometric measurements, and future studies of this duration could

dispense with measurements of skinfold thickness in assessing effectiveness of therapy. There is no greater weight gain in patients on prednisolone compared to placebo, and this suggests there is no significant water retention on this dose of prednisolone, and over this length of study.

The major drawback to using prednisolone as an appetite stimulant is its long-term effects. Although there is an initial stimulation of appetite, steroids are catabolic hormones in the long-term, and may induce dependence, with upsets in fluid and electrolyte balance and Cushingoid side effects. The dose of prednisolone used was chosen in an attempt to minimise these unwanted problems.

A future study should examine the effectiveness of prednisolone used over a longer period of time in those patients who show an initial response to it with increased appetite and dietary intake. The study would examine the duration of effectiveness of prednisolone on appetite stimulation, the effect on nutritional state and on survival, and look for any side effects from steroid administration. It may be that, in these patients, the drawbacks associated with long-term steroid administration will be outweighed by the benefits of improved nutritional state, with increased safe therapeutic margin for cancer therapy, and, perhaps, prolonged survival.

Other studies should examine the effectiveness of other appetite stimulants such as cyproheptadine and pizitofen against prednisolone

on appetite and dietary intake in cancer patients. This study could also be extended to prolong the arm of the drug which proves to be most effective and to study its usefulness in the long-term.

SECTION 4: CONCLUSIONS

CHAPTER 7: GENERAL CONCLUSIONS AND FUTURE WORK

The aims of this thesis were to examine in detail some of the nutritional and metabolic problems of cancer patients.

The problem of nutritional assessment was considered and dietary histories, clinical evaluation and biochemical estimations of deficiencies were compared and found to closely agree in assessing nutritional state in patients with significant depletion. The patients with deficiencies identified by all three methods were those who were most nutritionally depleted. Clincial signs of deficiency and biochemical tests of body status of vitamins, minerals and nutrients are shown to reflect long-standing nutritional deficiencies; dietary recall histories will give an early indication of potential nutritional problems and will reflect improvements and fluctuations in dietary intake and nutritional state. From the results obtained, the best way of assessing nutritional state is to combine clinical, biochemical and dietary intake information. Weight loss and rate of weight change, together with assessment of brittle nails, dry skin and dry eyes are the most useful clinical examinations; 24 hour dietary recall histories provide information on recent intake and can be used with intake histories taken on several previous occasions to assess changes in intake and hence nutritional state; and biochemical estimations of serum total protein, albumin, calcium, zinc and iron are the most useful and reliable laboratory tests. All of these will together give a clear picture of a patient's nutritional status.

The results obtained show good correlation between dietary

deficiences of energy and protein, and clinical measurement of weight loss and biochemical measurement of serum total protein and albumin levels. From these findings it is concluded that the 24 hour dietary recall histories with computer analysis provide a fast, easy and reliable method of anticipating future nutritional problems and thus allow their early correction. Repeated dietary histories give an estimate of present dietary intake, and comparison with previously recorded intakes will allow assessment of nutritional status at any particular time, and permit fluctuations in nutritional state over periods of time to be recorded. Low or decreasing intakes on a number of occasions indicate deteriorating nutritional status; increasing intakes indicate improvements in nutritional state; stable levels of intake must be used with serial weights and other nutritional asessments to indicate nutritional status for each individual patient. In assessing nutritional state of cancer patients, tumour type and spread, and chemotherapy or other form of treatment must be considered together with the other nutritional assessments used.

Future studies using dietary assessments to pinpoint likely deficiencies could then assess, with the techniques described above, the value of early nutritional supplementation in slowing or preventing the metabolic decline to cachexia. The effects of early supplementation on tolerance to cytotoxic treatment and its side effects, and on tumour growth should also be evaluated.

Section two looked at the effects of cancer and chemotherapy on

the nutritional and metabolic status of cancer patients and tumour-bearing animals.

A preliminary study of muscle biopsies in four cachectic cancer patients showed considerable disruption of the muscle fibres with particularly striking changes seen in the mitochondria. These changes are distinctly different from the changes seen in starvation, disuse, ageing and acute illness, and appear to be cancer-specific. This illustrates the unique metabolic changes seen in cachectic cancer patients. Future studies would aim to look at the changes in patients with less extreme nutritional and metabolic disturbances; and in those who have had no treatment, to allow the effects of the tumour alone to be more easily evaluated.

The effects of cancer and chemotherapy on saliva production, composition and microflora content, which may account for some of the dry mouths, difficulties in chewing, swallowing and digesting, loss of taste, decreased enjoyment of food, and anorexia seen in cancer patients, were studied in a group of cancer patients before starting treatment, and after one and three months of cytotoxic treatment. Saliva volume, flow rate, amylase and IgA content decreased as treatment progressed; and the incidence of bacterial and candidal infection increased over the period studied. Combinations of drugs which include Adriamycin, Cisplatin and Mitomycin C were particularly implicated in the increasing carriage of micro-organisms. Drug combinations including Cyclophosphamide and Methotrexate were more

likely to produce decreased saliva flow rate and decreased saliva volume, causing dry mouths. The significant incidence of decreased saliva production and increased micro-organism carriage in the cancer out-patients studied, suggests that time should be taken to regularly examine the mouths of these patients, to try to alleviate dry mouths, and treat and prevent dental caries. The mouth should always be considered a source of potentially virulent micro-organisms which may breech impaired host defences and produce life-threatening infections. Future work should examine the changes in saliva production and microflora in relation to alterations in taste sensations and the incidence of anorexia found in cancer patients.

The effects of tumour growth and chemotherapy on the metabolic and nutritional status of tumour-bearing Wistar rats were studied. Cyclophosphamide and Cisplatin were the cytotoxic drugs used. Drugs alone and in combination with tumour, and tumour alone groups were examined. All showed metabolic upset with weight loss, decreased carcass nitrogen content, decreased plasma protein, albumin and iron concentrations and increasing levels of ketone bodies and of liver enzymes. The tumour itself caused the greatest metabolic insult. Improvement in the metabolic state occurs when the tumour responds to treatment; however if there is no response to treatment there may be increased metabolic problems caused both by tumour growth and the cytotoxic drugs. This study provides a useful animal model for the human problem of cachexia and could be used for further studies of drugs which may modify tumour growth and the effects of tumour

on metabolism, while minimising unwanted drug effects. The effects of other cytotoxic drugs on metabolism may also be studied in the animal model, and a prediction of the likely nutritional and metabolic problems associated with their use in cancer patients may be made.

The effects of Cisplatin on nutrition and metabolism were studied in more detail in patients with teratoma who received Cisplatin as part of a chemotherapeutic regime. Preliminary animal studies showed that Cisplatin affects mitochondrial function particularly in the kidney, but also in heart, skeletal muscle and liver tissue, and these effects are dose dependent. The electron microscopy studies showing mitochondrial disruption may help to explain some of the metabolic alterations found in the rats receiving Cisplatin: the intracellular disruption accounting for the weight loss, decrease in nitrogen content and in plasma proteins, and the altered levels of liver enzymes in the serum. Future animal studies should use electron microscopy and histochemical methods to look at the intracellular structure of organs from animals with tumour, Cisplatin or tumour, and Cisplatin who show weight loss and nutritional depletion. This could be extended to look at other drugs using this model. It would then be possible to see whether a common intracellular mechanism is producing the metabolic alterations found, and ways of preventing the intracellular problem and, perhaps, the metabolic disturbance may be sought.

Clinical studies looking at Cisplatin examined the effects of the

drug, in combination chemotherapy, on trace metal levels in patients with teratoma. Levels of the trace metals were measured during the courses of treatment; and comparisons between courses were made. Cisplatin was shown to induce nausea, vomiting and anorexia in most patients. Trace metal levels were not particularly altered between first and fourth courses of treatment. Plasma iron levels did rise in most patients during and between courses of treatment. Iron levels were highest in those patients who required blood transfusions for anaemia: the cause of the anaemia being failure of iron utilisation following drug induced damage to erythroid precursors in the bone marrow.

Serum magnesium levels fell in the majority of patients over the four courses of treatment, and in some cases supplementation was required to treat symptoms of hypomagnesaemia. Similar falls in serum magnesium were seen in patients with ovarian carcinoma treated with Cisplatin in a different combination of drugs.

Further clinical studies compared the routine use of magnesium supplements during and between the first four courses of Cisplatin treatment with the standard regime which contained no supplements. Patients receiving routine supplements, which included intravenous supplements during inpatient chemotherapy and oral preparations between courses, showed no difference in rate of fall of tumour markers, response to treatment, or tumour growth rate as determined clinically, radiologically and biochemically, compared to non

supplemented patients. Nausea, vomiting and anorexia were found to occur with similar frequencies in both groups. The anorexia, which lasts for 8-12 days following intravenous Cisplatin administration, was mirrored by decreased dietary intake which affected all nutrients equally. Although not statisically significant, due to the low numbers of patients studied, there appears to be increasing duration of anorexia and poor dietary intake (which falls in some cases to less than 40% normal) with successive courses of treatment. This cumulative effect of Cisplatin on appetite causes some patients to become significantly nutritionally depleted and may decrease the safe therapeutic margin for Cisplatin in these individuals. Weight loss was common and paralleled decreased dietary intake and anorexia: those patients with the greatest weight loss had the poorest intakes and the most prolonged anorexia. Weight loss also correlated with poor response to treatment; the group of patients who showed least response to treatment had the most weight loss. From these observations it would indeed appear that nutritional state is determined both by tumour growth and by the effects of cytotoxic drug treatment, as suggested by the animal studies on Cisplatin and metabolism. If there is response to treatment, nutritional state improves; if there is no response, the combined effects of tumour and drug on nutritional state cause continued decline. Further studies should examine the usefulness of early nutritional support in preventing extreme depletion and permitting prolonged, aggressive chemotherapy.

The magnesium supplemented group had fewer treatment delays due to

neutropenic episodes than the non-supplemented group. This is important in allowing adequate and regular treatment to be given for what is often a successfully treated tumour. Serum magnesium levels were significantly higher, and serum potassium levels showed smaller falls, in the supplemented patients. Several of the non-supplemented patients required magnesium supplements by the end of the third course of treatment for serum magnesium levels below 0.45 mmol/l, and to prevent symptoms of hypomagnesaemia.

Renal function, as determined by serum creatinine and urea levels and by creatinine clearance levels, showed little change over the four courses of treatment. However measurement of N-acetyl glucosamine levels in urine showed deterioration in renal tubular function over the four courses of treatment. There was significantly less deterioration, however, in the supplemented group by the third course of treatment. This is an important observation since Cisplatin is an extremely useful cytotoxic drug whose use is limited by its nephrotoxicity. Future work should use N-acetyl glucosamine to monitor the reversibility of renal changes induced by treatment; and should continue the use of magnesium supplements to confirm their beneficial effects on renal function.

The methods of magnesium supplementation used were intravenous and oral. Both have advantages and disadvantages. The intravenous route is convenient when the patient is receiving inpatient intravenous chemotherapy; however it is difficult to administer in the sixteen

days between treatment courses, when the patient is at home. Oral supplements are ideal for outpatients; less useful for inpatients who are vomiting. There was poor compliance in some patients taking the oral magnesium mixtures supplied for the study. Part of the problem was the metallic taste of the supplements; part was the residual nausea and anorexia following discharge from hospital. Future work should be directed to finding an acceptable oral magnesium supplement, possibly in tablet form. Further studies would be useful to compare the effectiveness of intravenous inpatient supplements alone, with continuous inpatient intravenous,and outpatient oral, magnesium supplements.

From the results obtained, if magnesium supplementation allows treatment with Cisplatin to continue regularly, with fewer delays between courses and less effect on renal function, and if a suitable magnesium supplement can be found, it will be possible to use the drug more effectively to combat even the most aggressive tumours, while keeping the safe therapeutic margin of Cisplatin as wide as possible.

Section three looked at one way of improving nutritional state in cancer patients, and examined the problem of anorexia and appetite stimulation. Anorexia was a major complaint in 43% cancer patients attending the oncology outpatients clinic at Gartnavel General Hospital. Prednisolone was found to be a highly effective appetite stimulant when used over a 2 week period. A 50% placebo response,

however, indicated the partial psychological basis for anorexia in some patients and demonstrated the power of the higher brain centres on the appetite centre. Further studies should examine the effectiveness of prednisolone in the long-term, in patients who have an initial response to treatment. Other appetite stimulants may also be compared against prednisolone, using a similar double-blind crossover study design.

In conclusion, this thesis has examined the implications of cancer and its treatment on some areas of nutrition and metabolism in patients and animals. There remains a great deal of work to be done, and many of the results obtained in this work merely provoke further questions.

The studies presented here demonstrate some of the far-reaching nutritional and metabolic effects of cancer and chemotherapy in man and experimental animals; and present a method for easy identification and early anticipation of nutritional and metabolic problems. Further work is required to assess the value of prompt and adequate nutritional support in preventing the metabolic alterations and nutritional deficiencies seen in the cancer patient.

It is sincerely to be hoped that the state of cancer cachexia will become a comparative rarity, and that doctors treating cancer may no longer have to watch as their patients grow "pale, and spectre-thin and die" (Keats, 1820).

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