



NUTRITION AND CANCER

Studies on nutritional abnormalities, nutritional
support and protein metabolism in malnourished
cancer patients

JAMES MARSHALL TROTTER,
M.B., B.S. (Adelaide), F.R.A.C.P.

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JE VIS DE BONNE SOUPE

ET NON DE BEAU LANGUAGE

MOLIERE

LES FEMMES SAVANTES (1672)

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PREFACE

The work presented in this thesis was undertaken whilst the author was working, first as Oncology Registrar, then as Roussel Research Fellow, in the Department of Clinic Oncology, University of Glasgow, between February, 1978 and March, 1981. The clinical studies were undertaken on patients managed at Gartnavel General Hospital, Great Western Road, Glasgow, under the care of Professor K.C. Calman, Head of the Department of Clinical Oncology, University of Glasgow.

The studies forming the thesis are presented as they were planned, namely, as a series of separate but inter-related clinical projects with a common theme related to investigating the frequency and nature of the malnutrition often seen as a complication of malignant disease and examining possible reasons for these abnormalities. The thesis is divided into four sections: 1. an introductory review of cancer cachexia; 2. clinical studies on the nutritional abnormalities in cancer patients and the effects of enteral nutritional support; 3. studies on aspects of protein metabolism in malnourished cancer patients (amino acid profiles, albumin metabolism and plasma exchange as an investigational method) and finally; 4. a concluding discussion of the thesis results. This approach has, of necessity, meant some repetition but this has been kept to a minimum.

A large number of individuals have been involved in helping with the many aspects of this thesis. I am indebted to them all, especially the many patients who endured a multitude of investigations without complaint. Patients gave verbal informed consent for each study.

Appendix I lists abstracts and publications related to the work presented

in this thesis. The number of co-authors of these publications gives an indication of the many people involved. The extent to which others were involved in individual projects is detailed in the acknowledgements.

J.M. TROTTER,
Royal Perth Hospital.
1987.

ABSTRACT

A series of studies to evaluate the nutritional and metabolic abnormalities and role of nutritional support in malnourished cancer patients have demonstrated the following: 1. In an oncology outpatient population, anorexia is the commonest symptom and the one that concerns patients the most. 2. Dietary recall histories have a role in detecting potential nutritional deficiencies in cancer patients and reveal that inadequate diets are very common. 3. The palatability of oral liquid dietary supplements differ between cancer patients and control groups and the preferences of individual patients need consideration when providing dietary advice. 4. The taste thresholds for salt and bitter basic taste sensations were significantly elevated in cancer patients. Such abnormalities play a role in taste preferences. 5. Multiple abnormalities of anthropometric and biochemical tests of nutritional status are present in cancer patients with weight loss but there are poor correlations between the anthropometric and biochemical data. 6. Enteral nutritional support in malnourished cancer patients usually failed to reverse the nutritional deficits even if positive nitrogen balance was achieved. This is unlike the syndrome of pure protein-energy malnutrition and consistent with the concept of a hypercatabolic state associated with malignancy. 7. The plasma concentration of C-reactive protein was frequently elevated in malnourished cancer patients, suggesting an associated acute phase response. 8. Amino acid analysis in malnourished cancer patients suggests there are three groups of cancer patients - (a) those with an acute on chronic catabolic state (high branched chain amino acids); (b) a normal response to protein-energy malnutrition (low branched-chain

amino acids) and (c) a hypercatabolic response (normal or high branch chain amino acids). 9. Studies of albumin metabolism in cancer also suggested cancer patients may be hypo or hyper-catabolic in response to weight loss as evidenced by high or low fractional catabolic rates of albumin. In addition, one of the causes of hypoalbuminaemia in cancer is a redistribution of albumin to the extravascular space. 11. It is postulated that host or tumour derived products might be the cause of the increase in catabolic rate in cancer patients and that plasma exchange may help to demonstrate the presence of such substances. Preliminary studies with plasma exchange are discussed.

STATEMENT

The author declares that this thesis contains no material which has been accepted for the award of any other degree or diploma in any University and that, to the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the text of the thesis. The author consents to the thesis being made available for photocopying and loan if applicable if accepted for the award of the degree.

J.M. TROTTER

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SECTION I

LITERATURE REVIEW OF THE NUTRITIONAL PROBLEMS
AND NUTRITIONAL SUPPORT IN CANCER PATIENTS;
METABOLISM IN NORMAL AND CANCER SUBJECTS AND
METHODS OF NUTRITIONAL ASSESSMENT.

"The small bones of his nose, the jawbone
and the sharp chinbone behind his pointed
beard were all clearly visible. His ears
had thinned and become no more than
flat pieces of cartilage. He had only
to dry up a bit more and turn a little
blacker and he'd be a mummy."

Alexander Solzhenitsyn

Cancer Ward (1968)

SECTION I



LITERATURE REVIEW

STUDIES OF THE NUTRITIONAL AND METABOLIC ABNORMALITIES IN CANCER

INTRODUCTION

The association of weight loss and wasting of body tissues with cancer has been known for thousands of years. Hippocrates was aware of the association of weight loss with illness and of the morbidity of malnutrition:

"If the convalescent gain not strength,
notwithstanding that he eats well, it
shows unfavourably."

Hippocrates - Aphorisms.

Malignant disease is a frequent cause of malnutrition in the western world. The resultant malnutrition is a common cause of morbidity and mortality in cancer patients. Indeed, Warren (1932) suggested that malnutrition was the commonest cause of death from cancer. After analysis of over 500 autopsies of cancer patients, 22% were considered by Warren to have died as a result of malnutrition. It might be noted, however, that Wilks (1868) failed to be convinced that cachexia was a feature of malignant disease after analysis of 2000 autopsies. This belief was held by many for at least 50 years (Ewing 1922). Strain (1979) reviewed the reported incidence of cachexia by various authors and the range was 8% to 84%. Interpretation of this data is difficult due to inadequate reportage of stage, ages, degree of weight loss and other

nutritional variables. There is now general agreement that a cachectic syndrome frequently occurs with malignant disease but there is controversy as to whether it is unique in any way, whether it is reversible and, if so, whether it is beneficial to correct the abnormalities.

Malnutrition in the cancer patient is often called cancer cachexia, a term which has been used to denote a combination of progressive wasting of body tissues, anorexia, marked asthenia, and anaemia (Costa 1977a). These signs and symptoms are, however, common to all forms of established protein-energy malnutrition but unlike uncomplicated protein-energy (P.E.) malnutrition, increased basal energy expenditure is a common feature of the wasting syndrome which accompanies malignant disease. Some authors included the increase in the metabolic rate in their definition of cancer cachexia (Waterhouse et al 1951). The rise in metabolic rate is in excess of that expected for the nutritional state of the individual. This distinction between "cancer cachexia" and uncomplicated P.E. malnutrition is important. The studies which form this thesis attempt to define the nutritional and metabolic abnormalities of cancer patients with a wasting syndrome.

METABOLIC ABNORMALITIES IN CANCER

The metabolic problems of cancer cachexia have been the subject of a number of reviews (Mider 1951; Fenninger and Mider 1954; Costa 1963, Costa 1977, Theologides 1970, Strain 1979, Heber et al 1986, Jeevanandam et al 1984, Burt et al 1984, Brennan and Burt 1981, Waterhouse 1981). Despite the wealth of published work, the pathogenesis of cancer cachexia remains obscure. Abnormalities of carbohydrate, fat and protein metabolism are all described in association with malignant disease, as well as an increase in BMR and basal energy expenditure.

Brennan (1977) discusses the differences between uncomplicated starvation and cancer cachexia and concludes: "... the tumour-bearing host seems less well adapted to respond to an added insult of starvation than the non-tumour bearing host. The non-tumour-bearing host has clearly defined mechanisms to conserve lean tissue mass and to preserve total body protein. The tumour-bearing host seems less well able to utilize these lean tissue conserving mechanisms and to decrease gluconeogenesis from protein stores in the presence of host starvation. This results in on-going lean tissue mass destruction. These aspects in a tumour-bearing host are invariably compounded by a decrease in intake and a variable decrease in efficient utilisation of ingested nutrient."

ENERGY METABOLISM

Increased energy consumption in cancer was described by Pettenkofer and Voit in 1869. They found increased nocturnal CO₂ production and O₂ consumption in a patient with leukaemia. They deduced that leukaemic patients were unable to reduce oxygen demand but failed to suggest that this might have been due to a hypermetabolic state induced by the malignancy.

Wallersteiner (1914) studied energy metabolism in 33 cancer patients. He measured oxygen and carbon dioxide exchange at rest and discovered that five of the patients had a very high metabolic rate. Fifteen patients had an elevated metabolic rate (greater than 30 k.cal/kg/day) but two patients had reduced metabolic rates. These latter patients were the best nourished of all the patients. In one patient, surgical excision of the tumour caused a fall in basal metabolic rate which increased again on recurrence of the tumour. Apart from this study, there are few reports of lowered metabolic rates in cancer patients.

In 1917, Murphy, Means and Aub reviewed previous studies of energy metabolism in leukaemic patients and found that all reported elevated basal metabolic rates. Subsequent studies confirmed these findings, and also extended them to include other malignancies.

Waterhouse, Fenninger and Keutmann (1951) reported on nitrogen balance and calorie expenditure in a group of eight patients with extensive metastatic cancer. With forced oral feeding, a positive nitrogen balance could be established in all patients despite a pre-study negative caloric balance and weight loss in most of the patients. The ability to deliver large oral diets in this group of patients is surprising. Effective therapy reversed the negative caloric balance in two patients, but one, and possibly both of these received anti-tumour therapy during the study period. These data were interpreted as implying that tumours may act as "nitrogen traps", a concept which Fenninger and Mider (1954) had proposed after studying the effects of tumours on carcass weight in experimental animals. The same group had also reported loss of body fat during tumour growth of transplanted Walker 256 carcinoma in a rat model. The fat loss was greater than in control animals which were age, sex matched and on comparable diets. This was interpreted as meaning that the tumour had increased the energy expenditure of the host.

Other literature also confirms the frequent occurrence of an increased resting metabolic rate and energy expenditure in cancer patients (Warnold, Lundholm and Schersten 1978, Mider 1951, Waterhouse and Kemperman 1971, Waterhouse 1981). The study by Warnold et al clearly showed an elevated daily energy expenditure and resting metabolic rate in a group of cancer patients with weight loss when compared with a control group. In one patient, a return to normal levels of food intake and energy expenditure were noted following curative surgery.

Lactate is normally formed by resting adults in amounts of about 20 G daily. The main source is blood cells. Most of this is re-synthesised to glucose via the "Cori cycle". Increased Cori cycle activity has been noted in cancer patients, and because this process requires energy it has been proposed as a cause for the increased energy expenditure of cancer patients (Fenninger and Mider 1954; Gold 1974). Holroyde et al (1975) have shown that this increased lactate production occurs only in cancer patients with progressive weight loss. Young (1977), however, refutes Gold's claim that increased Cori cycle activity is a significant energy drain and suggests that only 10% of daily energy expenditure can be accounted for by this process. He provides evidence that protein turnover is more important in increasing the energy expenditure because it probably accounts for up to 50% of the energy required for basal metabolism (see also p.45 and Figure 1.3, p.46).

No hormonal alterations have been consistently demonstrated which might account for these metabolic abnormalities except for those tumours which excrete ectopic hormones. It is possible that chronic mild elevations of corticosteroids and adrenal medullary hormones might be involved.

Tumour-derived products (discussed later) might be responsible. Alterations in oxidative phosphorylation might result from the production of such substances and an elevation of oxidative phosphorylation has been shown to occur with several tumour types in animals but not substantiated with other tumour lines (Strain 1979). Waterhouse and Kemperman (1971) studied $^{14}\text{CO}_2$ production after glucose ^{14}C and palmitate-1- ^{14}C injection in cancer patients. They showed that oxidative metabolism was normal in cancer patients in the resting state but that after a glucose load "normal metabolic adjustments were severely limited". They concluded in contradistinction to many studies that the patient with metabolic disease

retains his fasted state of oxidative metabolism regardless of injected nutrient and that glucose is directed toward synthetic rather than oxidative channels. Only one patient was severely under weight which might account for these results.

More recently Dempsey et al (1984) studied energy expenditure in malnourished gastro-intestinal cancer patients and described, on the basis of resting energy expenditure measurements, three groups of cancer patients: hypo-, normo- and hypermetabolic. They considered that the primary tumour site was principally responsible for the energy expenditure. These results support the conclusions drawn from the studies that formed the basis of this thesis.

NITROGEN AND PROTEIN METABOLISM IN THE CANCER PATIENT

Nitrogen metabolism in the cancer patient also has a long history of investigation. In 1889, Müller determined the total nitrogen excretion of eight cancer patients and compared this with a control group of four women who had negligible food intake. Two of the cancer group excreted no more nitrogen than the control group but all others had excessive nitrogen loss. Indeed, one patient with a metastatic carcinoma of the penis remained in negative nitrogen balance despite a daily intake of 21G nitrogen and 3067 K.cal. Most of these patients, however, were febrile, which suggests that at least part of the catabolic responses may have been induced by infection. These data were interpreted by many as implying that degenerating or infected tumours produce toxic destruction of protein tissues. Other investigators provided further data in support of this claim.

There were, however, opponents to the theory of tumour-induced toxic destruction. Wallersteiner (1914) studied 12 patients with advanced cancer and concluded that 7 were in nitrogen balance or in positive

balance. In those patients who were in positive balance he concluded that the reason was nitrogen retention by tumour, a concept supported by Mider some 35 years later. In the early 1950s many workers corroborated these results, reporting nitrogen retention by patients with advanced neoplastic disease, particularly if nutritional support was provided (Fenninger et al (1953) and Waterhouse et al (1951)).

The association of negative nitrogen balance and increased metabolic demand in cancer patients was therefore first suggested in the last century. Published data in the first half of this century lent support to these findings.

Abnormalities of protein metabolism have usually been examined by measuring nitrogen balance, either in tumour-bearing animals or cancer patients. Despite the problems inherent in this approach (discussed in the section on The Assessment of Nutritional Status), much of the present understanding of this subject was the result of such early work by Mider, Fenninger, Waterhouse and others.

Watkin (1961) found that "normal subjects and those ill with chronic-non-neoplastic diseases stored nitrogen when fed an adequate diet in a metabolic study unit; however, patients with active neoplastic disease demonstrated nitrogen equilibrium, positive nitrogen balance or negative nitrogen balance". He deduced that high protein and calorie dietary intake during active tumour growth, and in the presence of an already high protein turnover, may merely increase energy and protein metabolism without increasing net nitrogen retention. In addition, nitrogen retention of the tumour in Walker 256 carcino-sarcoma bearing rats may exceed the dietary nitrogen intake of the host (Mider 1951). To explain this phenomenon, Mider proposed the "nitrogen trap" therapy which postulated that tumours utilised host protein nitrogen for their own autonomic growth.

Labelled amino-acid uptake of tumours was subsequently studied by Wiseman and Ghadially (1958) in vitro who concluded that neoplastic cells took up required amino acids more avidly than normal liver cells. Norton et al (1980) confirmed this work in humans by measuring the amino acid differences in the venous drainage from normal limbs and limbs bearing sarcomas. Tumour-bearing limbs released less than half the amount of amino acids compared with the normal limb.

Other abnormalities of protein metabolism have been described relating to albumin, urea and whole body protein. These are discussed in Section III. In general, a greater protein turnover than that expected for the nutritional state of the cancer bearing host has been described (Burt et al 1984, Carmichael et al 1980, Brennan and Burt 1981, Emery et al 1984). There would seem little doubt that abnormal protein metabolism frequently occurs in the cancer host and is detrimental to survival. It seems unlikely that such events may in fact be beneficial to the host in the long term but the concept that cachexia is a host defence mechanism has been recently proposed (Murray and Murray 1980). Indeed, tumour necrosis factor (see above) is consistent with this hypothesis since TNF (cachectin) is produced by the host.

THE CAUSES OF MALNUTRITION IN CANCER

.....For extreme diseases.....extreme methods of cure are most suitable.....
When a person is recovering from a disease, has a good appetite, but his body weight does not improve in condition, it is a bad symptom..... We must consider, in which cases food is to be given once or twice a day, and in greater or smaller quantities, and at intervals.

Hippocrates.

INTRODUCTION

There are many causes of malnutrition in malignant disease (Table 1.1) and the recent increased use of cytotoxic and combined modality therapy have added further to the problem. One of the biggest problems facing the clinical oncologist and cancer nutritionist is to what extent each variable is contributing to malnutrition in an individual patient. Attempting to divorce the nutritional side effects of treatment from those of the primary disease is often difficult.

The nutritional complications of cancer and their causes have been reviewed by a number of authors (Schein et al 1975, Costa and Donaldson 1979, Shils 1977b, Heber et al 1986, Brennan and Burt 1981, Waterhouse 1981, Jeevanandam et al 1984). Many of the causes of malnutrition in Table 1.1 are self explanatory. Anorexia, taste abnormalities and cancer cachexia will be discussed in detail as they are particularly relevant to the clinical studies which form this thesis.

TABLE 1.1 Causes of malnutrition in Cancer

1. Tumour-induced Malnutrition

cancer cachexia
anorexia
taste abnormalities
bowel obstruction
fistulae
malabsorption
protein-losing enteropathy
depression
pain
mechanical obstruction to gut

2. Treatment-induced Malnutrition

(a) Surgery

Oropharynx - taste abnormalities, chewing
and swallowing problems.
Oesophageal - vagotomy effects, fistulae.
Gastrectomy - dumping syndrome, malabsorption.
Intestinal resection - blind loop syndrome,
short bowel syndrome.
Pancreatectomy - exocrine secretion deficiency
Partial hepatectomy - hypoalbuminaemia

(b) Radiotherapy

Concomitant - mucositis
xerostomia
taste abnormalities
nausea, vomiting
anorexia
radiation enteritis
diarrhoea

TABLE 1.1 continued.

Subsequent - enteritis

xerostomia

taste abnormalities

dental problems

(c) Cytotoxic chemotherapy

anorexia

nausea, vomiting

mucositis

taste abnormalities

diarrhoea

constipation

malabsorption

paralytic ileus

radiation "sensitisers"

psychological

ANOREXIA

A mortified appetite is never
a wise companion.

R.L. Stevenson

A Christmas Sermon.

Anorexia (poor appetite) is one of the commonest symptoms in cancer patients. Its severity does not always reflect the extent of disease but its prevalence usually increases as tumour bulk increases. Anorexia may be largely responsible for the wasting syndrome of cancer. Indeed, the anorexia may be so profound that even the sight of food causes nausea. The senses of taste and smell are essential parts of the normal appreciation of food, and both are important for normal appetite. Poor presentation of food (a not uncommon problem in hospitals) may enhance anorexia.

The causes of anorexia are listed in Table 1.2 (Trotter and Calman 1981). Iatrogenic causes of anorexia are common. In addition, anxiety, depression and pain may exacerbate underlying anorexia and the contribution of these problems often tends to be underestimated.

Appetite regulation in health and in cancer

The pathophysiology of anorexia has been reviewed by DeWys (1977) and recently by Bernstein (1986), von Meyenfeldt and Soeters (1986) and Garattini et al (1980). Appetite is controlled principally at the level of the hypothalamus. Food intake is governed by two catecholamine-mediated mechanisms: (i) alpha-adrenergic (via the medial hypothalamus) which increases feeding behaviour and (ii) beta-adrenergic and dopaminergic (via the antero-lateral hypothalamus) which reduce feeding behaviour. The lateral hypothalamus is innervated by adrenergic

TABLE 1.2 Causes of Anorexia in Malignant Disease.

1. Tumour Induced
 - (a) Metabolic
 - malignant cachexia
 - taste abnormalities
 - "anorectic peptides"
 - amino acid abnormalities
 - hormone abnormalities
 - (b) Mechanical
 - gastric stasis
 - delayed gastric emptying
 - bowel obstruction
2. Therapy Induced
 - (a) Cytotoxic chemotherapy
 - (b) Radiotherapy
 - (c) Surgery - head and neck
 - thoracic
 - abdominal
 - (d) Other drugs - antibiotics
 - analgesics
 - tranquillisers
 - allopurinol
3. Psychogenic - anxiety
 - depression
 - pain

Modified from Trotter and Calman 1981a (see Appendix VII).

pathways from the midbrain. Drug control of appetite usually is mediated by these central pathways. For example, amphetamines exert an anorectic action by stimulating the beta-adrenergic pathways. It is possible that the stress of illness causes anorexia by the same mechanism.

Barret (1978) and Booth (1978) have emphasized the importance of the dopaminergic system in appetite suppression. Antagonists of 5-hydroxytryptamine (5-HT) such as methysergide, cyproheptadine and pizotifen have all been shown to increase appetite and, in experimental animals, to block the anorexic effect of fenfluramine (an appetite suppressant).

Krause et al (1979) studied brain tryptophan metabolism in young, anorectic rats bearing the Walker 256 carcino-sarcoma and reported that brain tryptophan, brain 5-HIAA and plasma free tryptophan were higher in tumour-bearing rats than in pair fed control rats. The authors suggested that altered brain tryptophan may be responsible for the anorexia of tumour-bearing animals, and therefore be a cause of the anorexia-cachexia syndrome. Further studies are needed to establish a causal relationship but the results provide further justification for studies of the role of serotonin antagonists in reversing the anorexia of cancer.

Sensory input, such as sight, taste, smell and food temperature are important appetite regulators, and the oral stimulation by food causes an increase in saliva and gastric secretions (DeWys 1977, Nielsen et al 1980). Peripheral neurones at other sites may also be important in appetite modulation from other sites, such as the autonomic innervation of the liver. The visceral sensing effects of food may, in addition, be volumetric, osmotic or chemical in origin (Navin, D. 1976).

The influence of these factors may be largely learned (Booth 1978). Indeed, Bernstein (1981 and 1986) suggests that learned food aversions may contribute to cancer cachexia. Experience dictates what appearances, flavours, textures and after-effects of food are to be sought or avoided. Chemical composition of food is also important. For example, rats will reject diets which are deficient in an essential amino acid, and carbohydrate-rich foods are preferred to low carbohydrate foods when rats or humans are hungry (Booth 1978). These findings imply that the types of food eaten also affects appetite and may explain in part why, as will be described later, cancer patients who have anorexia and easy satiety prefer savoury foods or less sweet foods than they would normally eat.

Appetite may be partly regulated by the amount of heat released from both the metabolism of food and its "specific dynamic action", i.e. the increase in oxygen consumption following ingestion of food. This "thermostatic hypothesis" is purported to explain anorexia in fever and the stimulation of appetite in tumour-bearing animals exposed to cold (Stephenson et al 1963).

Sensors for plasma FFA (free fatty acids) and glycerol, are believed to mediate satiety (Kennedy 1953, Oomura 1976). Neurones to the ventro-medial hypothalamus and lateral hypothalamus are sensitive to the local application of FFA (Oomura 1976).

Plasma amino acids are often deranged in malnutrition and abnormalities in the plasma aminogram have been described in cancer patients (see Section III). It is possible that these changes contribute to anorexia in cancer patients since the concentration and pattern of amino acids in the blood is involved in appetite regulation (Mellinkoff et al 1956).

Many hormones influence appetite. There is little data, however, on the effect of hormonal abnormalities on appetite in cancer patients. Three pancreatic hormones may produce effects on food intake - insulin, glucagon and pancreatic polypeptide (PP). It is well known that parenteral insulin can cause increased food intake and, in the longer term, obesity. Glucose intolerance and peripheral insulin resistance are found in up to 50% of patients with malignant disease (Lundholm, Holm, Schersten 1978; Holroyde et al 1975; Schein et al 1979). Since insulin is the major anabolic hormone (essential for protein synthesis and ensuring bioavailability of amino acids) these abnormalities may contribute to malnutrition.

Glucagon injected into humans causes reduced food intake (Schulman 1957). Pancreatic polypeptide (PP) may play a role in the regulation of food intake and several studies have suggested that it can contribute to obesity (Bray 1978). These hormones have not been studied in cancer patients.

The following intestinal hormones are involved in the modulation of food intake: gastrin, secretin, cholecystokinin, vasoactive intestinal polypeptide (VIP), enteroglucagon, protelin and gastrointestinal inhibiting polypeptide (GIP). Somatostatin, neurotensin and thyrotrophin-releasing hormone (TRH) may also be important in appetite control and have been found in tissues other than the hypothalamus (including intestine and pancreas) (Bray 1978). Once again, it would appear that these hormones have not been studied in cancer patients in relation to anorexia and malnutrition.

In humans, GH tends to rise in fasting and PEM (Turner 1978) but the changes in malignancy have not been documented. It could be rewarding to study GH in more detail because of its action in promoting lipolysis, a metabolic process frequently increased in the cancer patient (Costa

1977a). Somatomedin C levels fall in PEM, probably due to resistance to GH. The increase in GH in PEM may be due to a lack of somatomedin C feedback on the pituitary/hypothalamus.

Cortisol levels are elevated in the acute phases of PEM and this is the result of increased adrenal gland mass, which in turn is probably the result of increased ACTH production by the pituitary. With more chronic protein restriction, adrenal size decreases (Fleck 1978). Corticosteroids are potent catabolic hormones and may play a significant role in the pathogenesis of cancer cachexia, as well as contributing to the insulin resistance mentioned above. Hyperactivity of the adrenal gland in cancer patients has been reported (Theologides 1974, Begg 1958). Cortisol does, however, increase hepatic albumin and fibrinogen synthesis (Miller and Griffen 1975). An effect of physiological levels of cortisol on appetite is not described in humans nor clearly demonstrated in animals, except in special circumstances (for example, Cushing's syndrome). However, castration in lean rats can cause an increase in body weight and food intake which is abolished by adrenalectomy (Bray 1978).

Both thyroxine and triiodothyronine, the principal thyroid hormones, cause an increased food intake if elevated and a fall in food intake if reduced (Bray 1978). However, there are inverse changes with metabolic rate such that a low serum T3 protects against catabolism in chronic illness.

Gonadal hormones, both androgens and oestrogens, increase protein synthesis. Androgens are thought to have direct effect upon muscle metabolism, whereas oestrogens are thought to exert their action by increasing insulin and growth hormone concentrations (Buttery et al 1978). Diethylstilboestrol has been shown to reduce the plasma concentration of both the essential and non-essential amino acids in

steers (Oltjen et al 1973). Rao (1972, Personal Communication 1978) has shown that lung cancer patients who excrete low levels of the (principally adrenal) hormones androsterone, etiocholanolone, 17 oxo-steroids and 17-hydroxycorticoids have a poor one year survival when compared to high excretors. Pre-operative and post-operative urine specimens were compared in patients undergoing lung resection as part of their management. The reason for these changes is not clear but they may reflect nutritional changes and these in turn, extent of the disease.

Progesterone in rodents causes a dose-related increase in food intake and this is both lean body tissue and adipose tissue. Oestrogen has the opposite effects. The weight gain of castrated lean animals can be abolished by administering oestrogen (or by adrenalectomy which removes a source of progesterone). (Bray 1978)

TASTE ABNORMALITIES IN CANCER PATIENTS

When the bells jostle in the tower
The hollow night amid
Then on my tongue the taste is sour
Of all I ever did.

A.E. Housman

Collected poems (1939),

Additional poems 9.

DeWys and Walters (1975) demonstrated abnormalities of taste in a significant number of cancer patients. Patients who complained of abnormal or reduced taste usually had an elevated threshold to sucrose compared with controls, and also a reduced threshold to urea (bitter). The threshold they used was defined as the "taste recognition threshold", i.e. the concentration of solution (salt, acid, sweet or bitter) at which

the subject recognised the basic taste sensation under test. The concentration of solution at which "something" could be detected, the "detection threshold" was not found to be useful. The lowered urea threshold may explain the aversion to red meats experienced by some cancer patients. Gallagher and Tweedle (1983) have published similar results.

In another study, Hall et al (1980) studied 90 patients in 3 groups: gastro-intestinal cancer, benign gastro-intestinal disease and no clinical evidence of disease. They, too, reported a lower threshold for urea (bitter) in the cancer patients compared with the other groups. However, Williams and Cohen (1978) found a lowered recognition threshold for sour but not for sweet or bitter.

Carson and Gormican (1977) discovered that cancer patients receiving 5-F.U. (5-fluorouracil) chemotherapy had decreased salt and sweet sensitivity. Clearly this variation in reports between various authors is difficult to interpret but some possible reasons are the effect of chemotherapy, of nutritional status and tumour type and bulk. The results of these studies do, however, clearly demonstrate that many cancer patients have taste abnormalities which need to be taken into account when assessing the causes of anorexia in cancer patients and providing dietetic advice.

Taste changes in cancer patients may also affect the palatability of oral foods and oral nutritional supplements. Testing palatability of foodstuffs provides a more direct assessment of food acceptance by the cancer patient than assessing taste by the methods mentioned above because taste is influenced by the appearance, aroma, texture and temperature of the food. Indeed, loss of smell may be one of the commonest causes of loss of taste (Editorial 1976).

Cancer patients often have difficulty in chewing solid foods because of xerostomia, weakness and mucositis. A number of commercial liquid food preparations are available for help in providing high protein, high carbohydrate nutritional supplements. DeWys and Herbst (1977) reported that dietary supplements which contained free amino acids (i.e. elemental diets) as the principal nitrogen source were rated poorly by patients when asked to comment on their palatability. Milk-based products fared best with whole protein semi-synthetic scoring better than the free amino acid low fat supplements ("elemental diets"). Comparison of these data with the taste tests described earlier led the authors to conclude that patients with low urea thresholds were more likely to rate products poorly. The range of average scores for products was broader for the controls than the cancer patients which suggested a restriction of food preferences may have been operative in the patients.

THE PATHOGENESIS OF CANCER CACHEXIA

The precise pathogenesis of cancer cachexia remains obscure but is likely to be multifactorial (e.g. metabolic disturbances, toxins, tumour or host metabolites). Although cancer cachexia has certain similarities to other pathological states (e.g. the catabolism of acute trauma), there are differences. Abnormalities of carbohydrate, lipid and protein metabolism have all been described and have been discussed above. The causes of these abnormalities have for long been postulated to be due to substances produced by tumours or by the host which alter host metabolism (Trotter et al 1981b; Theologides 1976). This not a new concept. It arose in part because investigators found it hard to explain how small tumours could produce severe metabolic derangement in the host without postulating the elaboration by the tumour of "toxins" or "chemical mediators". Some tumours do produce substances which can be readily

assayed in the plasma, e.g. ectopic hormones. The anaemia of malignant disease has been attributed in part to such "tumour toxins" (Jepson 1974). Fever is not uncommonly found in patients with advanced malignant disease and it is not always caused by infection. The best known example is the fever which develops in some patients with Hodgkin's disease and non-Hodgkin's lymphoma. Although endogenous leucocyte pyrogens or aetiocholanolone (Molavi 1970) may be responsible for the fever this is not proven and it might result from the secretion of metabolically active substances by the tumour. Patients with these malignancies who have either a fever or a significant loss of weight have in addition an abnormality of collagen metabolism expressed as a pathologically increased excretion of hydroxyproline (Nehlawi et al 1979). Exploration of the role of plasma exchange as an investigative and therapeutic modality in this situation, it was considered, might prove rewarding. Indeed, a trial of plasma exchange in a patient with Hodgkin's disease provided temporary relief of pruritus and night sweats (Shaw, Trotter, Calman 1980).

In addition to the above, a number of authors have purported to have isolated specific tumour toxins which could affect host metabolism (Costa 1963; Israel et al 1977; Jepson and Vas 1974). "Toxohormone" is probably the best known of these toxins and has been shown to depress hepatic catalase in vivo (Nakahara and Fukuoka 1949). Cell-free extracts of tumours have been shown to have metabolic effects on the liver in mice (Jones et al 1968). In this model, reductions in acetyl-CoA and citrate were described. There is therefore increasing evidence for the existence of tumour derived (and perhaps host-derived) substances which alter host metabolism.

It is possible that anorexia, one of the components of cancer cachexia, may also be induced by metabolites released by the tumour or

host. These metabolites may also alter host metabolism. Theologides (1974, 1976) proposed that "peptides, oligopeptides and other small metabolites" might be the cause of anorexia in the cancer-bearing host by exerting both a peripheral effect on neuroendocrine cells and neuroreceptors and a direct effect on hypothalamic and other central nervous system cells.

More recently, tumour necrosis factor has been isolated and shown to produce a wasting syndrome in cattle not unlike the cachectic syndrome of cancer in man (Beutler et al (1985), Kawakami and Cerami (1981), Carswell et al (1975), Editorials 1985 a, b). This finding is the strongest lead yet as to at least one of the presumed causes of cachexia, and is discussed further in Section IV.

NORMAL NUTRITION: FOOD ABSORPTION AND METABOLISM

And what can we expect
if we haven't any dinner
But to lose our teeth and eyelashes
and keep on growing thinner?

Edward Lear.

INTRODUCTION

A balanced and adequate supply of carbohydrate, fats (lipids), protein, vitamins and minerals is necessary for the maintenance of body homeostasis and the prevention of deficiency states. The nutritional needs of individual substances can vary widely, not only by normal physiological variation, but also by a multitude of pathological states. Nutritional requirements vary with age, sex, occupation and climate. They increase at times of stress, such as trauma and surgery. Malignant disease can alter host metabolism and nutritional requirements in a variety of ways. Abnormalities of carbohydrate, fat, protein, mineral and vitamin metabolism have all been described in cancer patients.

A normal diet contains about 12% protein, 42% fat and 46% carbohydrate. A United States Senate Select Committee on Nutrition and Human Needs (McGovern Report) in 1977 suggested optimally that fat intake should reduce to 30% and carbohydrate increase to 58% (comprising 43% starches and only 15% of the more highly refined sugars). Protein intake should remain the same.

Meat, milk, eggs and fish supply protein of high biologic value. Cereals and wholemeal breads are a rich source of dietary fibre and carbohydrate whilst vegetables and fruit provide additional fibre plus minerals and vitamins. Soya bean and yeast contain high biologic value protein and can be substituted for protein sources of animal origin.

NORMAL DIETARY REQUIREMENTS

Protein

Dietary protein is essential as the source of amino acids. Some proteins are of less biologic value to man than others because of their inferior amino acid composition. Most of these proteins are derived from plant sources. Egg protein is considered to have an optimal protein content and is given a chemical score of 100. Gliadin, a protein of wheat, is deficient in lysine and has a low chemical score as a consequence. Gelatin is another deficient protein; it lacks valine, tyrosine and tryptophan with cystine present in only small amounts.

The amount of dietary protein required to maintain nitrogen balance was shown by Chittenden (1907) to be as low as 25 grams of protein of high biological value. This was much less than the 118 grams suggested by Voit (1866) in his studies on German labourers in the latter part of the Nineteenth Century. With an ordinary mixed diet, Chittenden claimed that 40 to 50 grams of protein from mixed sources was sufficient for the "average" 70 kilogram man.

Nitrogen balance studies have shown that total nitrogen losses for a 70 kilogram male in the steady state (that is, no weight gain on a constant diet) averages about 5.2 grams per day. Faecal nitrogen loss averages 1.0 gram per day providing there is no diarrhoea or protein-losing enteropathy. Small additional losses of nitrogen occur via desquamated skin, nail clippings, hair loss, exhaled breath, sweat and tears. Urinary nitrogen is principally urea but the proportion of urea falls on a low protein diet. Nitrogen balance studies, however, tend to underestimate nitrogen losses (Isaksson and Sjogren, 1967). One gram of nitrogen is derived from approximately 6.25 grams of protein so that a protein loss of 30 to 40 grams for a 70 kilogram man per day is about average. Allowing for normal individual variation, for less than

100% utilization and for a mixed protein diet, normal allowance recommended is 0.8 grams per kilogram per day. In catabolic states, requirements may be higher and to provide for a margin of safety, one gram per kilogram body weight per day of protein is recommended (Food and Nutrition Board 1980, Thomas S. and Corden M. 1977).

Those amino acids essential for normal growth are listed in Table 1.3. Arginine is essential for the growth of rats, but not humans. Methionine is essential for normal growth and although cystine can provide up to one-sixth of methionine requirements, this is not sufficient during times of active growth or tissue repair. Plant proteins tend to be lower in tryptophan, lysine and methionine content than animal proteins, and are often less readily digestible. However, appropriate combinations of various vegetable proteins will prevent any deficiencies from occurring. Such combinations of proteins, however, must be made in the same meal because there is no storage facility for amino acids in the body.

Carbohydrate

Carbohydrate is not an essential source of energy but caloric requirements can be cheaply met using this energy source. In addition, high fat, high protein diets are probably not nutritionally optimal. Carbohydrate usually provides between 50 to 60% of the calories of most Western diets. Eskimos have a much greater proportion of fat to carbohydrate and the Asian farmer a high proportion of carbohydrate with very low fat intake. Low carbohydrate diets tend to cause ketonuria because of the mobilization of fat stores (see below). Dietary carbohydrate provides about 4 kilocalories per gram and intake should

TABLE 1.3 ESSENTIAL AMINO ACIDS

* Arginine	* Not essential in man
Lysine	
Tryptophan	
** Histidine	** Essential in children, not adults.
Phenylalanine	
Leucine	
Isoleucine	+ Cystine can spare Methionine but
Valine	only by about one-sixth. Methionine
+ Methionine	is essential for growth.
	Threonine

exceed 75 grams per day to avoid ketonuria. Adaptation to ketosis can, of course, occur and the ketosis may resolve after several weeks of carbohydrate restriction.

Fat

Fat is important in aiding the absorption of the fat soluble vitamins - vitamins A, D, E and K. Increased loss of these vitamins can occur in the presence of steatorrhea. Fat provides a source of arachidonic and linoleic acids which are essential for infant growth and as precursors of the prostaglandins. Essential fatty acid deficiency is probably rare in the adult but has been reported following long term fat-free parenteral nutrition. Fats increase the palatability of food and are an excellent caloric source, 1 gram of fat providing 9 kilocalories of energy. Fat usually constitutes 40-45% of the energy value of a Western diet, but this is far in excess of that necessary for health.

DIGESTION AND ABSORPTION OF PROTEIN, CARBOHYDRATE AND FAT

Protein

Endogenous protein derived from gastric, biliary, pancreatic and intestinal secretions is added to dietary (exogenous) protein in the gut. Endogenous protein amounts to 25 to 200 gram per day (Sleisenger and Kim 1979). Most digested protein is absorbed in the proximal jejunum, some being absorbed in the ileum (Silk 1980). Endogenous protein may be absorbed in the colon. Protein digestion commences in the stomach where denaturation occurs by acid and pepsin releasing principally large polypeptides. Collagen requires digestion by pepsin in the acid pH of the stomach. Pancreatic proteolytic enzymes (trypsin, chymotrypsin and carboxypolypeptidase) further hydrolyze the large polypeptides to small polypeptides and amino acids in the duodenum. In addition, intestinal

brush border and cytoplasmic intestinal mucosal amino oligopeptidases are found in the intestinal contents and, particularly in the ileum, may have a role in hydrolysing peptides in the gut lumen. The end result of proteolysis is the formation of free amino acids (one third) and small peptides of 2-6 amino acid residues.

Amino acid transport occurs, like glucose, by an active mechanism which is dependant on a sodium ion gradient across the brush border of the epithelial cell (Wiseman 1953). Free amino acids are absorbed by at least three group-specific carrier systems - (1) acidic amino acids, (2) neutral amino acids, (3) dibasic amino acids.

In addition to the transport of free amino acids, there is now strong evidence to support the idea that peptides are absorbed. This is not a new theory. Physiologists in the late nineteenth century believed that polypeptide absorption occurred but this theory lost ground when free amino acids were discovered in the intestinal contents. The "classical theory" of protein absorption was born. Experiments in the 1950s demonstrated the ability of some dipeptides to pass across the intestinal mucosa. Subsequently Craft et al (1968) demonstrated that peptides not only have a separate transport system from amino acids but one which is more efficient. Other studies have since confirmed these findings, establishing that transport of both dipeptides and tripeptides occurs. These findings are of clinical importance because they suggest that oral protein hydrolysates and whole protein diets may be superior to amino acid solutions for enteral nutritional support providing the gut is intact (Trotter and Calman 1981) (Appendix VII).

Carbohydrate

Almost all carbohydrates are absorbed as monosaccharides. A very small percentage of disaccharides are absorbed. Absorption of monosaccharides is dependent on sodium. It is thought that sodium

transport is coupled to sugar transport in such a way that movement of sodium across the cell membrane uses a carrier to which glucose also binds. In this way, energy expended in transporting sodium allows glucose to be moved into the cell without any additional expenditure of energy.

Starches are hydrolysed to maltose and isomaltose by the enzymes ptyalin in saliva and pancreatic amylase. The maltose is then converted to glucose by intestinal maltase and isomaltase. Lactose is converted to galactose and glucose by lactase. Sucrose is converted to fructose and glucose by sucrase. These enzymes are situated in the intestinal brush border microvilli where they convert any disaccharides into monosaccharides immediately prior to absorption. Lactose deficiency can occur as an acquired defect in the malnourished patient and results in the accumulation of lactose which, in turn, causes flatulence, abdominal cramps and diarrhoea.

Lipids

Most fat digestion occurs in the small intestine by pancreatic lipase with less than 1% digested in the stomach by gastric lipase. Bile salts emulsify the dietary fat and by their detergent action break the fat down into small enough particles to allow efficient enzyme activity. Pancreatic lipase breaks fat into monoglycerides, fatty acids and glycerol. Bile salts help remove monoglycerides and free fatty acids by forming micelles. Because of the reversible nature of triglyceride hydrolysis, removal of the products of hydrolysis is important otherwise further fat digestion would be blocked. Micelles, composed of between twenty and fifty molecules of bile salt, have a central core of fat in which the free fatty acids and monoglycerides become trapped. The free fatty acids and monoglycerides are then

transported to the intestinal epithelium where they are absorbed releasing the micelles into the gut lumen to repeat the process.

Monoglycerides and fatty acids, being fat soluble, diffuse through the epithelial cell membrane. Once inside the epithelial cell, the monoglycerides are further hydrolysed to glycerol and fatty acids by an epithelial cell lipase. Triglycerides are then re-synthesized from the fatty acids and formed into globules together with cholesterol, phospholipids and coated with beta-lipoprotein. These globules (chylomicrons) are then extruded from the cells and enter the lymphatics through which they pass into the venous system via the thoracic duct.

NUTRITION AND FOOD ABSORPTION IN CANCER

I am convinced digestion is the great secret of life.

Reverend Sidney Smith.

Normal assimilation of foodstuffs is dependent on an intact gut. The widespread use of enteral nutrition in the cancer patient implies the knowledge that the gut is intact and functioning normally. There have, however, been a number of reports that cancer, radiotherapy and cytotoxic drugs can all interfere with intestinal structure and function. This topic has been reviewed by Shaw, Spector and Ladman (1979) who conclude that some patients may develop malabsorptive problems due to malignancy but that these effects are much more likely to occur following chemotherapy or abdominal radiotherapy. For these reasons, patients entered into studies in this thesis were not to have had chemotherapy within 3 weeks of study and no history of abdominal radiotherapy. Although this does not necessarily exclude persisting malabsorptive problems induced by previous chemotherapy, three weeks was considered of sufficient duration to allow adequate recovery of any cytotoxic-induced

cellular damage. There is little evidence that in the majority of cancer patients, the absorptive capacity of the gut is significantly compromised except perhaps where major portions of the gut have been resected or where endocrine pancreatic insufficiency exists.

Some degree of small intestinal villous atrophy is common in PEM (James 1977) and similar findings in cancer (Stuart 1979; Shils 1977b) may similarly reflect malnutrition. In some tumours there is a clear association with malabsorption and primary gut lymphoma frequently co-exists with subtotal villous atrophy. Lymphoma should be considered if the diagnosis of adult coeliac disease is being contemplated (Schein et al 1975; Shils 1977b).

NORMAL METABOLISM OF PROTEIN, FAT AND CARBOHYDRATE

Overview

All organisms require energy for homeostasis and growth. Energy is made available by the utilization of fuel which is provided by food. Energy for most metabolic processes is provided by the high energy phosphate bond which is predominantly produced in the mitochondria. Glucose is the main substrate for energy production in man although both amino acids (from protein) and keto acids and fatty acids (from lipid) can be utilized as energy sources. Energy production is triggered by the presence of ADP and energy storage by the accumulation of ATP.

Acetyl CoA, which is the major mitochondrial energy source, is formed from the breakdown of carbohydrates, fatty acids, keto acids and a number of amino acids. Acetyl CoA enters the tricarboxylic acid (TCA) cycle for the ultimate production of high energy phosphate bonds. ATP thus generated has a large number of uses which include the maintenance of electrolyte gradients across cell membranes, the main energy source for muscle contraction and the synthesis of storage compounds (for

example glycogen, fatty acids). In addition, heat is generated to maintain body temperature, much of which is liberated during the formation of ATP. The synthesis of storage compounds is crucial to survival. Animals rely on such stores in times of nutritional deprivation or stress. Lipid is the most important of the energy stores. Glycogen stores amount to between 100 and 150 grams which are sufficient for only about 12 hours of energy needs. In fact, glycogen stores are usually depleted during the usual overnight fast which occurs during sleep. The energy value of both carbohydrate and protein is 4 kilocalories per gram, that of fat 9 kilocalories per gram. An average of 12 kilogram of fat in a 70 kilogram male could therefore supply 108,000 kilocalories (447 MJ) of energy.

Protein Metabolism

Amino acids derived from dietary protein are rapidly removed from the blood after absorption, usually within 5 to 10 minutes. Cells throughout the body take up amino acids which are probably rapidly converted to protein within the cell. There is, in addition, a rapid turnover of amino acids in the blood and the entire plasma amino acid pool probably turns over every few hours. Amino acids are transported into cells by facilitated diffusion or active transport. Amino acids are released from cells after protein degradation to replenish low serum concentrations.

Plasma concentrations of amino acids are maintained at fairly constant levels after an overnight fast. Hormones aid in this regulation. The adrenal corticosteroids increase protein catabolism and insulin and growth hormone increase protein synthesis. Albumin is an exception in that adrenal corticosteroids seem to increase its synthesis. Other plasma proteins include the globulins and fibrinogen. As with the plasma amino acids, the genesis of plasma protein can be very rapid and

the liver is capable of synthesizing up to 50 grams per day. Large protein losses such as occur with the nephrotic syndrome, protein losing enteropathy or from burns can often be matched by hepatic synthesis. In addition, there is evidence that plasma proteins, in particular albumin, can be used as a source of amino acids during malnutrition. Whole proteins are taken up by the reticulo-endothelial system where they are degraded into amino acids. Plasma albumin normally has a plasma half life of 21 days. Plasma albumin infused to correct hypoalbuminaemia often has a much shorter half life, due in part to its digestion for use as a food source. Other reasons for a short plasma half life of albumin include increased loss, increased catabolism and an increased extravascular to intravascular ratio.

Amino acids in excess of body requirements are metabolized to acetoacetate or to products of glucose oxidation. Energy can then be generated by oxidation or, alternatively, used to synthesize glycogen or fat for storage. Degradation of amino acids occurs principally in the liver and involves deamination which releases the amino groups. Most of the ammonia so formed is converted to urea which is then excreted by the kidneys. Conversion to urea involves the urea cycle (Figure 1.1). About 20 per cent of urea is excreted in the bile and degraded in the gut to CO_2 and NH_3 ; the CO_2 is excreted by the lungs and the ammonia is recycled.

Deaminated amino acids form keto acids which can be oxidized to produce energy. Oxidation occurs via the citric acid cycle. The formation of glycogen from amino acid (gluconeogenesis) and of keto acids and fatty acids (ketogenesis) can readily occur from most of the amino acids (Figure 1.2). The glycogen and fatty acids can be metabolised for energy needs as outlined below.

FIGURE 1.1

UREA CYCLE

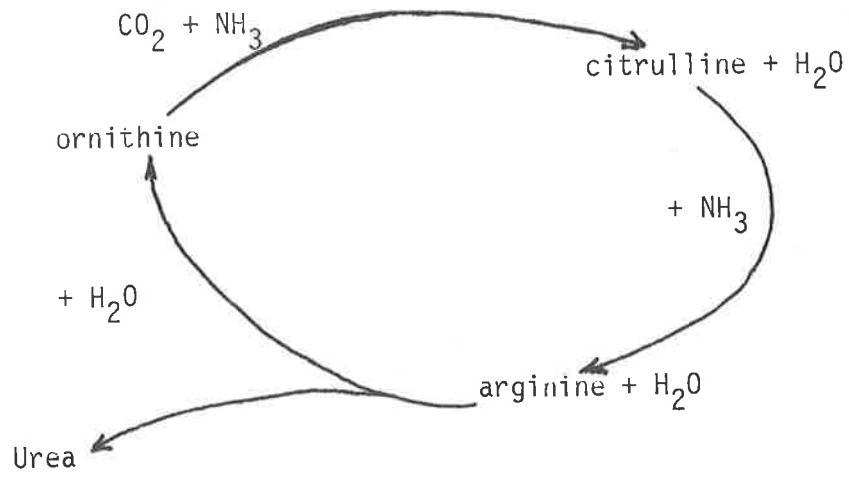
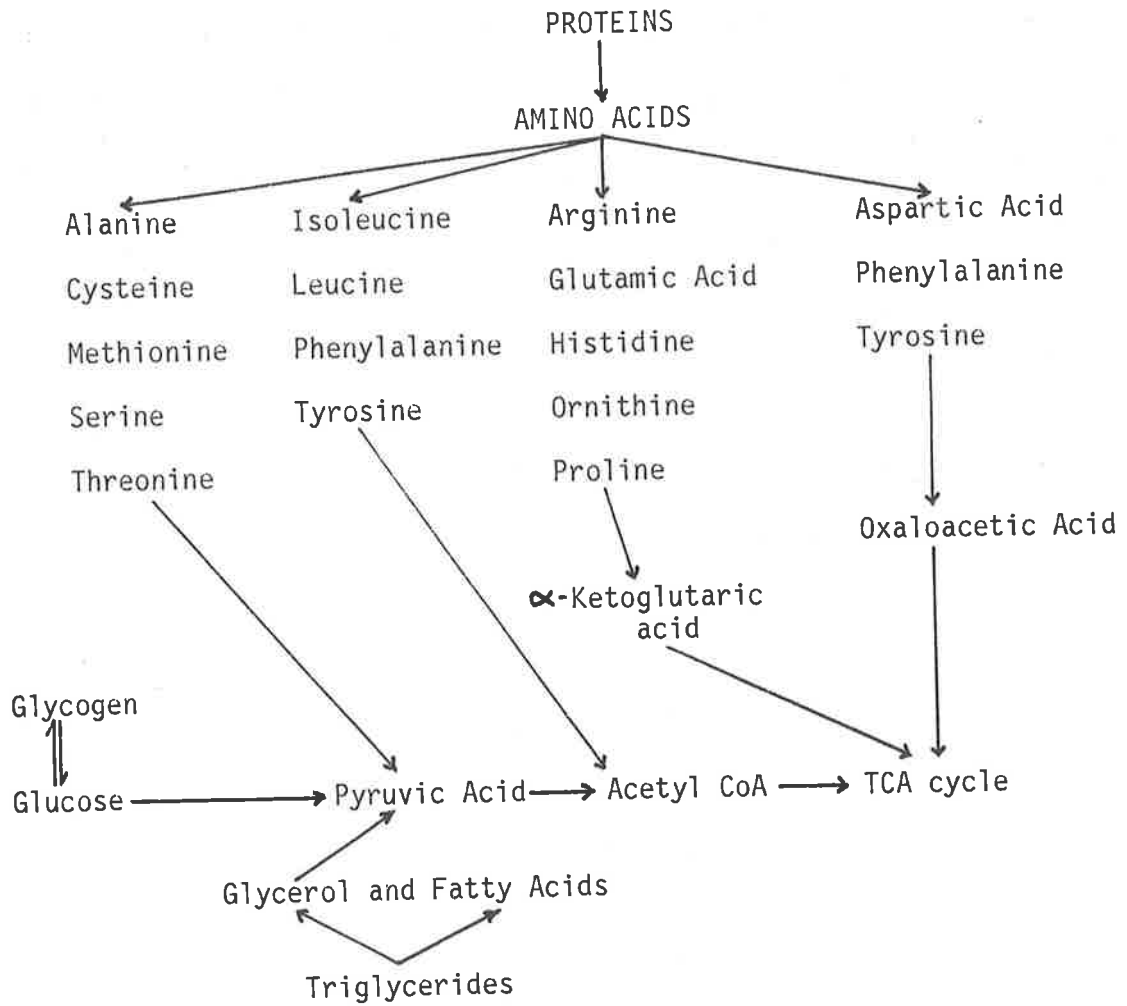


FIGURE 1.2

ENERGY PRODUCTION FROM AMINO ACIDS AND LIPIDS



Carbohydrate Metabolism

Fructose and galactose absorbed from the gut are converted in the liver to glucose. Glucose uptake by cells is facilitated by insulin which is essential for ensuring glucose availability for cells. In the absence of insulin, there is increased lipolysis, glycolysis, gluconeogenesis and acetoacetate production which result in hyperglycaemia, protein loss and metabolic acidosis. These abnormalities are often presenting features of uncontrolled juvenile onset diabetes mellitus.

Glycogen, a branched-chain polysaccharide, is formed in liver and muscle which contain 100 grams and 250 grams respectively. Glycogen can be broken down into glucose by the action of, first, phosphorylase which forms glucose -6- phosphate, then by glucose -6- phosphatase which splits the phosphate from the glucose -6- phosphate. Glucose -6- phosphatase is present only in liver cells. The phosphorylase can be activated by adrenaline or glucagon which increase the amount of cellular cyclic adenosine monophosphate (cyclic AMP).

Glucose is metabolized by the glycolytic pathway to form pyruvic acid. This process generates 2 moles of ATP per mole of glucose. Pyruvic acid is then converted to acetyl CoA which enters the citric acid cycle to undergo degradation to carbon dioxide, hydrogen and oxaloacetic acid. This cycle is self-regenerating and produces a further two molecules of ATP as stored energy. The bulk of the energy formed during oxidation of glucose is formed by oxidative phosphorylation of the hydrogen atoms formed during glycolysis and the citric acid cycle. A further 34 molecules of ATP are formed by oxidative phosphorylation making a total of 38 molecules of ATP per molecule of glucose. Control of glycolysis occurs by the presence or absence of ADP (adenosine diphosphate). Adenosine diphosphate is required during glycolysis so

that ATP can be generated. If all the ADP has been used to form ATP, glycolysis ceases until further ADP is generated from ATP.

Glucose can also be metabolized via the phosphogluconate pathway (hexosemonophosphate shunt). This pathway is important for conversion of carbohydrate to fat.

In the absence of oxygen, glycolysis can continue (by anaerobic glycolysis) but very little energy is produced per molecule of glucose. Pyruvic acid must be converted to lactic acid to allow the process to continue (Cori cycle) (Figure 1.3). Some workers have shown that there is an increase in Cori cycle activity in cancer patients and the importance of this as a metabolic drain is discussed further below.

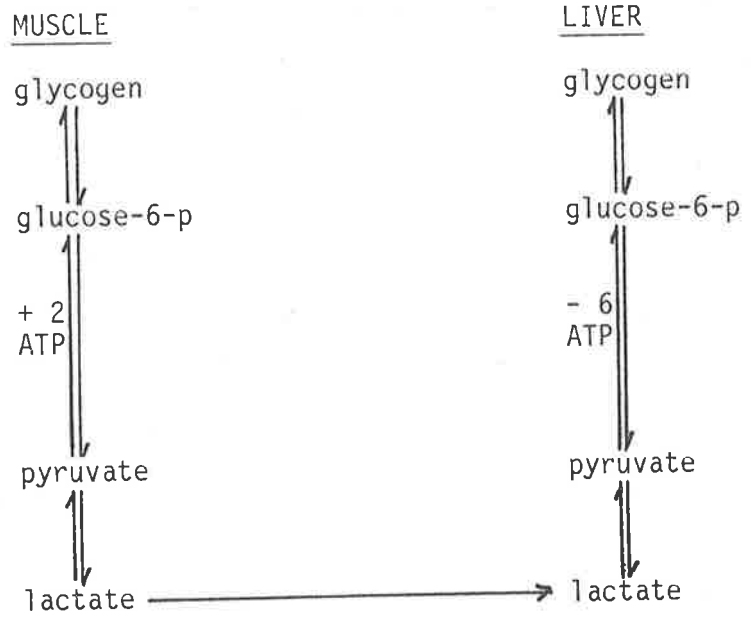
Lipid Metabolism

After absorption from the gut, lipids are transported as chylomicrons in the lymph from where they drain into the venous blood. They are rapidly removed from the blood by liver cells and fat cells. Lipoprotein lipase, present in the cell membrane of fat cells, hydrolyses triglycerides to glycerol and fatty acids. The fatty acids pass into the fat cells where they are reformed into triglycerides by combination with glycerol. Glycerol is produced within the cell from glyceraldehyde, a breakdown product of glucose.

When fat is required for energy, the stored triglycerides are hydrolysed to form fatty acids and glycerol. This process is controlled by hormone-sensitive triglyceride lipase. The activity of this enzyme is increased by adrenaline and noradrenaline and possibly also by glucocorticoids and growth hormone. Insulin increases fat storage and thyroxine increases fat mobilization. Fatty acids are transported in the blood bound to albumin where they are called free fatty acids or non-esterified fatty acids (FFA or NEFA). The plasma turnover of free fatty acids is very rapid and they have a half life of only a few

FIGURE 1.3

CORI CYCLE (LACTIC ACID CYCLE)



minutes. Free fatty acid concentration is kept at fairly constant levels under basal conditions, but increases in protein-energy malnutrition and diabetes mellitus.

Lipids are also transported in the body as lipoproteins, which are complexes of protein, cholesterol, triglycerides and phospholipids. Most lipoproteins are formed in the liver and are the principal means by which cholesterol and phospholipids are transported. There are several classes of lipoproteins but these are not discussed further here. Cholesterol and phospholipids are essential for the structural integrity of the cell membrane and of the membranes of the cell organelles.

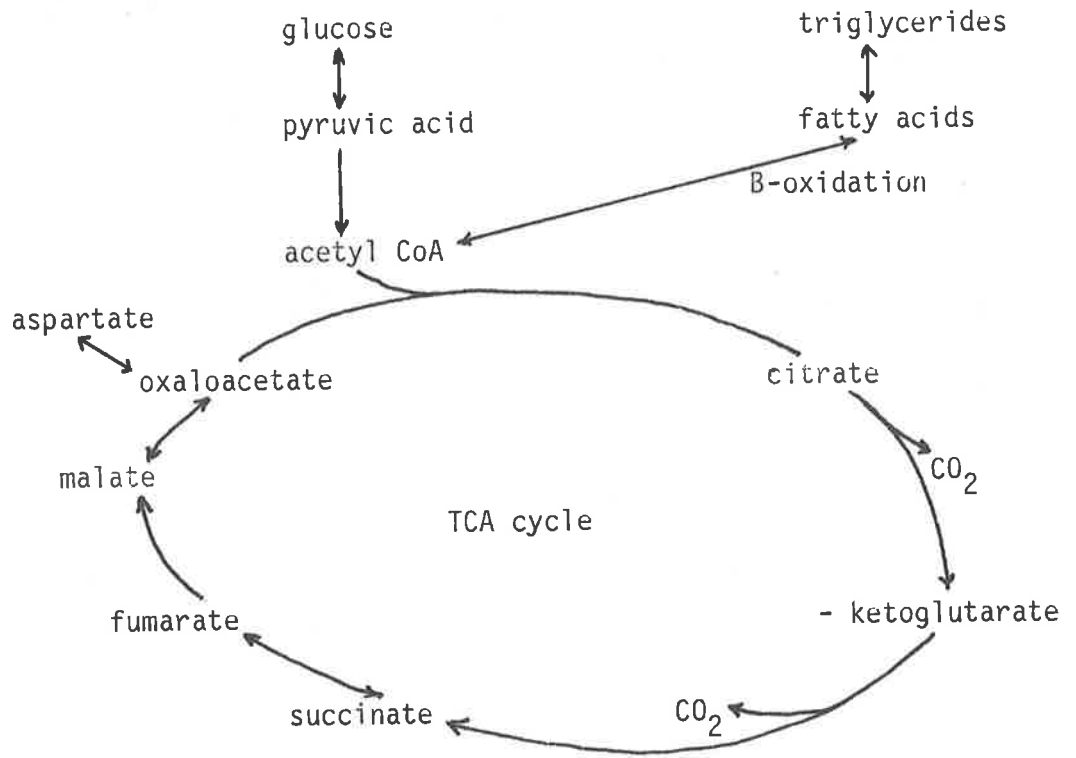
The liver has an important role in lipid metabolism and not only metabolizes fatty acids but also synthesizes cholesterol and phospholipids from fatty acids and synthesizes triglycerides from proteins (amino acids) and carbohydrates.

The oxidation of fatty acids occurs in the mitochondria. They are transported to the mitochondria with carnitine acting as a carrier. Once inside the mitochondria, the fatty acids are converted to acetyl CoA by "beta oxidation". By this process, acetyl CoA is regenerated each time a two-carbon segment of fatty acid is oxidized. Oxidation of the acetyl CoA in the citric acid cycle and of the hydrogen atoms released (by oxidative phosphorylation) yields a large amount of ATP per fatty acid molecule (Figure 1.4).

Much of the acetyl CoA produced by the liver is converted to acetoacetic acid by the condensation of two molecules of acetyl CoA. Most of the acetoacetic acid is converted to B-hydroxybutyric acid and acetone. These "ketone bodies" are then transported to the peripheral tissues. Here, they are reconverted to acetyl CoA for entry into the citric acid cycle for the formation of ATP and energy.

FIGURE 1.4

ENERGY PRODUCTION FROM LIPIDS



BODY COMPOSITION

A 70 kilogram male of body surface area 1.73 m^2 has a total body water of approximately 43.0 litres, total body fat 11.0 kilogram and total body protein of 12.0 kilogram. A 57 kilogram female of body surface area 1.60 m^2 has a total body water of 29 litres, total body fat 17.0 kilograms, total body protein 8.0 kilograms (Keele and Neil, 1965). Although these values vary between individuals, they provide a guide to the body reserves of protein and fat. Total body fat varies between 12 to 20 per cent of body weight and an estimate can be obtained from skin fold thickness measurements (discussed below). Body cell mass varies from 35 to 45 per cent of body weight (Moore et al, 1963). Percentage of body water increases as the percentage of fat decreases.

Lean body mass is the whole body less non-essential or excess lipids. The lean body mass is relatively constant, unlike total body fat which varies considerably and reduces body density. Specific gravity is usually substituted for density because of its greater ease of measurement and is simply the ratio of body weight to volume. Body volume is readily calculated by water displacement using Archimedes' principle. The measurement of lean body mass can be made using K^{40} analysis or neutron activation analysis and if available, those techniques are simpler than the derivation from densitometry.

METABOLIC CHANGES IN STARVATION

Fasting in excess of 24 hours results in lipolysis which releases fatty acids for muscle metabolism. Net protein catabolism occurs as insulin levels fall with the falling plasma glucose. The amino acids produced from protein are converted to glucose by gluconeogenesis in the liver. In acute starvation, urinary nitrogen losses average 12 grams per day. This is equivalent to about 75 grams of muscle protein or 320

grams of wet muscle mass per day. If this loss were to continue, 30 per cent of the total muscle mass would be lost in 20 days. (Brennan 1977). Normally, however, adaptation to the use of fat as a major energy source occurs and the brain changes to keto acids as its principal source of energy (the brain is responsible for consuming 25 to 30 per cent of basal energy expenditure). Urinary nitrogen excretion falls to 3 to 4 grams per day. There is a rise in the keto acids acetoacetate and B-hydroxybutyrate which results in a mild metabolic acidosis. These conservation mechanisms ensure that only about 400 grams of muscle mass (2 per cent of the total) is lost in 20 days of chronic fasting. Any major trauma or illness may result, however, in a hypercatabolic state such that the catabolism of protein continues unabated. Marked and rapid loss of lean body mass results.

The consequences of uncomplicated protein-energy malnutrition were comprehensively studied by Keys et al (1950) in one of the most famous of human metabolic experiments. A group of 32 young adults, all conscientious objectors to war, were housed in a football stadium for periods of up to a year and subjected to carefully monitored dietary caloric restriction. Instead of their usual average dietary intake of 3490 kilocalories, only 1570 kilocalories were provided. A loss of 25 per cent body weight occurred over the 24 weeks of dietary deprivation. Subjects developed generalized wasting of body tissues, dry skin, increased pigmentation, slow hair growth and moderate alopecia. Cuts healed more slowly and wounds bled less freely. Heat tolerances increased but there was cold intolerance with associated cold hands and feet. Muscle cramps were frequent, movement became slower. There was loss of ambition and a narrowing of interests, depression, irritability and loss of libido. There were falls in body weight, packed cell volume, blood volume, total plasma protein, plasma albumin, pulmonary

ventilation, basal oxygen consumption, pulse rate and hand grip strength. Body weight changes were often masked by the development of oedema. Polyuria and polydipsia were common as were flatulence, colic and diarrhoea. Basal metabolic rate fell by 20 to 40 per cent with a persistent negative nitrogen balance. Recovery with re-feeding was often slow. Apathy and lethargy improved rapidly but cramps, flatulence and stomach ache often persisted for some time or appeared during rehabilitation. Fat accumulation preceded a feeling of well-being by several months.

NUTRITIONAL SUPPORT IN CANCER PATIENTS

INTRODUCTION

Malnourished patients should have nutritional support considered as part of therapeutic strategy. Johnston (1981) wrote that "...no patient with a reasonable chance of response to treatment should ever be asked to forego his true nutritional requirements at any time".

Nutritional support can be provided by either enteral or parenteral routes (Table 1.4) (Shils 1977, Lee 1979, Smith 1978, Copeland et al 1977, Dudrick et al 1977, Kelly 1986, Torosian and Daly 1986, Nixon 1986). Where the gut is intact, most authors agree that enteral nutritional support, by oral or tube feeding, is the most appropriate. Parenteral nutrition should be reserved for those patients in whom gastro-intestinal integrity is compromised.

Until recently, tube feeding was often poorly tolerated due to the use of wide bore naso-gastric tubes and bolus feeds. The introduction of fine-bore (1 mm. internal diameter) naso-gastric tubes with continuous drip feeding has markedly improved patient tolerance. Enteral nutrition has largely replaced parenteral nutritional support in the cancer patient. Parenteral nutrition is still necessary where nausea and vomiting, gastro-intestinal obstruction or malabsorption prevent adequate nutritional support with oral or tube feeding.

Much nutritional support for the cancer patient can be provided by the dietitian who instructs the patient (and spouse if appropriate) on suitable high protein and high energy foods whilst paying particular attention to flavour, texture and presentation. Oral supplemental feeds are provided when necessary. There is often little experimentation with different foods within the home. Smaller and more frequent meals are often helpful.

TABLE 1.4

Methods of Nutritional Support.

Enteral:	Oral dietary supplements
	- whole protein
	- defined formula diets
	protein hydrolysates
	"elemental" diets
	Soft diets
	Tube feeding
	Enterostomy feeding
Parenteral:	Peripheral venous supplementary feeding
	Central venous total parenteral nutrition
Supplements:	Vitamins (A, C, thiamine, folate)
	Minerals (Zn, Mg, Ca)
	Electrolytes (Na, K, Cl, P)

ENTERAL NUTRITION

Tube feeding is the preferred initial approach to nutritional support once oral intake has proven inadequate. Some cancer patients are unable to tolerate therapeutic amounts of tube feeds because of severe nausea, vomiting or abdominal bloating (Trotter and Calman 1981). These patients may require parenteral nutritional support, as will some patients undergoing bowel surgery, who have malabsorption or a short bowel syndrome. In most instances, unless anticancer therapy is contemplated, such intensive support is not warranted. Certainly, a proportion of patients improve significantly following vigorous nutritional support but in the absence of effective anticancer treatment the nutritional response is usually short-lived.

Terepka and Waterhouse (1956) reported on the effects of forced feeding, by intubation if necessary, in a group of nine cancer patients. Increases in body weight were usual but weight rapidly returned to baseline values on cessation of feeding. The increase in body weight was assumed to be due to fluid retention after analysis of body compartments. This report demonstrated that nutritional supplementation could improve anorexia but failed to provide evidence that retained nitrogen was used for protein synthesis. In a sub-group of patients, host metabolic rates and caloric expenditure were accentuated by force-feeding, and it was suggested that tumour growth might have been stimulated. Peden, Bond and Maxwell (1957) studied four patients with cancer and compared protein repletion induced by oral nutritional supplements or tube feeds with a control group of four malnourished non-cancer patients. They found that increases in total circulatory albumin and weight gain was greatest in non-cancer malnutrition suggesting a fundamental difference in the metabolic response of the two groups to nutritional support.

Pareira et al (1955) addressed the questions of whether cancer cachexia was tumour-induced or due simply to anorexia and whether "nutritional rehabilitation" of the cachectic cancer patient could be achieved. Sixty-four terminal cancer patients were studied; all were fed by naso-gastric tube for an average of 21 days. Many bedfast patients improved sufficiently to enable home care to be re-instituted for a while. Improvement in anorexia was almost universal except in those patients who survived no more than a few weeks after admission to hospital. It was concluded that cancer cachexia was due to malnutrition induced by anorexia and that hyperalimentation could break the anorexia-malnutrition cycle. It should be noted that although haemoglobin improved and nitrogen balance was recorded as positive, there was no change in plasma albumin. It was also recorded that "tumours that were palpable or visible seemed to increase in size pari-passu with gain in body weight". Tumour size was not measured.

These early studies suggested that nutritional support was of benefit to some cancer patients but that for many others the nutritional repletion was inadequate.

Attempts to reverse the malnutrition of malignant disease gathered momentum in the late 1970s with the development of suitable intravenous solutions for feeding and improvement in the equipment and techniques for central venous parenteral nutrition. In addition, fine-bore nasogastric tubes have simplified the administration of enteral feeds to the anorectic patient.

Fine bore naso-enteric tubes have required the development of suitable low viscosity liquid foods. These tubes have high patient acceptance, allow more mobilization, easier home feeding and reduce both complications and nursing time when compared with parenteral nutrition. (Shils 1977).

Nixon et al (1978) fed ten cachectic cancer patients, most with gastro-intestinal malignancies, via fine-bore naso-gastric tube and concluded that it was as successful as parenteral nutrition in improving serum albumin, triceps skin-fold thickness and urine creatinine. However, only five gained weight rapidly with tube feeding alone and peripheral parenteral nutrition was also utilized in three patients making interpretation of results difficult. In a subsequent publication (Nixon et al 1981) it was reported that nutritional support is less successful in cancer patients than in non-cancer patients. Elemental balances, serum proteins, anthropometrics and creatinine/height ratio were monitored. There were no differences between enteral or parenteral nutrition.

Enteral nutritional support for patients undergoing surgery for head and neck cancer was shown to be useful by Tweedle et al (1979) who observed a positive nitrogen balance in such patients. It should be emphasized, however, that positive nitrogen balance does not necessarily equate with an increase in lean body mass. Nevertheless, in patients responding to anti-neoplastic therapy, it has been reported that lean body tissue can be restored as evidenced by total body potassium measurements and nitrogen flux studies (Burt et al 1984). These studies were on patients with limited carcinoma of oesophagus which studies in this thesis have suggested are more likely to be hypometabolic and to therefore respond well to nutritional repletion. Other authors have also suggested that nutritional support can improve the cachexia of cancer (Ballantine et al 1978, Ching et al 1978).

The importance of patient selection is highlighted in a study by Elkort et al (1981). Twenty-four well nourished breast cancer patients were given enteral nutritional support during either adjuvant chemotherapy or chemotherapy for advanced disease. Some patients were

obese. All malnourished patients were excluded. Comparison with a control group eating a free choice diet showed no survival advantage for the nutritionally supported group and a suggestion that weight gain was associated with an increased risk of recurrent disease and mortality. The importance of advising weight reduction for obese breast cancer patients is highlighted.

Tube feeding has the advantage of obviating some of the problems associated with product palatability and even allows the use of the "elemental" diet. There is, however, little evidence of a benefit of such diets over whole protein foods (Trotter and Calman, 1981) (Appendix 7). In fact, Silk (1979) considers that in many instances whole protein diets are better than elemental diets because there is strong evidence that many dipeptides and tripeptides are better absorbed than single amino acids. The beneficial versus adverse effects of enteral nutritional support are listed in Table 1.5.

PRACTICAL ASPECTS OF TUBE FEEDING

The methods and benefits of tube feeding have been reviewed by Lee (1979), Alison et al (1979) and Fearon and Calman (1986). There are several types of fine-bore tubes available, some with a weighted tip, others which require a guide wire to aid insertion. It is important to ensure that the tip of the tube is placed in the stomach (or jejunum if required) prior to commencement of feeding because intubation of the bronchial tree is possible. Where feasible, feeds should be given by continuous drip as this minimizes bloating, reflux and satiety. Patients should be encouraged to eat and drink to supplement the tube feed. Advantages of naso-enteric feeding over parenteral nutrition are

TABLE 1.5

Effects of Enteral Nutritional Support

	<u>Beneficial</u>	<u>Adverse</u>
Subjective:	Increased well-being Appetite	Comfort Aesthetic
Objective:	Response rates Morbidity Toxicity Tumour kinetics Positive nitrogen balance Weight gain Increase adipose tissue.	Fluid retention Diarrhoea Hyperosmolality Intubation problems Stimulate tumour growth.

shown in Table 1.6. Preparations containing lactose are usually satisfactory but occasionally cause diarrhoea due to the relative lactose deficiency present in some patients. A change to a non-lactose product (for example soya-based) will usually obviate this problem. Patients should be encouraged to mobilize as exercise is a potent anabolic stimulus. Teaching patients how to administer their own feeds allows feeding to continue at home although night-time administration may not be feasible. If problems with gastric retention, reflux or nausea occur, duodenal or jejunal siting of the tube may obviate them.

A regular drip flow is often difficult to achieve by gravity alone and continuous infusion pumps designed for use with naso-enteric tubes are now available. Most of these pumps are small and mobile enough to enable patients to remain ambulant.

Energy intake should approximate 130-150 kilojoules (30-35 kilocalories) per kilogram body weight per day. Most cancer patients will require at least 11,000 kilojoules (2,500 kilocalories) per day although many will not tolerate the 2.5 to 3 litres of fluid required to deliver this amount of food. Attempts to reduce the volume of liquid feed and maintain caloric content increases the osmolality which predisposes to diarrhoea. Patients whose gut has been rested for lengthy periods (such as those on long term parenteral nutrition) or who have had long term severe anorexia may require diluted feeds initially. Concentration of feeds should be half strength or less initially and increased to full strength over several days. Patients eating moderately well will usually tolerate full strength feeds.

A protein load of about 1.0 gram per kilogram body weight is normally adequate but may need to be escalated if excessive protein loss is occurring, for example from a fistula. A nitrogen:kilocalorie ratio of between 1:200 to 1:150 is probably optimal in allowing for full

TABLE 1.6

ADVANTAGES OF TUBE FEEDING OVER PARENTERAL NUTRITION

Ease of administration

Economic

Less nursing time

Better patient acceptability

Patient mobility greater

Ease of outpatient application

Fewer side effects

utilization of the protein. The more catabolic patient may require a higher ratio of energy to nitrogen (Bozetti, 1979).

Metabolic abnormalities in patients on enteral tube feeding can include hyperglycaemia, hypoglycaemia, hypernatraemia, hyperkalaemia, hypophosphataemia, hypozincaemia and hypomagnesaemia (Vanlandingham et al 1981). Periodic evaluation for these metabolic abnormalities should be undertaken.

PARENTERAL NUTRITION

The methods, uses and complications of parenteral nutrition have been well described (Silk, Leiberman, Sharott 1978; Smith 1978; Ausman and Hardy 1978; Lee 1974) and only a brief review is described here.

Although the first intravenous injection was given as long ago as 1657 when Sir Christopher Wren and Robert Boyle gave tincture of opium to a dog, it took over 300 years for parenteral nutrition to become a viable proposition. The pioneering work of Dudrick in the late 1960s was a milestone in medicine and paved the way for the routine introduction of parenteral nutrition in clinical practice. Early studies clearly demonstrated a reduction in peri-operative morbidity as a result of the use of energetic parenteral nutritional support. In 1977 Copeland, Daly and Dudrick reported the results of parenteral nutrition in four hundred and six cancer patients who had received parenteral hyperalimentation for periods up to one hundred and forty seven days (average 23.9 days). In many (one hundred and seventy-five patients) chemotherapy was given concurrently with the nutritional support making results difficult to interpret. In addition, this was not a randomized study. However, weight gain was usual (mean 2.5 kilogram). A tumour response was obtained in 27.8 per cent of patients.

Blackburn (1977) also described weight gain in a selected patient population who had survived at least three weeks of concurrent treatment (chemotherapy, radiotherapy or surgery). Patients receiving enteral nutrition were not separated from those receiving parenteral nutrition. Improvement in the visceral proteins, albumin and transferrin, were recorded although the rise in albumin failed to reach significance. A more recent study has confirmed the safety of parenteral nutrition in cancer patients (Dindogru, 1981) but the overall value remains the subject of controversy. Indeed, Nixon (1986) restricts his use of parenteral nutrition to three groups of patients; those with compromised gut function, cachectic patients with responsive neoplasms requiring nutritional support and patients studied in trial settings.

BENEFITS AND PROBLEMS OF NUTRITIONAL SUPPORT

Many have voiced concern that tumour growth could be stimulated by nutritional support. Some animal studies devised to examine this issue have provided data which suggests that tumour growth can be stimulated by nutritional support but the relevance to humans is debatable. Tannenbaum and Silverstone (1953) reported that tumour growth in the experimental animal was dependent on nutritional status. These findings have been confirmed by others (Ota et al 1977; Lowry et al 1978). Of more importance is that most studies suggest that tumour weight increases pari passu with host body weight. Tumour growth has also been shown to accelerate when initial dietary restriction is replaced with an ad-lib diet. Tumour growth, however, eventually plateaus at a level similar to rats fed an ad-lib diet commenced at the time of tumour inoculation (Daly et al, 1980).

Cameron and Rogers (1977) showed in hepatoma-bearing rats treated with hydroxyurea that hyperalimentation improved response rates but

shortened survival. It is possible that the increased response rates reflected an alteration of tumour kinetics such that more cells were recruited into the cell cycle. A cell kinetic study in man, however, has reported little evidence of increased tritiated thymidine uptake by colonic tumours following several weeks of parenteral nutrition (Mullen, Buzby and Gertner et al, 1980). The shortened survival of rats in the Cameron paper is important and lends some support to a study by Nixon et al (1983) in which gut carcinoma patients on parenteral nutrition and receiving chemotherapy had a shorter survival than patients not receiving nutritional support but having the same chemotherapy. Although others have not yet confirmed these findings (Brennan (1981) reported no change in survival in a literature review), they demand further investigation.

There have been a number of prospective randomized trials in the use of parenteral nutrition as an adjunct to cancer therapy. Most studies have accrued only small numbers of patients making the results difficult to interpret or statistically valueless. No survival advantage has been demonstrated for either enterally or parenterally supported patients compared with non-nutritionally supported patients. Amelioration of treatment-induced toxicity has been examined in some studies. Issell (1978) has suggested a reduction in chemotherapeutic toxicity with parenteral nutrition but Popp (1982) did not substantiate this claim. Serrou (1979) reported an improved response to chemotherapy following nutritional support but a subsequent report was less favourable (Serrou 1981). Valerio (1978) reported results which failed to demonstrate a benefit with TPN as adjunctive therapy with radiotherapy.

In a comprehensive trial Levine et al (1982) studied 42 patients with diffuse histiocytic lymphomas who were treated with prednisolone, high dose methotrexate, adriamycin, cyclophosphamide and VP-16-213. Subsequent consolidation therapy employed nitrogen mustard, vincristine,

procarbazine and prednisolone. Patients were randomized to receive adjuvant parenteral nutrition or a standard diet. There was no difference in drug tolerance, degree of myelosuppression or lean body mass between the groups. Initial nutritional status also made no difference to the outcome. A second study reported in the same article examined the use of parenteral nutrition in 32 young patients receiving intensive chemotherapy for metastatic sarcomas. Again, nutritional supplementation produced no benefit over a control group with respect to response rates and median survival. There was no suggestion that patients had a poorer prognosis as a result of nutritional support. These and other similar results suggest that there may be fundamental metabolic abnormalities in cancer patients which prevent adequate nutritional repletion.

One other problem inherent in these studies is the use of different patient populations and therapies making direct inter-study comparisons difficult. It is quite feasible that cancers from different primary sites respond in different ways to nutritional support and that, as a consequence, the outcome of treatment may be modified. In many studies tumours with normally low therapeutic response (for example colon, lung) have been examined. It could be justifiably argued that any lack of therapeutic efficacy in such tumour groups is predictable because of their normally low response rate to any form of therapy. Conversely, tumours which respond readily to therapy could be inappropriate to study since such patients usually do well without nutritional support.

METHODS OF ASSESSMENT OF NUTRITIONAL STATUS AND THEIR
USE IN MONITORING RESPONSE TO NUTRITIONAL SUPPORT.

Ideally, tests of nutritional status should: (1) detect early malnutrition; (2) quantify the nutritional deficit; (3) be applicable to all patients with malignant disease; (4) be reproducible and reliable; (5) be easy to perform and interpret. No one test fulfils all these requirements.

At present, therefore, a number of tests are necessary to adequately document the state of the following: lean body mass, adipose tissue, vitamins and minerals.

PHYSICAL SIGNS OF MALNUTRITION

Most physical signs of malnutrition are not specific for individual deficiencies (Van Itallie 1977). Some vitamin deficiencies, however, produce specific abnormalities such as corneal and conjunctival xerosis, keratomalacia and Bitot's spots in vitamin A deficiency, calf muscle tenderness, leg weakness, cardiomyopathy (thiamine), angular stomatitis, cheilosis (riboflavin), nasolabial seborrhoea, glossitis, peripheral neuropathy (vitamin B₆), petechiae, bleeding gums, follicular hyperkeratosis (vitamin C), rickets (children) osteomalacia (adults) (vitamin D), anaemia, paraesthesiae, areflexia, dementia (vitamin B₁₂).

Deficiencies of trace metals usually produce non-specific signs and symptoms such as weakness and lethargy. Zinc deficiency may cause acrodermatitis enteropathica in children and similarly a diffuse skin eruption has been described in adults.

Protein-energy malnutrition may produce hair dyspigmentation and loss, a dermatosis, increased skin pigmentation particularly over the malar prominences, weakness and bradycardia (Jelliffe 1966). Detection of less major disturbances of protein and energy intake is on clinical

grounds more difficult; loss of body fat and lean body tissue may only be evident after careful measurement. In addition, documentation of the nutritional changes during longitudinal studies needs objective measurement. Table 1.7 lists the tests of nutritional status currently available.

DIETETIC HISTORY

The estimation of food intake forms an essential part of determining overall nitrogen balance. A long dietary (seven day) diary is a more accurate method of assessing protein-energy intake than a shorter diary but is difficult to perform in practice. A 24 hour dietary recall history is almost as accurate and simpler to administer (Costa 1977b). The most common problem with the shorter history is the overestimation of low intakes (Madden et al 1976). Therefore, the studies in this thesis which utilised a dietary history are likely to have overestimated intakes. As an added precaution, for the dietetic study, a 20% reduction in the minimal daily allowances for nutrients was made to ensure that the documented dietary deficiencies were real. The results therefore probably underestimate the extent of dietary deficiencies.

ANTHROPOMETRIC DATA

The use of body measurements is one of the simplest ways of assessing nutritional status (Jelliffe 1966). Such measurements have been extensively validated in the assessment of PEM. In developing countries body weight, percent weight loss, upper arm circumference and skin fold thickness have an established place in nutritional assessment in the field. Body weight is an unreliable index of acute nutritional changes but becomes more reliable once PEM is established (weeks to months) (Editorial 1973). Weight changes are unreliable when there is

TABLE 1.7

Assessment of Nutritional Status

Dietetic History:	Calories	Protein	Vitamins	Minerals
Anthropometric Measurements:	Weight, % weight loss			
	Upper arm circumference			
	Skinfold thicknesses			
Biochemical:	Urine:	Nitrogen balance		
		Hydroxyproline		
		3-Methylhistidine		
		Creatinine - Height index		
	Blood:	Proteins - Albumin, Transferrin		
		Retinol binding protein		
		Pre-albumin		
		Amino Acids		
		Hormones		
		Minerals		
		Vitamins		
Haematological:	Lymphopenia			
	Anaemia: haematocrit			
	Skin anergy			
Hair root analysis				
Body Composition:	K40 estimation (lean body mass)			
	Body density (adipose tissue)			
	Isotope dilution (fluid compartments)			
	Neutron activation analysis (minerals, nitrogen)			
	CT scanning (adipose tissue)			
	Ultrasound (adipose tissue)			
Basal Metabolic Rate:	Oxygen consumption			
	Whole body calorimetry			

fluid retention (e.g. kwashiorkor, ascites, peripheral oedema) or an increased extravascular fluid volume (e.g. cancer).

Measurement of height is useful because it correlates with sex and weight. Hume (1966) has produced a formulae for predicting lean body mass from height and weight. His study was undertaken on a Glasgow population. This formula for lean body mass was utilised for data analysis in the albumin metabolism study but was not considered a useful adjunct to the standard anthropometric data used in the other studies.

Assessment of body fat from the measurement of skin-fold thickness using standardized skin-fold calipers has been shown to be reliable and reproducible (Durnin and Womersley 1974; Durnin and Rahaman 1967; Frisancho 1974). Body fat can be predicted from skinfold measurements with an error of $\pm 3.5\%$. Different skinfold thicknesses produce correlation co-efficients of around -0.80. There is therefore little need to measure more than one skinfold thickness because the increase in accuracy is marginal. Sites measured by Durnin and Womersley were the triceps, subscapular, biceps and suprailiac. All measurements were performed on the right side of the body on a Glasgow population. Although Jelliffe (1966) has suggested that the non-dominant (left side) might be the more appropriate, measurements in this thesis refer to the right arm so that comparison could be made with Durnin's Glasgow data. For optimum reproducibility, these tests are best performed by a single observer because there can be a relatively large inter-observer error.

Upper arm circumference measured at the midpoint of the humerus can be corrected for triceps skinfold thickness (TSFT) to produce an estimate of the mid-arm circumference (MAMC) and hence of lean body mass (i.e. $MAMC = \text{arm circumference} - \pi(TSFT)$). MAMC has been shown to correlate reasonably well with lean body mass and with weight (Martorell et al 1976; Loewenstein and Phillips 1973; Jelliffe 1966).

ESTIMATION OF LOSSES

(a) ENERGY STATUS

Measurement of energy output is difficult and requires either direct or indirect calorimetry (Shenkin 1979a). Energy expenditure depends on basal metabolic rate, physical activity, age and climate (Costa 1977b). Controlling for these variables is not easy and in most situations basal metabolic rate is determined at rest under standard conditions of temperature. Most calorimetric studies are indirect due to the difficulty of using direct calorimetry in humans. Energy expenditure is calculated from measurement of oxygen consumption and carbon dioxide production.

The production of ketones as possible markers of the utilization of fat stores has been investigated and Rich and Whitehouse (1979) have shown an association between the failure of post-operative ketone production and mortality. Lack of a ketone response probably represents the persistence of protein catabolism with a rapid loss of lean body mass. This is confirmed by 3-Methylhistidine excretion (see below) which is higher in patients who have not shown keto-adaptation to hypocaloric feeding (Williamson et al 1977). Cancer patients frequently show a poor keto-adaptation to starvation and may be a part explanation for the high incidence of cancer cachexia. Non-excretion of ketones, however, also occurs with adequate caloric intake and therefore the use of ketone production as a nutritional marker is limited to their presence which implies keto-adaptation.

(b) PROTEIN STATUS

(i) Urine Tests

Nitrogen balance

Despite inaccuracies, nitrogen balance studies have remained one of the most-used tests of protein turnover because of their ease of

application. There has, however, been some controversy about the validity of the technique (Costa 1977; Isaksson and Sjogren 1967).

Total urinary nitrogen increases with the amount of net protein catabolism, and can be very large (up to 50 g/day) (Shenkin 1979b). Allowance of 2 g of nitrogen per day for losses other than urinary (e.g. skin and faecal) is usually sufficient. If fistulae, large amounts of exudate, diarrhoea or malabsorption are present losses may be greater. Allowing for loss of nitrogen in vomit can also be difficult and, as a rule, over-estimation of intake and under-estimation of output occurs which results in a more positive nitrogen balance than actually exists. The test, however, gives a useful guide to the extent of overall protein metabolism.

Costa (1977b) raises the question of other losses such as expired nitrogen, and presents some data to suggest that this might be an important source of unaccounted nitrogen loss. There would seem considerable doubt in the majority of people, that this represents an important route of nitrogen excretion. It is true however, that a net positive nitrogen balance using this urinary nitrogen technique is common despite clear evidence of continuing net protein catabolism. The exact reasons for this frequent anomaly remains an enigma (Hegsted 1976).

3-Methylhistidine

3-methylhistidine is a catabolic product of muscle breakdown. It cannot be re-utilised and is excreted unchanged in the urine. Its rate of excretion is proportional to the rate of skeletal muscle catabolism which can be estimated providing dietary intake is known. Meat products cause an increase in excretion of 3-methylhistidine which can persist for up to three days following withdrawal from the diet (Tomas, Ballard and Pope 1979). There is also a suggestion that the increased catabolism associated with the increased anabolism of a good diet may increase the

urinary excretion (Shenkin and Steele 1978). This test is potentially useful (Haverberg et al 1975) providing problems of the muscle content of 3-methylhistidine can be resolved (Holbrook, Gross, Irving 1979). Further research is necessary to define its role before this test can be used routinely as an index of skeletal muscle catabolism.

Creatinine-height index

The production of creatinine from creatine in muscle is irreversible and occurs at a fairly constant rate. Creatinine excretion therefore gives an estimate of total skeletal muscle mass providing there is no rapid muscle catabolism. The 24 hour excretion of creatinine, expressed as a percentage of the calculated ideal value (as obtained from "ideal" body weight tables) is called the creatinine-height index. The index requires accurate urine collections and frequently fails to correlate the estimates of skeletal muscle mass as determined by MAMC (Shenkin and Steele 1978). (Shenkin personal communication 1981).

Urinary Hydroxyproline

Hydroxyproline excretion increases with muscle breakdown but is not a useful index of muscle catabolism in cancer patients where bone destruction, which also increases its excretion, may be present.

(ii) Total body potassium

^{40}K can be measured in whole body monitors and from this lean body mass can be estimated (Hawkins and Goode 1976). This method is difficult with ill patients, requires facilities for the equipment and has errors which are greatest in patients with the most muscle wasting (DeWys, personal communication 1981).

(iii) Total body nitrogen

The measurement of total body nitrogen provides the most accurate assessment of whole body protein status available at present. The

methodology involves neutron activation analysis (Oxby et al 1978). The technique has been used to follow the changes in body composition in surgical patients (Hill G.L. et al 1978). Neutron activation analysis is not available in most centres and for application to ill patients requires on-site facilities. Using this technique Cohn et al (1981) have shown that weight loss in cancer patients with solid tumours was mainly due to loss of body fat and muscle mass. Muscle mass was lost at the expense of adipose tissue. Visceral protein mass was largely spared.

(iv) Hair Root Analysis

Hair root morphology has been reported as a sensitive index of malnutrition and one which can detect marginal degrees of malnutrition (Bradfield 1972a, 1972b). Hair matrix cells proliferate at a rate greater than all other tissues with the exception of bone marrow. Hair synthesis occurs principally in the bulb and the entire germinative matrix can be replaced in less than a day. This rapid turnover of protein makes the hair bulb sensitive to dietary protein deprivation. Changes in the bulb have been shown to occur within ten days of dietary protein restriction, and significant reductions in bulb diameter have been noted after 15 days of protein deprivation in normal volunteers (Bradfield 1972b).

This makes hair root analysis a more sensitive index of PEM than plasma albumin, which takes up to 3 weeks to show a response, and probably a less sensitive test than the shorter half-life plasma proteins (RBP and PA). Jordan (1976) has confirmed that hair root changes precede serum albumin changes.

Normal hair exists in a growing phase (anagen) and resting phase (telogen). Intermediate, or involuting hairs are known as catagen hairs. Normally, anagen hairs comprise greater than 80% of total hair

counts but there is a wide normal variation. Johnson et al (1976) reported $80.1 \pm 16.3\%$ anagen hairs in a group of well nourished children and $48.1 \pm 23.8\%$ for severely malnourished children. They failed to find, however, significant differences from normal in anagen counts or percent of atrophic hairs in moderately malnourished children (weight/height ratio 71.89% of standard). Other morphological changes in anagen hairs, described by Bradfield, include bulb atrophy, bulb dyspigmentation, sheath changes and shaft changes. Many of these changes, such as bulb and shaft dyspigmentation are difficult to quantify in an adult population where dyspigmented hair is common. Minor changes such as bulb fraying are also difficult to evaluate (Johnson et al 1976). An additional problem in the cancer patient is the effect of cytotoxic changes on the hair matrix which frequently results in epilation, bulb atrophy or shaft thinning (Van Scott, Reinertson, Steinmuller 1957; Crouse and Van Scott 1960).

Although some authors have claimed the technique of epilation as traumatic (Kanawati and McLaren 1970), others have found this is not a problem (Bradfield 1970b; Jordan 1976). Most authors are agreed, however, that the procedure of examining the hairs by light microscopy to determine morphology is tedious, and Johnson et al (1976) concluded, largely because of this problem, that this method had little to offer over conventional anthropometric tests.

The protein content of the anagen hair root can also be assayed (Jordan 1976; Crouse, Bollett, Owens 1970; Zain et al 1977). Hair root protein is reported to correlate well with bulb diameters and simply reflects bulb volume, and Bradfield has suggested, that the technique has no added value over and above morphological assessment. It is of interest, however, that Zain et al found that hair root protein and DNA content reflected the severity of PEM in children.

More recently Bradfield (Bradfield, Chan, Stephens 1981) has confirmed the abnormalities noted above in malnutrition and placed greater emphasis on the contribution of transitional forms (i.e. bulb atrophy, fraying, dyspigmentation, shaft narrowing and sheath absence) to the variance in bulb diameter. Jourdan (1980) has also concluded, in a study on surgical patients, that hair root morphology provides an easy assessment of protein status. Morphological changes correlated well with serum albumin changes but not with anthropometric measurements. He noted significant changes in the anagen percentage within ten days of major surgery.

(v) Blood tests

Plasma transport proteins

Albumin (Alb), pre-albumin (PA), retinol-binding protein (RBP) and transferrin (TF) have all been shown to be useful markers of nutritional status in PEM. (Ingenbleek et al 1975; Shetty et al 1979b; Editorial 1973).

Albumin

Albumin metabolism is discussed in detail in Section III. Compared with the other plasma proteins mentioned above, albumin has, in normal man, the longest half life of about 21 days. This long half life means that dietary changes may not be reflected in changes in plasma albumin for several weeks. In fact, plasma albumin may change very little even with moderate PEM of several months duration. Keys et al (1950) showed little change in albumin levels in induced uncomplicated PEM after 26 weeks of semi-starvation. Albumin concentration has been frequently used, however, as a marker of nutritional status, despite this fact. Hypoalbuminaemia in PEM is more a feature of kwashiorker than marasmus due to a relatively greater protein deprivation. In this situation its

concentration may serve as an index of the severity of the malnutrition (Shetty et al 1979a).

The commonest cause of hypoalbuminaemia in the Gartnavel/Western Infirmary Hospitals, Glasgow is cancer (A. Fleck, unpublished observations). Hypoalbuminaemia can occur early in the clinical course of cancer and this suggests that causes other than malnutrition may be operative.

Transferrin

Transferrin is a plasma transport protein with a half life of about 7-8 days. Normal values vary over a large range which limits its usefulness as an index of early malnutrition (Shetty et al 1979b). Iron deficiency, not uncommon in malignancy, also interferes with its interpretation by stimulating synthesis.

RBP - PA

Retinol binding protein (RBP) circulates as a complex bound to pre-albumin (PA). Pre-albumin has a short half life of about 3 days whereas that of RBP is a mere 12 hours. These short half lives make these proteins potentially sensitive indices of PEM and both Shetty et al (1979) and Ingenbleek (1975) have reported that this is the case.

Amino Acids:

PEM produces a characteristic plasma aminogram which is discussed in detail in Section III together with the reported abnormalities in cancer, and their role as tests of nutritional status.

Acute phase Reactants

The acute phase reactants are a group of plasma proteins whose concentrations increase as a response to physical stress e.g. trauma, infections. Examples include fibrinogen, alpha-1-antitrypsin and C-reactive protein. The presence of an acute phase response in cancer has been shown in a number of reports (Coombes et al 1977; Child et al

1980, Huggins C. 1949, Raynes and Cooper 1983, Grindulis et al 1981, Durdey et al 1984).

The relevance of this acute phase response to the metabolic changes of cancer is not clear, but the concentrations of other plasma proteins, especially albumin, may be reduced as a consequence. Because of the complex interactions of acute phase proteins with other plasma proteins and because of their potential importance in determining or in monitoring metabolic events, C-reactive protein was monitored in patients under study in this thesis.

The acute phase response of infection causes a slight to moderate decrease in the plasma concentrations of the hepatic export proteins albumin, RBP, PA, TF (Johnson 1979). These changes are important and reinforce the need to monitor the acute phase reactants during nutritional studies in cancer patients.

VITAMINS

Vitamin status can be assessed with reasonable accuracy from a dietary history. Potential deficiencies may be detected before laboratory tests become abnormal. Assays for some vitamins are also difficult and Vitamin A was selected for assay for the nutritional studies in this thesis because it is bound to RBP-PA, is often abnormal in cancer patients (Soukop and Calman 1979), and may be important for chemotherapeutic response (Soukop and Calman 1978), tumour induction (low levels)(Wald et al 1980) and prevention (normal or high levels) (Newberne and Rogers 1973; Sporn 1976; Editorial 1980a).

Vitamin A has an important role in the maintenance of cell membrane function (especially of epithelial tissue) (DiPalma and McMichael 1979; Sporn 1979). Vitamin A and its analogs (retinoids) may be useful in cancer prevention by stabilising cell membranes although Willett et al

(1984), in a review of epidemiological data, failed to show an increased risk of cancer with low serum vitamin A levels. Hennekins et al (1986) consider, however, that the weight of data is in favour of a relationship between low vitamin A levels and cancer and call for prospective randomized trials to answer this important question.

Smith et al (1973) have suggested a defect in hepatic retinol release as a cause of reduced Vitamin A, RBP and PA in PEM. It is known that children with PEM placed on high protein diets devoid of Vitamin A can result in a rise in Vitamin A. This suggests that the fall of the carrier protein is the limiting factor, and needs to be borne in mind when investigating the cancer patient. Zinc may also play a role in hepatic retinol release (see below).

TRACE ELEMENTS

The role of trace elements in cancer has been reviewed by Schwartz (1975). Those essential (from animal experiments) are: iron, iodine, fluorine, copper, manganese, zinc, cobalt, chromium, selenium, molybdenum, tin, vanadium, silicon and nickel. Of these, only zinc is discussed further. Because of its potential role in many of the abnormalities investigated in this thesis, it was considered appropriate to measure serum zinc levels in association with the other tests of nutritional status.

"Zinc metallo-enzymes are of basic importance to many intracellular biochemical mechanisms; in particular they regulate various stages of protein and nucleic acid synthesis" (Fell and Burns 1976 and 1978). Zinc deficiency is associated with poor wound healing, presumably because of its role in protein synthesis. It may be important, as is Vitamin A, for cell membrane integrity. There has been a suggestion, too, that zinc deficiency, as a result of increased urinary losses seen in chronic

alcoholic cirrhosis can cause a reduced liver synthesis of RBP and reduced retinine reductase activity. It has been suggested that vitamin A levels in lung cancer may be low because of reduced RBP production as a result of low zinc levels (Atukorala et al 1979). In addition, low plasma zinc and vitamin A levels may be co-factors in the cause of oesophageal carcinoma (Mellow et al 1983).

Zinc deficiency has also been incriminated as a cause of smell and taste abnormalities (Henkin 1971).

Most zinc (98%) is intracellular but this is difficult to measure and the usual measurement is plasma zinc by atomic absorption spectrophotometry (Delves 1976). Infection, drugs, and moderate-severe PEM lower plasma zinc which often remains within the normal range in the early phases of PEM. Fifty to sixty percent of circulating zinc is bound to albumin, 20-30% to an alpha-2-macroglobulin, and 10% to amino acid complexes, with 3% found in white cells. There is also a circadian rhythm for plasma zinc and higher values are found in the afternoon than the morning.

About 70 zinc metallo-enzymes have been isolated of which alkaline phosphatase is but one. Alkaline phosphatase falls with zinc depletion, as do tissue levels of zinc, RNA, DNA and total protein (Fell and Burns 1978).

Zinc deficiency has also been shown to cause impairment of cell mediated immunity in mice (Fernandes et al 1979) and atrophy of lymphoid tissue and thymus. Children with PEM also have similar immunological changes and anergic delayed skin hypersensitivity reaction can be restored with a topical zinc preparation (Golden et al 1978). Zinc absorption through skin is great enough to correct zinc deficiency in the rat (Kean and Hurley 1977).

IMMUNOLOGICAL AND HAEMATOLOGICAL TESTS

Law, Dudrick and Abdou (1973) evaluated the immunocompetence of patients with PEM and found impaired T cell function (depressed delayed skin reactivity and in vitro lymphocyte responses to phytohaemagglutinin). The B-lymphocyte was evaluated by determining serum IgM antibody responses to keyhole limpet haemocyanin and was also found to be impaired. They found that TPN could reverse these abnormalities. None of their patients had cancer.

Bistrrian et al (1975) found reductions in total lymphocyte count and in delayed skin hypersensitivity in a group of semi-starved hospitalized patients. The disease types were not discussed. There were no carefully conducted studies in cancer patients to verify the value of delayed hypersensitivity tests as tests of nutritional status at the time this thesis was planned, although they had been widely advocated as being of value for this purpose. Copeland, Daly and Dudrick (1977) provide data which suggests that skin immunocompetence is frequently restored with nutritional repletion but the effects of anti-cancer therapy cannot be dissected from the effects of nutritional support in this study.

Blackburn et al (1977) reported that all patients who failed to respond to nutritional support were anergic and subsequently died in hospital but failed to mention the number of responders who were anergic or to correlate anergy with nutritional status. Lymphocytic activity and skin reactivity to antigenic stimuli have been reported depressed in leukaemia, Hodgkin's disease and lung cancer, but this may be a result of surgery, chemotherapy, the cancer or of malnutrition, making the interpretation of lymphopaenia and skin anergy difficult. In fact, normal controls and even relatives of cancer patients, may have skin anergy (Morris et al 1979a). Douglass (1980) found total lymphocyte counts the least predictive parameter of potential response to

nutritional therapy that he measured, but was a better test of predicting response to nutritional support or antineoplastic therapy than were skin recall tests to antigen.

Daly, Dudrick and Copeland (1979) published a paper examining "nutritional indices as prognostic indicators". Criteria of malnutrition included two of the following: recent weight loss greater than 10%, serum albumin less than 3.5 g/l and negative reaction to a battery of five recall skin test antigens. They found greater weight loss in skin test negative patients, a lower plasma albumin and an increase in postoperative mortality and morbidity. This paper however fails to clarify whether nutritional problems per se were the cause of the poor prognosis or type and staging of disease, and in addition whether skin anergy is a specific or non-specific problem.

More recently, Twomey, Ziegler and Rombeau (1982) reviewed the usefulness of skin tests as an assessment of nutritional status. Of two hundred publications reviewed only 15 provided objective data correlated with patients! In addition, only three used aged-matched controls. They had to conclude that the value of "skin testing in nutritional assessment remains unproved".

Keys et al (1950) suggested that haematocrit correlated best with weight loss in uncomplicated PEM. In cancer patients, anaemia is common both as a complication of the disease and of its treatment rendering this test invalid as an index of nutritional status.

MONITORING NUTRITIONAL STATUS IN CANCER PATIENTS

There have been few publications in which the measurement of nutritional status in the cancer patient was the purpose of the study. In most publications, evaluation forms part of another study in which variables have been correlated with prognosis or used to assess response

to nutritional support. In most, only a few selected variables have been examined.

Stuart (1979) sums up well when he writes "nutritional assessment is more of an art than a quantitative science at present. No formulas allow precise estimation of nutritional well-being ...". At the time the studies in this thesis were planned (1978), it was clear that nutritional status should be assessed as fully as possible. Lack of ready availability of some of the more sophisticated tests and the need to consider the welfare of ill patients meant that tests of nutritional status were confined to locally available laboratory and clinical expertise. Table 1.8 lists the "nutritional screen" which became the basis for assessing the nutritional status of patients studied in this thesis.

What's past is prologue.

Shakespeare

Tempest 11

TABLE 1.8

Tests of Nutritional Status used in this thesis.

1. Dietary recall history (24 hour).
 - Total energy + protein intake
 2. Anthropometric data.
 - Weight. Height.
 - %weight loss
 - Mid arm muscle circumference (MAMC)
 - Triceps + subscapular skinfold thicknesses
 3. Urinary data (24 hour collections).
 - Total urinary nitrogen
 - Urinary urea, creatinine
 - Urinary zinc
 4. Blood.
 - Serum: albumin
 - pre-albumin
 - retinol binding protein
 - transferrin
 - total protein
 - "Acute phase" proteins
 - C-reactive protein
 - alpha-1-antitrypsin (albumin study)
 - Liver function tests
 - Renal function - urea
 - creatinine
 - Vitamin A
 - Plasma zinc
-

5. Skin recall antigen tests

Trichophyton rubrum

Mumps

Candida

P.P.D. 1:1000

6. Hair root morphology

AIMS

The studies described in this thesis investigate malnutrition in the cancer patient in two separate, but interrelated areas. The first field of research (Section II) was designed to investigate the impact of cancer on the nutritional status of the host and to evaluate the role of enteral nutritional support in the cancer patient. In this regard, the following studies were conducted:

- (1) An investigation of the prevalence of anorexia and other gastro-intestinal symptoms in an oncology outpatient population.
 - (2) An evaluation of dietary recall histories in determining the incidence and nature of dietary insufficiency in cancer patients.
 - (3) An assessment of the palatability of various commercial oral dietary supplements and the possible influence of palatability on adequacy of oral nutritional supplementation.
 - (4) An examination of the prevalence and type of taste abnormalities in the cancer outpatient population.
 - (5) An assessment of the extent and nature of the nutritional deficit in a group of clinically malnourished cancer patients using anthropometric and biochemical tests of nutritional status with a multivariate analysis of each test.
 - (6) An evaluation of the role of enteral nutritional support in improving the nutritional status of cancer patients, using the tests of nutritional status measured in (5) above, in the absence of the influence of cytotoxic chemotherapy.
-

- (7) Hair root morphology was evaluated for changes with nutritional support and to determine the value of this technique for monitoring nutritional status in cancer patients.
- (8) C-reactive protein was monitored in malnourished cancer patients as a possible marker of an acute phase response and possible indicator of changes in whole body metabolism.

The second field of research (Section III) involved investigation of abnormalities of protein metabolism in cancer patients with weight loss. The following studies were undertaken.

- (1) Plasma amino acid profiles in cancer patients with weight loss were measured as a possible index of changes in protein metabolism.
- (2) Albumin metabolism (rate of synthesis and catabolism) and distribution was studied to assess the causes of hypoalbuminaemia in malignant disease and by inference, the metabolic rate of cancer patients.
- (3) Changes in plasma proteins were studied following plasma exchange as a way of testing a hypothesis that many of the metabolic abnormalities induced by malignant disease are the result of products released by the tumour tumour-bearing host and which alter host metabolism.

The thesis concludes with a discussion which integrates the results of the separate studies (Section IV).

SECTION II

STUDIES OF THE NUTRITIONAL ABNORMALITIES
IN CANCER PATIENTS AND OF THE EFFECTS OF
ENTERAL NUTRITIONAL SUPPORT.

One swears by wholemeal bread, one by sour milk; vegetarianism is the only road to salvation of some, others insist not only on vegetables alone, but on eating those raw. At one time the only thing that matters is calories; at another time they are crazy about vitamins or about roughage.

The scientific truth may be put more briefly; eat moderately having an ordinary mixed diet and don't worry.

Sir Robert Hutchison
Newcastle Medical Journal, vol.12, 1932.

SECTION II

STUDIES ON THE NUTRITIONAL ABNORMALITIES IN CANCER PATIENTS
AND THE EFFECTS OF ENTERAL NUTRITIONAL SUPPORT

1. THE PREVALENCE OF ANOREXIA AND OTHER
GASTRO-INTESTINAL SYMPTOMS IN CANCER

Now good digestion wait on appetite,
And health on both!

Shakespeare (1564-1616)

Macbeth iv 3

Introduction

As part of a larger study (Trotter et al 1981c and appendix VII), the prevalence of gastro-intestinal complaints presenting to the liaison health visitor were documented in patients attending a medical oncology outpatient department.

Method

The liaison health visitor working with the oncology unit documented the reason for her assessment of outpatients and the source of referral over a five month study period. Symptoms of anorexia, nausea, vomiting, constipation and diarrhoea were amongst those documented (see Trotter et al 1981c - Appendix VII for details).

Results

Of the symptoms volunteered by patients, anorexia was by far the commonest and the one that seemed to concern patients most. Of 237 assessments made during this study period, anorexia occurred in 121 patients (51% of those interviewed) and was often associated with nausea (31%) and vomiting (18%) (Table 2.1).

TABLE 2.1

GASTROINTESTINAL SYMPTOMS

	<u>Number of patients (sample size = 237)</u>	<u>Percent of total assessments</u>
Anorexia	121	51.0
Nausea	75	31.6
Vomiting	44	18.6
Constipation	54	22.8
Diarrhoea	10	4.2

TABLE 2.2

CAUSES OF ANOREXIA

	<u>Number of patients (sample size = 237)</u>	<u>Percent of total assessments</u>	<u>Percent of patients with anorexia</u>
Caused by cytotoxic chemotherapy	59	24.9	48.8
Caused by radiotherapy	20	8.4	16.5
Caused by analgesics	9	3.8	7.4
No obvious therapeutic or iatrogenic cause	33	13.9	27.3
	<u>121</u>	<u>51.0</u>	<u>100.0</u>

In almost half those patients the major cause of anorexia was cytotoxic chemotherapy, with radiotherapy and analgesics implicated in 16% and 7% respectively (Table 2.2). Thirty-three (27%) of the anorectic patients, however, had no obvious iatrogenic cause for their anorexia, which may have been caused by the malignant disease itself, psychological factors, or both. Oral nutritional supplements were supplied to 38 patients by the visitor during home visits. Constipation, probably related to analgesics, worried 23% of patients interviewed. Diarrhoea was an infrequent problem, occurring in only 4% of patients.

Discussion

This study has clearly shown the high incidence of anorexia in oncology outpatients, and demonstrates the importance of the liaison health visitor as a link in the chain of nutritional support. The high incidence of other gastro-intestinal symptoms such as nausea and vomiting, in association with anorexia, suggests a high probability of malnutrition in the study population.

2. DIETARY RECALL HISTORIES IN ONCOLOGY PATIENTS

Give me neither poverty nor riches;
Feed me with food convenient for me.

Proverbs 30.8

Introduction

The dietitian, whose expertise is fundamental in establishing the composition of dietary intake by patients, has a central role in the dietary management of patients. Dietary history information is essential for nitrogen balance studies and for providing a basis for designing oral dietary supplementary regimens.

In view of the high incidence of anorexia noted in oncology outpatients, it was considered useful to determine the extent and nature of dietary insufficiency in a cancer population attending a clinical oncology unit, and to assess the efficacy of a linear analogue scale assessment of anorexia in detecting changes in energy and protein intakes.

Method

A 24 hour dietary recall history was obtained by the dietitian from oncology outpatients. Two groups were evaluated: those with symptomatic anorexia and a second group, not previously seen by the dietitian, selected at random from the outpatient population. A record was kept of specific food aversions and food fads.

The dietary data was analysed on an ICL 1900 computer using a programme devised by Tayside Health Centre based on the McCance-Widdowson tables of the composition of food (Paul & Southgate 1978). Analysis of individual foods was made by the computer and combined to provide the

total intake of the elements (sodium, magnesium, copper, chloride, potassium, phosphorus, zinc, calcium, iron, sulphur); vitamins (thiamine, nicotinic acid, riboflavin, B6, pantothenic acid, vitamin C, vitamin E, vitamin A (as retinol), carotene, vitamin B12, folate, vitamin D) and of protein, fat, carbohydrate, total nitrogen and total energy content. Values for zinc were based on a British normal daily intake of 10 mg. which is considerably less than the 15 mg. reported in the U.S.A. and Canada. Potassium intakes can vary over a wide range but increased requirements are often necessary in cancer patients and therefore 40 mmol per day was taken as the lower acceptable level of intake.

These results were then compared with tables of recommended daily intake of nutrients (D.H.S.S. recommendations 1969, Shenkin and Wretland 1977) and with figures for the national norm (Darke, Disselduff and Try 1980, Spring, et al 1979). Table 2.3 lists intakes the D.H.S.S. recommendations for energy and protein intakes for males and females with a sedentary life-style and amounts calculated at 80% of recommended daily intake (R.D.I.) are shown. All results in this study were compared with 80% of R.D.I. because of the wide safety margin given to all tables of recommended intake.

Statistical analyses were carried out on the University of Glasgow computer (ICL 2976) using the Mini-Tab Package, Pennsylvania State University.

Dietetic evaluation by the nutritionist (24 hour dietary recall history) was undertaken on two occasions with a two month interval in a group of malnourished cancer patients. A linear analogue scale assessment of appetite was also obtained from this group of patients at the same time points. Patients were asked to mark a 20 cm. line at the point which they considered most represented their appetite. Extremes

TABLE 2.3

RECOMMENDED PROTEIN AND ENERGY INTAKES (DHSS)

	<u>Age</u>	<u>Energy</u> <u>(M.J.)</u>	<u>(k.cal)</u>	<u>(Energy)</u> <u>(-20%)</u> <u>(k.cal)</u>	<u>Protein</u> <u>(g)</u>	<u>(Protein)</u> <u>(-20%)</u>
Men (sedentary)	18-34	10.5	2510	2000	63	50
	35-64	10.0	2400	1920	60	50
	65-74	10.0	2400	1920	60	50
	75+	9.0	2150	1720	54	43
Women (sedentary)	18-54	9.0	2150	1720	54	43
	55-74	8.0	1900	1520	47	38
	75+	7.0	1680	1344	42	34

of the line were marked "worst appetite ever" and "best appetite ever". Marks were placed at 5, 10, 15 cm. and labelled "bad appetite", "moderately good appetite" and "good appetite" respectively.

Results

Fifty-nine oncology outpatients were studied, of whom 26 were patients referred to the dietitian with symptomatic anorexia and 33 were randomly selected for dietary analysis from the outpatient population.

Table 2.4 documents the energy and protein abnormalities detected. Fewer (57.6%) randomly selected patients failed to attain 80% of the R.D.I. of energy than anorectic referred patients (73.1%) as expected but this difference fails to reach significance. There were significantly fewer patients who were ingesting inadequate protein (30.5%) than energy (64.4%) and most of those were in the symptomatically anorectic group (p less than 0.01). Intakes bore no relationship to chemotherapy, perhaps because significant numbers of patients with advanced disease and anorexia had had active therapy withdrawn.

Many patients were ingesting inadequate amounts of Mg, Cu, Zn, Fe and K (Table 2.5). For all these deficiencies, there was no statistical difference between either group.

All of the vitamins evaluated showed a high prevalence of deficient intake except riboflavin and vitamin C in the randomly selected group (Table 2.6). Folate intake was low in almost all the patients and intake of other vitamins low in the diets of over half. The D.H.S.S. recommended intake of vitamin C at 30 mg. is 20 mg. lower than U.S. recommendation. Over 70% of anorectic patients and 57.7% of randomly selected outpatients were low in ascorbic acid intake. Significant differences between the two groups is indicated in the tables and reaches

PROTEIN - ENERGY DATA : DIETARY RECALL HISTORIES

Nutrient deficits in the diets of 59 oncology outpatients
(26 referred to the nutritionist for advice, 33 selected
at random from the oncology outpatient population).

Nutrient	No. (%) of total <0.8 (RDI)*	No. (%) of 33 random selected <0.8 (RDI)	No. (%) of 26 referred patients <0.8 (RDI)	Chi Square	P
Energy	38 (64.4)	19 (57.6)	19 (73.1)	1.5	0.3
Protein	18 (30.5)	5 (15.1)	13 (50)	8.3	<0.01

* RDI: Recommended daily intake (table 2.1)

TABLE 2.4

MINERAL AND POTASSIUM DATA : DIETARY RECALL HISTORIES

Nutrient	R.D.I.	0.8 (RDI)	No. (%) of patients \leq 0.8 (RDI)	No. (%) of random selected patients \leq 0.8 (RDI)	No. (%) of referred patients \leq 0.8 (RDI)	Chi Square	P
Magnesium	250 mg.	200 mg.	46 (78.0)	25 (75.8)	21 (80.8)	0.2	0.7
Copper	1.5 mg.	1.2 mg.	50 (84.7)	28 (84.8)	22 (88.5)	0.0	1.0
Zinc	10 mg.*	8.0 mg.	31 (52.5)	14 (42.4)	17 (65.4)	3.1	0.08
Iron	10 mg.	8.0 mg.	40 (67.8)	21 (63.6)	19 (73.1)	0.6	0.4
Potassium	40-80 mmol.	40 mmol.	32 (62.7)	16 (48.5)	16 (61.5)	1.0	0.3

*Canadian and U.S. recommendations 15.0 mg. but British national average 9-10 mg. (Spring et al 1979)

TABLE 2.6

VITAMIN DATA : DIETARY RECALL HISTORIES

Nutrient	R.D.I.	0.8 (RDI)	No. (%) of total ←0.8 (RDI)	No. (%) of random selected patients ←0.8 (RDI)	No. (%) of referred patients ←0.8 (RDI)	Chi Square	P
Thiamine	1.0 mg.	0.8 mg.	34 (57.6)	17 (51.5)	17 (65.4)	1.2	0.3
Vitamin B6 ¹	1.0 mg.	0.8 mg.	35 (59.3)	17 (51.5)	18 (69.2)	1.9	0.2
Riboflavin	1.6 mg.(M) 1.3 mg.(F)	1.3 mg. 0.8 mg.	19 (32.2)	7 (11.9)	12 (46.2)	4.1	←0.05
Vitamin C	30 mg.	25 mg.	39 (66.0)	24 (12.7)	15 (57.7)	1.5	0.2
Nicotinic Acid ²	18 mg.	14 mg.	51 (86.4)	28 (84.8)	23 (88.5)	0.2	0.8
Retinol equiv.	750 mcg.	600 mcg.	31 (52.5)	16 (48.5)	15 (57.7)	0.5	0.5
Folate	300 mcg.	240 mcg.	58 (98.3)	33 (100.0)	25 (96.1)		0.6 ³

1. Normal values as recommended by Shenkin and Wretlind 1977.
2. No correction for tryptophan content of diet.
3. Fisher's exact test.

TABLE 2.6

significance only for protein and riboflavin, intakes of both being better preserved in the randomly selected group.

Of the group of 59 patients, only 10 met the daily energy requirements for age and sex (Table 2.7). Despite this, potentially inadequate intakes of Mg, Cu, Fe, vit. C and folate were documented in some of these patients.

The linear analogue assessment of anorexia was used in 15 patients on two occasions 8 weeks apart together with dietary recall history analysis. Increases in energy and protein intake in excess of 25% in three patients were reflected in an increase of more than 25% in the linear analogue assessment of anorexia. Eight patients with a change in energy or protein ingestion of $\pm 25\%$ between each assessment had changes in subjective assessment of appetite on the linear analogue scale within the same range but not necessarily in the same direction. There was no statistical correlation. Four patients had a fall in protein/energy intake of greater than 25%, but again without a correlation with the linear analogue scale assessment. Two of the 15 patients even had divergent changes in the linear analogue scale and energy/protein intakes of more than 25%.

Discussion

These results clearly demonstrate that cancer patients are a high risk group with respect to the development of nutritional deficiencies and that these deficiencies may also apply to those patients who meet the daily recommended intakes of energy and protein. Although this does not necessarily mean that patients will develop a specific vitamin and mineral deficiency or even PEM, it does mean that reserves of vitamins and minerals may be low so that, should a period of increased requirement, increased loss or further reduced intake occur, specific

TABLE 2.7

DIETARY NUTRITIONAL DEFICITS IN 10 CANCER PATIENTS
MEETING THE DAILY ENERGY REQUIREMENTS FOR AGE/SEX

	0.8 R.I.**	R.I.
Protein	0	0
Magnesium	3	8
Copper	4	7
Zinc	0*	2
Iron	2	3
Potassium	0	0
Thiamine	0	2
Vitamin B6	1	3
Vitamin C	2	4
Nicotinic acid	6+	7
Retinol equivalents	0	0
Folate	10	10
Riboflavin	0	0

* From figures for West of Scotland (Lyon et al 1979)
and Great Britain (Darke et al 1980)
(Spring et al 1979)

+ No allowance for tryptophan added.

** Recommended intake (R.I.) as suggested by the D.H.S.S.
(England) or Food and Nutrition Board (U.S.A.).

See also Ministry of Agriculture, Fisheries and Food (1978)
and Thomas, S., Corden, M. (1977).

deficiency syndromes or general malnutrition may result. The general lack of statistical differences in nutrient intakes between randomly selected patients and referred patients means that in many patients potential nutritional deficits are being overlooked.

Burke et al (1980) also found a significant decrease in energy intakes in cancer patients compared with the D.H.S.S. recommendations. In addition, they found a relative sparing of protein intakes which mirrors the results in the present study. Unfortunately further breakdown of the nutritional intake was not undertaken in their study. They concluded that since the main dietary deficiency appeared to be energy content, supplementing cancer patients with an energy source should prevent weight loss in most patients.

The high prevalence of protein and energy deficient diets in this study suggests a high prevalence of PEM in the cancer patient which should be reversible with appropriate nutritional support providing the metabolic response is normal. That this is too simplistic an interpretation is demonstrated in subsequent studies.

The low dietary folate intake in almost all patients is a reflection, in part, of a widespread phenomenon in the study community (Spring et al 1979) and is the result of inadequate dietary intake of green vegetables. Low vit. C intake is also a reflection of poor vegetable and fruit consumption. The generally low intakes of nearly all basic nutrients leads one to suggest that mineral and vitamin supplementation should co-exist with protein and energy supplementation in the cancer patient in the population under study.

A linear analogue scale assessment of changes in anorexia was found to be an unreliable index of changes in dietary intake.

3. A STUDY OF THE PALATABILITY OF ORAL LIQUID DIETARY SUPPLEMENTS

An article of food and drink which is slightly worse, but more palatable, is to be preferred to such as are better but less palatable.

Hippocrates (460-377 B.C.)

Introduction

It will be appreciated from the first two studies discussed above that there is a frequent need for nutritional supplementation to be provided for the oncology patient. To ensure optimal compliance with taking these supplements, the products need to be palatable. In addition, to avoid "taste fatigue" it is preferable to have several preparations for use in rotation.

This study set out to determine which of the most frequently used oral supplementary products patients preferred and to compare preferences with several control groups.

Method

Six commercial oral nutritional supplements were chosen for evaluation. They are listed in Table 2.8.

Each product was made up following the manufacturer's instructions and subjects were provided with a 50 ml. sample of each to test in sequence and asked to drink it all if possible. The mouth was rinsed with distilled water between tasting. Subjects were asked to rate each product on a seven point scale, ranging from very bad taste to very good taste (after De Wys and Herbst 1977) (Table 2.9). The subjects' rating was later scored from +3 to -3.



TABLE 2.8

<u>Product</u>	<u>Flavour</u>
Complan (Farley Health Products Ltd.)	Strawberry
Triosorbon (Pfrimmer & Co.)	Strawberry
Flexical (Mead-Johnson Research & Bristol Labs.)	Strawberry
Build-Up (Carnation)	Vanilla
Clinifeed 400 (Roussel Labs. Ltd.)	Vanilla
Clinifeed LLS (Roussel Labs. Ltd.)	Chicken

TABLE 2.9

RATING SCALE FOR SOLUTIONS

	<u>Score</u>
Very bad taste	-3
Moderately bad taste	-2
Mildly bad taste	-1
Indifferent taste	0
Mildly good taste	+1
Moderately good taste	+2
Very good taste	+3

In addition, subjects were asked to describe why they liked or disliked a product and the comments noted. Sequencing of solutions was re-randomized every 8 subjects.

Four groups of subjects were assessed: 1. a group of cancer patients selected at random from the outpatient population; 2. normal controls selected from volunteer members of staff; 3. non-cancer medical inpatients and; 4. elderly, fit controls from a geriatric home.

Statistical analysis was undertaken using Willcoxon's Rank Sum Test.

Results

Table 2.10 lists the subject numbers, mean ages and age range in each group. The mean age of the cancer patients in group 1 was 52.0 years and that of the other three groups combined 47.8 years.

Overall mean preference scores are listed in Table 2.11. Products are listed in order of preferences. Adjectives used by subjects in describing products are listed in Table 2.12 and Table 2.13 shows the distribution of product description by subjects. The sweetest products (Complan, Build-Up and Triosorbon) were all more frequently described as too sweet by cancer patients, whereas Clinifeed vanilla, a less sweet product, was less often rated excessively sweet by cancer patients and more thought it was bland. More control patients than cancer patients thought this product had an unpleasant taste and smell than did control patients. There was general agreement on most other descriptions except perhaps a greater incidence of a powdery, dry texture reported by control than cancer patients for the chicken flavoured Clinifeed. More controls than cancer patients recorded an unpleasant smell for Flexical, and an unpleasant appearance for Triosorbon.

Comparing the product ratings for each of the four study groups (Figure 2.1), there are some clear differences are evident between the

TABLE 2.10
PALATABILITY STUDY
DISTRIBUTION OF SUBJECTS WITHIN GROUPS

<u>Group</u>	<u>Number of subjects</u>	<u>Mean Age (years)</u>	<u>Age Range (years)</u>
1. Cancer patients	51	52.0	19-76
2. Normal controls	44	28.8	17-49
3. Elderly controls	20	82.1	71-94
4. Medical patients	26	53.7	43-60

Mean age of combined groups 2, 3, 4 = 47.8 years

TABLE 2.11
PRODUCT PREFERENCES

<u>Product</u>	<u>Overall mean preference score</u>	<u>SEM*</u>	<u>Product rating</u>
Build-Up	1.73	0.123	1
Complan	1.14	0.122	2
Triosorbon	0.32	0.138	3
Clinifeed (vanilla)	-0.01	0.157	4
Clinifeed (chicken)	-1.46	0.138	5
Flexical	-2.51	0.10	6

*SEM = Standard error of the mean

TABLE 2.12

PRODUCT DESCRIPTION CODE

1. Sweet, too sweet, sickly.
 2. Pleasant, O.K., lovely, nice, very nice, tasty, very good, great.
 3. Awful, horrible, unpleasant, bad taste, disgusting.
 4. Unpleasant smell, smells off, horrible smell.
 5. No taste, tasteless, flat, watery, bland, insipid.
 6. Like soup, chicken, meaty, savoury, pea soup, crisps.
 7. Milky, icecream, creamy, milkshake.
 8. Like a medicine.
 9. Papery, dry, powdery, chalky, gritty.
 10. Bitter.
 11. Unpleasant after taste, leaves a funny taste.
 12. Other (coffee, walnuts, banana, oily).
 13. Indifferent, not too bad.
 14. Looks unpleasant.
-

TABLE 2.13

PRODUCT DESCRIPTION - NUMBERS OF CANCER PATIENTS (TOTAL 51) vs CONTROLS (TOTAL 89)

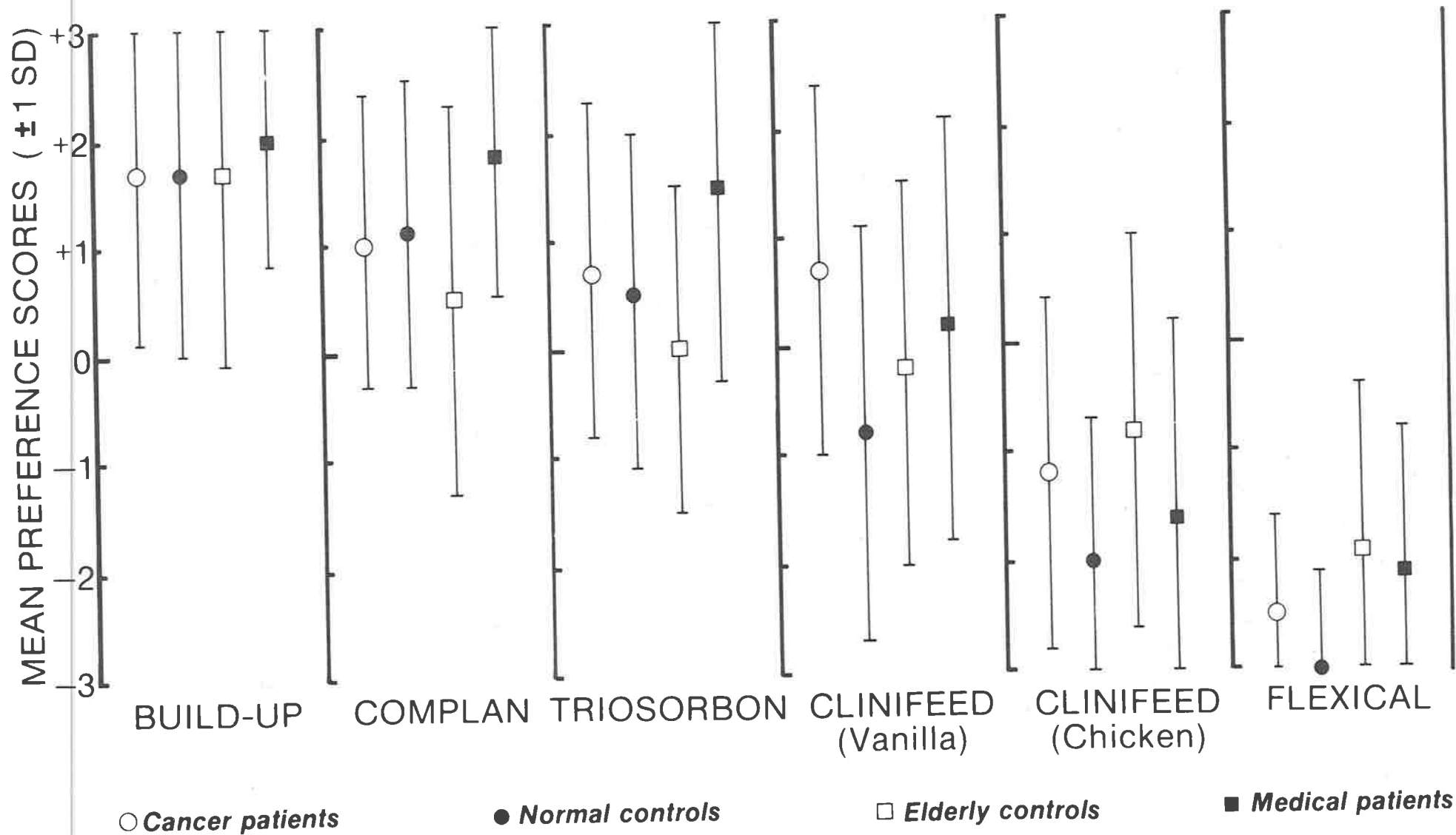
DESCRIPTION CODE (SEE TABLE 2.12)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	Product
11	22	2	0	8	0	0	1	3	0	1	1	2	0	Cancer
8	48	5	1	18	0	1	0	4	0	0	1	3	0	Complan Control
18	26	0	0	0	0	6	0	0	0	0	0	1	0	Cancer
23	43	3	1	1	0	14	0	0	0	1	1	2	0	Build-Up Control
4	18	6	1	12	0	2	1	3	0	1	1	1	1	Cancer
10	21	20	8	12	1	8	0	2	0	2	1	4	0	Clinifeed (vanilla) Control
0	5	16	1	3	17	0	1	2	0	0	1	4	1	Cancer
0	7	32	4	3	23	1	0	10	2	0	0	5	2	Clinifeed (chicken) Control
11	23	6	0	3	0	0	1	2	0	0	0	5	0	Cancer
11	41	9	1	9	0	2	0	4	0	2	1	5	4	Triosorbon Control
1	0	38	3	1	1	1	0	1	4	0	1	0	0	Cancer
0	3	59	12	0	7	0	0	0	4	0	0	4	0	Flexical Control

TABLE 2.13

MEAN PRODUCT PREFERENCE SCORES

2.1



groups (Figure 2.2). Non-cancer medical patients rated Complian significantly better than all the other groups. There were no statistical differences between each of the other three groups. All groups rated Build-Up the best and mean scores were very nearly identical. Vanilla flavoured Clinifeed was rated significantly better by cancer patients than normal controls, whose rating was significantly worse than the elderly controls and medical patients. Although the mean score for cancer patients was greater than all other groups, significance was reached only for the younger normal controls (group 2). Chicken flavoured Clinifeed was rated the same by the younger control group and medical patients. Cancer patients and elderly controls also rated this product the same and gave a higher score than did normal controls and medical patients. The increased score for both groups 1 and 3 was significantly different from that of group 2 (P less than 0.05).

Triosorbon was rated significantly better by cancer patients than elderly controls and significantly worse than medical patients. Medical patients rated this product as good as Build-Up, producing a score significantly greater than all the other groups.

Flexical was clearly rated uniformly poorly by all groups and its mean negative score was greater than the Build-Up score was positive. The younger control group rated this product worse than did all other groups.

Discussion

The mean age of the two groups with illness (cancer and medical patients) was similar (52.0 vs. 53.7) and the mean age of cancer patients and of the other groups combined was also similar. In the study of De Wys and Herbst (1977), age of controls is not mentioned. In addition, only a 5 cc. aliquot of solution was given to subjects to taste.

FIGURE 2.2

STATISTICAL DIFFERENCES BETWEEN STUDY GROUPS FOR EACH NUTRITIONAL SUPPLEMENT

	Cancer Patients	Normal Controls	Elderly Controls	Medical Patients
Complan	a	b	c	a, b, c
Build-Up				
Clinifeed (vanilla)	d	d, e, f	e	f
Clinifeed (chicken)	g	g, h	h	
Triosorbon	k, l	m	k, n	l, m, n
Flexical	o	o, p, q	q	p

Statistical correlation as follows:

- | | |
|---------------------|---------------------|
| a: $p < 0.01$ | h: $p < 0.05$ |
| b: $p < 0.05$ | k: $0.1 > p > 0.05$ |
| c: $p < 0.01$ | l: $p < 0.05$ |
| d: $p < 0.001$ | m: $p < 0.01$ |
| e: $0.1 > p > 0.05$ | n: $p < 0.005$ |
| f: $p < 0.05$ | o: $p < 0.02$ |
| g: $p < 0.05$ | p: $p < 0.01$ |
| | q: $p < 0.005$ |

In this present study, a 50 cc. aliquot was used which was drunk from a cup, as it would be in practice. It can be difficult to determine subtleties of flavour with a 5 ml. sip.

Cancer patients found some products excessively sweet, a finding confirming a clinical impression. More cancer patients than controls thought vanilla Clinifeed bland. A bland product is not necessarily a bad thing if several tumblers of the feed are expected to be drunk daily. Fewer cancer patients than controls thought this product tasted unpleasant and this reflects the higher score given by cancer patients to this product.

The highest rated product, one which was milk-based (Build-Up), scored well in all groups, and the milky quality was often commented upon. Vanilla Clinifeed also received comments that it, too, tasted milky or like ice cream. Clinifeed (vanilla) obtained a mean preference score of almost zero, suggesting indifference to the product. This attribute might be useful for long term use and, perhaps allow different flavours to be added.

All groups were unanimous in scoring the free amino solution Flexical the lowest. The range of scores was lowest for the younger control group (group 2) than the others, suggesting more fixed taste preferences. This was also true for several other products, and did not confirm the finding of De Wys and Herbst that a narrowing of taste preferences occurred in cancer patients.

Age in the older population may have less effect on taste preferences than the younger normal group whose taste preferences fell outside those of the other three groups more often. It is suggested that populations with an age range under 30 are more likely to rate free amino acid solutions and bland or savoury supplements lower than older

populations. Both these latter products (Clinifeed chicken (savoury) and vanilla (bland)) the cancer patients and elderly controls rated (statistically) better than younger controls. Medical patients had no greater preferences for chicken Clinifeed than the younger control group, despite the same mean age as cancer patients.

This study has clearly demonstrated that different groups of people can have different taste preferences and, in particular, that cancer patients may have taste preferences which are different from those of the staff who supply dietary supplements. This is an important factor to be taken into account by dietitians who are planning dietary support for cancer patients. The broader taste preferences of the cancer patients compared with younger controls may represent a change in basic taste recognition thresholds, a point which is investigated in the next study which examines taste in cancer patients.

4. TASTE THRESHOLDS IN CANCER PATIENTS

Things sweet to taste prove in digestion sour.

Shakespeare (1564-1616)

Richard II iii 236.

Introduction

Abnormalities in taste threshold in cancer patients (the concentration of solution at which a basic taste is recognised by the subject) have been discussed previously (see Section I). Most reports have been at variance with each other, probably because of different patient selection and control groups. Elevation of the threshold for sucrose and reduction of the threshold for bitter were described by De Wys and Walters (1975) but others (Williams and Cohen 1978) reported a lowered threshold for sour but not for sweet or bitter. Carson and Gormican (1977) reported reduced salt and sweet sensitivity.

It was decided to investigate possible abnormalities of taste sensation in a Scottish oncology outpatient population, by using a range of concentrations of urea, sodium chloride, sucrose and hydrochloric acid in solution to determine the taste thresholds for bitter, salt, sweet and sour respectively.

As abnormalities of plasma zinc concentration have been incriminated as a cause of taste abnormalities (Henkin 1971), plasma zinc concentrations were also measured. Finally, as recent exposure to cytotoxic chemotherapy may also influence taste (Carson and Gormican 1977), patients who had recently received (within one month) cytotoxic therapy were compared with those who had never received, or not received within two months, such therapy.

Method

Sixty-two patients were selected at random from the outpatient and inpatient population of the oncology department and twenty-eight controls from volunteer members of staff. The age range of patients was 24 to 71 years and of controls was 20 to 40 years (mean ages 47 and 27 respectively).

Two groups were examined: (1) using three concentrations of solution; (2) using seven concentrations of solution. The concentrations of solutions are listed in Table 2.14. Initially, three dilutions of each test solution were used. Subsequently, a pilot study was undertaken to evaluate whether the use of seven dilutions of each test solution was more discriminatory than the use of three.

Solutions were tested by placing 1 ml. of test solution on the tongue using a plastic teaspoon. Solutions were tested in ascending order of concentration and the tasting stopped when each taste was correctly identified. The mouth was rinsed with water between each test solution.

Plasma zinc concentration was also measured (by atomic absorption) in a group of normals and cancer patients concurrently with the taste testing.

A record was kept of the date of the most recent exposure, if any, to cytotoxic chemotherapy. Patients who had not had chemotherapy for at least 2 months were regarded as not receiving chemotherapy. Patients whose most recent pulse had been not more than one month previously were regarded as receiving chemotherapy.

Results

The taste study results are presented in Figures 2.4-2.8. Figure 2.4 plots taste recognition thresholds using three concentrations of

TABLE 2.14

CONCENTRATIONS OF TASTE SOLUTIONS (mmol/l)

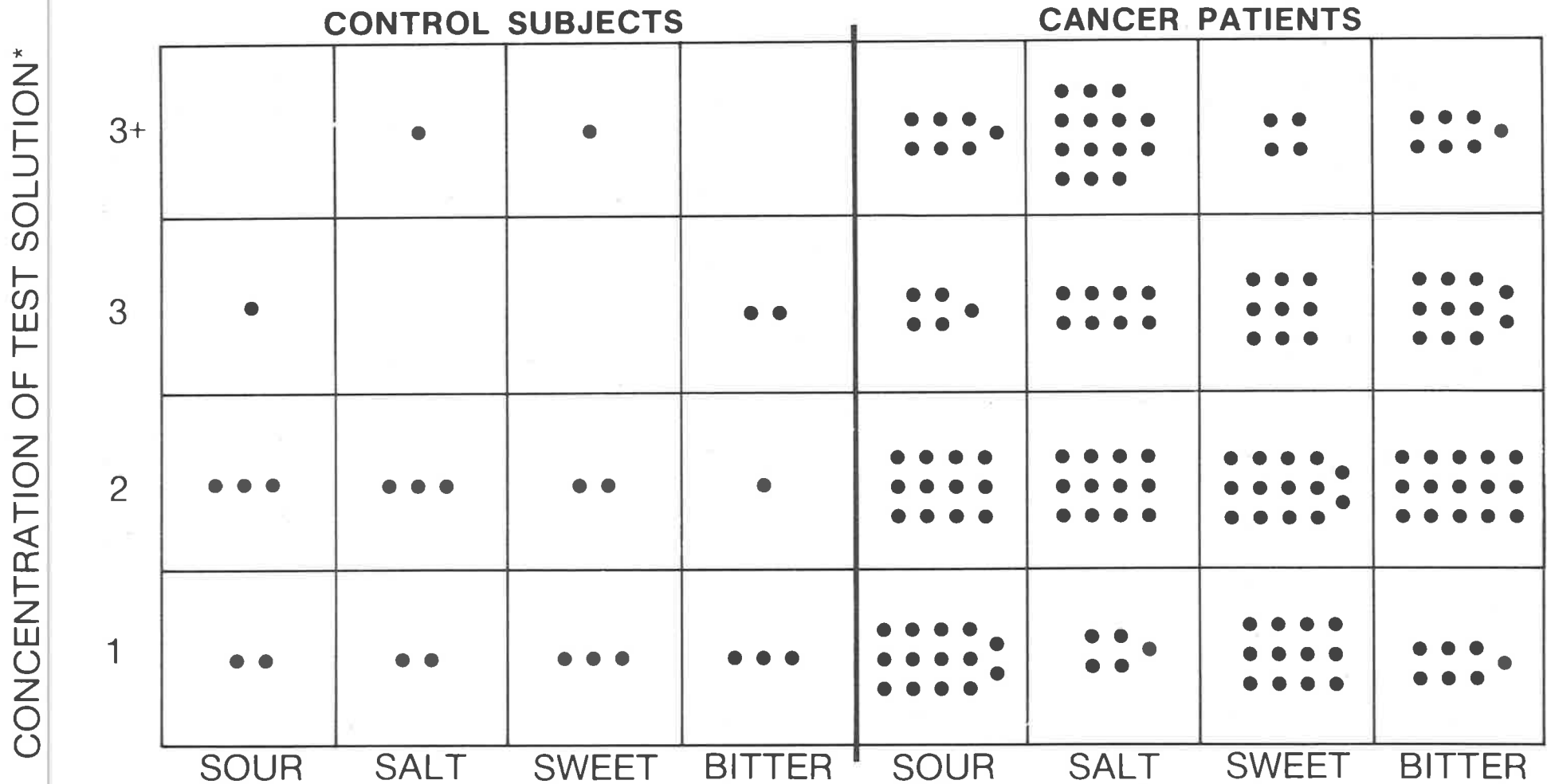
<u>Strength</u>	<u>Urea</u>	<u>Sodium chloride</u>	<u>Sucrose</u>	<u>Hydrochloric acid</u>
1a	29.97	7.24	7.24	1.50
1b	59.94	15.38	14.49	3.01
1c	71.93	22.62	22.64	4.52
1 *	89.91	29.86	29.88	6.02
2a	179.82	45.24	45.28	9.03
2 *	299.7	59.71	59.77	15.05
3 *	599.4	90.47	90.56	30.1
3 **				

* These concentrations were used for the assessment of patients described in figs. 4.1, 4.3 - 4.5

** Patients unable to recognise taste solution at highest concentration (3) were designated 3+.

TASTE RECOGNITION THRESHOLDS

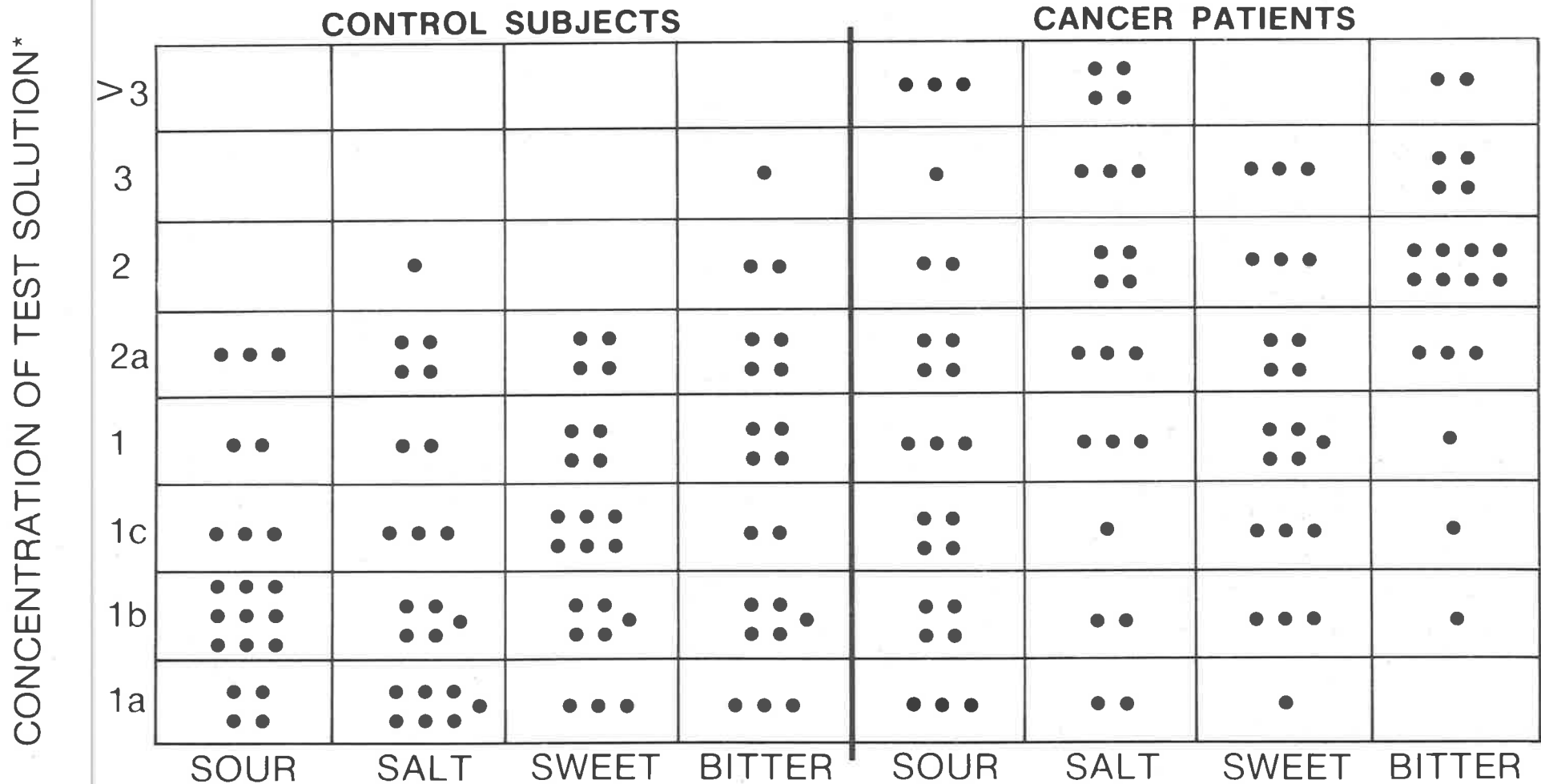
CANCER PATIENTS vs. CONTROL SUBJECTS (using 3 dilutions of test solution)



*Refer to table 2.14 for concentrations

TASTE RECOGNITION THRESHOLDS

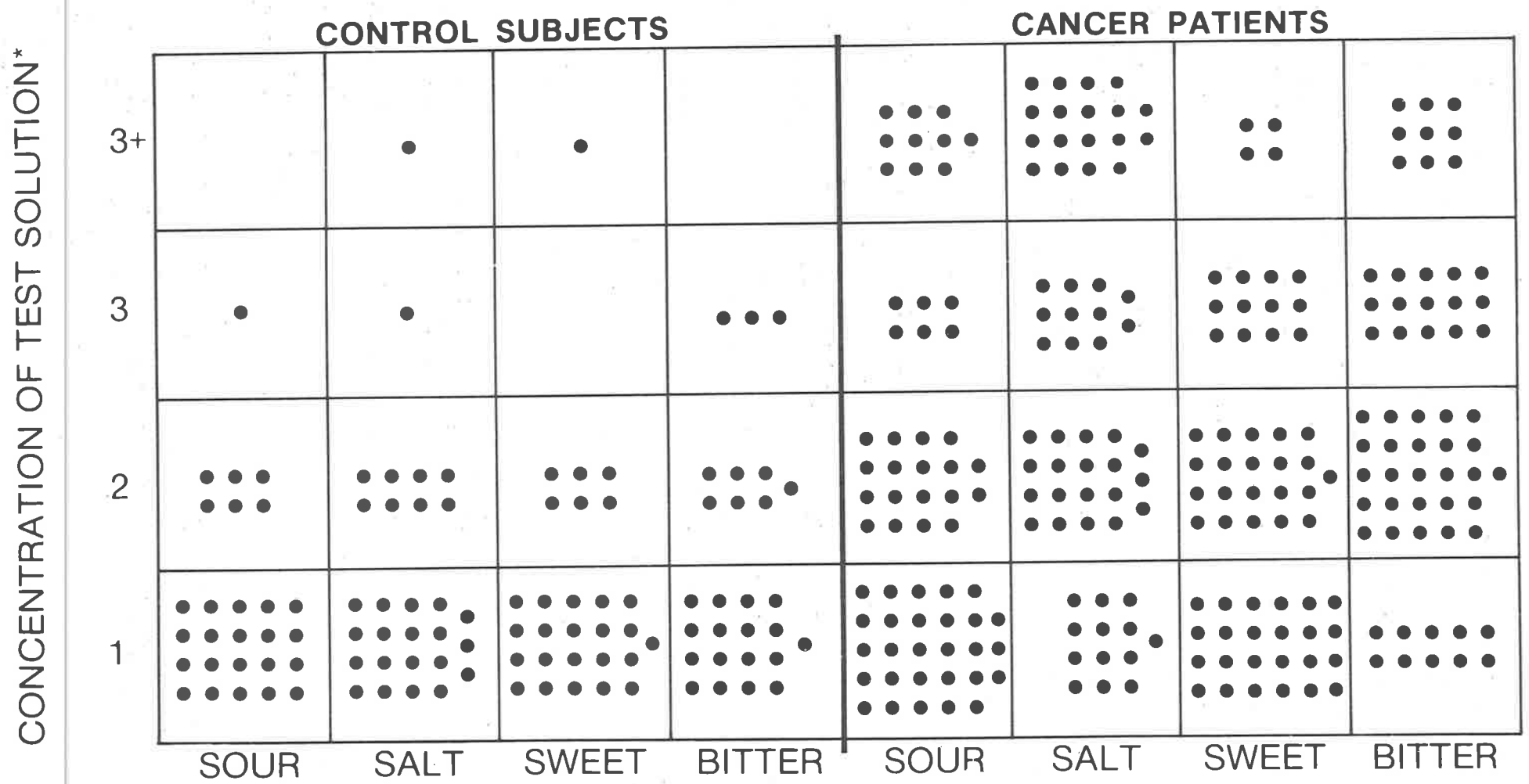
CANCER PATIENTS vs. CONTROL SUBJECTS (using 7 dilutions of test solution)



*Refer to table 2.14 for concentrations

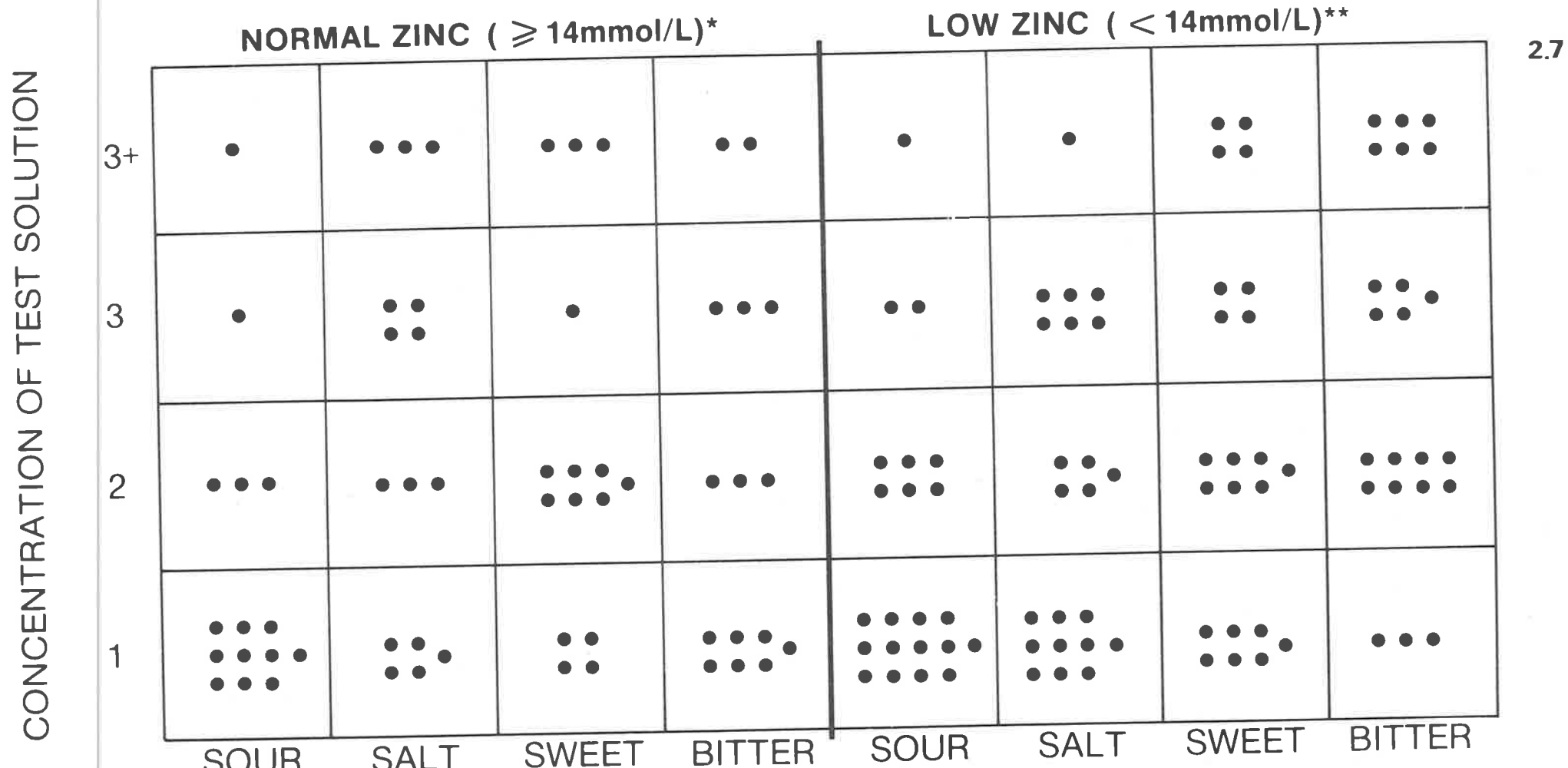
TASTE RECOGNITION THRESHOLDS

COMBINED DATA Figs. 2.4 and 2.5



*Refer to table 2.14 for concentrations

TASTE THRESHOLD IN CANCER PATIENTS RELATED TO PLASMA ZINC CONCENTRATION



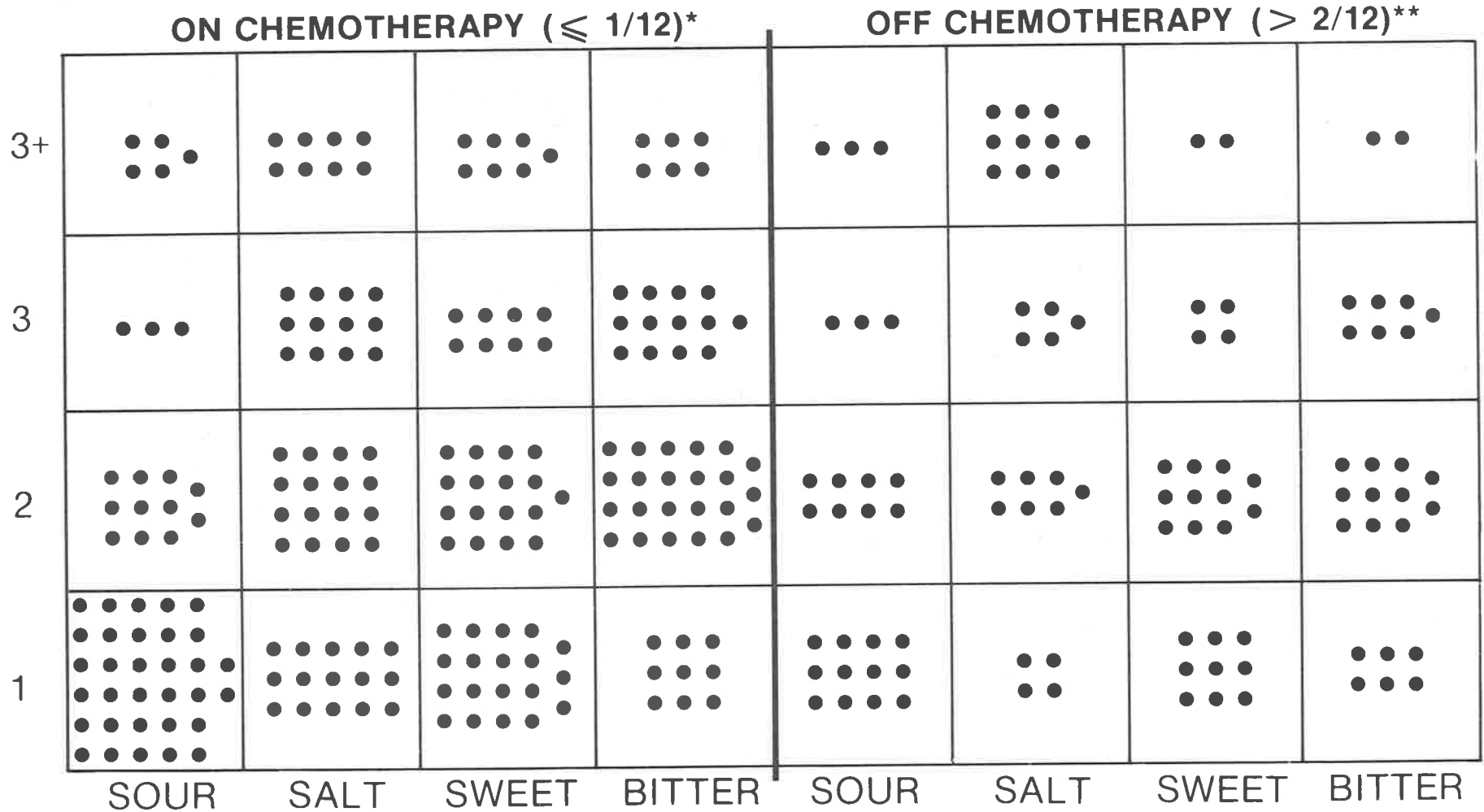
2.7

*Number on chemotherapy 8/15

**Number on chemotherapy 17/22

TASTE THRESHOLD IN CANCER PATIENTS
CHEMOTHERAPY vs. NO CHEMOTHERAPY

CONCENTRATION OF TEST SOLUTION



*51 patients

**26 patients

solution and reveals that cancer patients had a wide scatter of taste thresholds and considerable numbers of patients were unable to detect the nature of the taste of the strongest solution (3+). There is a suggestion that taste thresholds were higher in cancer patients.

Intermediary strengths were therefore introduced in an attempt to increase discrimination and a larger group of control subjects was studied. These results are shown in Figure 2.5. Statistical analysis (Chi Square tests) revealed P values of 0.06, less than 0.01, 0.07 and less than 0.01 for the threshold differences for sour, salt, sweet and bitter respectively between cancer patients and normal controls. There is clearly an elevation of bitter and salt thresholds and a strong suggestion that this also applied to sour and sweet as well.

Statistical analysis of the combined data of 28 controls and 62 cancer patients (Figure 2.6) now reveals significant differences for all four test solutions (P less than 0.05, P less than 0.001, P less than 0.01 and P less than 0.001 for sour, salt, sweet and bitter respectively). The percentage of control vs. cancer subjects with taste thresholds at a concentration of 3 or greater was as follows: sour 3.7 vs. 25.8; salt 7.1 vs. 47.5; sweet 3.7 vs. 26.2; bitter 11.1 vs. 40.0.

The mean age for the control group was 27.3 years and for the cancer population 46.8 years for the results depicted in Figure 2.6.

Plasma zinc analysis was available on 37 patients (Figure 2.7). Comparison is made between patients with normal plasma zinc concentrations (14-18 mmol/l) and low zinc levels (less than 14 mmol/l). There are no significant differences between the groups (Fisher's t-Test). Seventeen of the 22 patients with low zinc levels were receiving chemotherapy at the time of the study whereas only 8 of 15 were on chemotherapy in the normal zinc group.

Figure 2.8 compares patients either receiving or not receiving cytotoxic chemotherapy at the time of study. Results on an additional fifteen patients are included in this figure. There are no statistical differences (Chi Square Tests) between the groups and both groups therefore show the same increases in thresholds evident in the combined group depicted in Figure 2.6.

Patients who smoked had no obvious evidence of a difference in thresholds despite subjective complaints of taste abnormalities. Unfortunately, although it was planned to record smoking habits, there were too few adequately completed assessment forms for statistical analysis.

Discussion

This study presents evidence of a difference in taste thresholds between cancer patients and a younger control group for all the four basic taste sensations. Significantly, no correlation between plasma zinc concentration and taste thresholds was demonstrated. In addition, a definite effect of cytotoxic chemotherapy on taste thresholds was not demonstrable, suggesting that malignancy per se is of more importance in producing taste abnormalities.

The demonstration of significant elevation in the taste thresholds of all four basic taste sensations almost certainly is a factor contributing to altered dietary patterns in cancer patients. Selection of controls and patients in this study mirrors closely that of De Wys and Walters (1975) who were only able to demonstrate an elevation of threshold for sucrose and showed a reduction for bitter. The reason for the differences between studies is not clear. The main difference between the two groups studied was age although this does not explain the differences between the De Wys study and this present study since the

ages of the groups were comparable (29 vs 27 years and 61 vs 47 respectively).

In another study, Williams and Cohen (1978) reported a reduction in sour thresholds in lung cancer patients but no alteration in the other taste sensations. Their study is at marked variance from both this study and that of De Wys. Results of other studies are discussed in the introduction. Clearly taste thresholds vary widely in different patient populations, reinforcing the need to individualize therapy.

Chemotherapy did not appear to affect taste thresholds. Carsen and Gormican (1977) found reduced salt and sweet sensitivity in patients on 5-Fluorouracil. There was no such trend in the present paper.

Elevation of taste thresholds however, may explain why cancer patients tended to have broader taste preference scores in the palatability study discussed in the previous section. Subjective complaints of taste abnormality frequently failed to coincide with abnormalities of taste threshold.

Despite suggestions that zinc is important for normal taste, there is no evidence from this study that low plasma zinc correlates with abnormal taste thresholds. It is of interest, however, that more than half the patients (22/37) had low plasma zinc levels!

This study does not explain why some cancer patients have specific food aversions. Increased taste thresholds will, however, flatten taste appreciation by cancer patients and may account for the increased use of savoury foods by some patients but fails to explain the usual concomitant aversion of sweet foods.

Conclusions

Cancer patients frequently have elevated thresholds of all basic taste sensations which will contribute to an alteration in appreciation

of common foodstuffs. This problem would be expected to contribute to a different appreciation of commercial nutritional supplements (as demonstrated in the palatability study, p.100) and is likely to contribute to anorexia and dietary inadequacy (demonstrated in the first two studies).

* * * * *

The four studies presented above establish that cancer patients have a high prevalence of anorexia, altered taste appreciation and dietary inadequacy, factors which are reflected in a frequent dislike of available commercial food supplements.

The studies which follow evaluate the nutritional abnormalities in cancer patients, the role of various tests of nutritional status and the value of enteral nutritional support in a selected patient population.

5. NUTRITIONAL ABNORMALITIES IN CANCER PATIENTS WITH WEIGHT LOSS

Imprisoned in every fat man a thin one
is wildly signalling to be let out.

Cyril Connolly (1903-1974)

Part II Te Palinure Petens

Introduction

The aim of this study was to examine the nature and extent of the nutritional deficit in cancer patients with significant weight loss, by anthropometry and measurement of selected serum protein concentrations. Details of the tests selected for use have been discussed in Section I (p.65) and listed in Table 1.8 (p.82). In addition, possible correlations with particular tumour types and length of survival were sought.

Patients and Method

Fifty-two hospitalised cancer patients were studied, with a primary tumour distribution of 11 lung, 18 gut (5 oesophageal, 6 gastric and 7 colon carcinomas) and 23 others (including 5 Non-Hodgkin's lymphomas, carcinomas of lip, larynx, ovary, parotid, seminoma, malignant melanomas and paraganglioneuroma). Complete details are listed in Appendix II. The selection criteria were weight loss equal to or greater than 10% of normal body weight within the preceding 6 months or weight loss exceeding 5% of normal body weight within the preceding 4 weeks. Patients were excluded if they had had cytotoxic chemotherapy, radiotherapy or surgery within the preceding three weeks. Some patients had never received chemotherapy. Most patients had advanced disease.

Anthropometric data (weight, % weight loss, MAMC, TSFT), serum proteins (albumin, PA, RBP, TF and total protein), vitamin A, zinc and CRP were measured in all patients. Results of these tests were documented on specially prepared forms (Appendix IV) and analysed on the University of Glasgow ICL 2976 computer using the Mini-Tab Package, Pennsylvania State University.

Weight was measured using an Avery beam balance. TSFT was measured on the right arm by using Harpenden skin fold calipers (British Indicators Ltd.) and MAMC obtained from measurement of the mid upper right arm circumference as described in Section I. Reduction in MAMC and TSFT were expressed as a percentage of normal using reference to the tables of Jelliffe (1966), and converted to a grading between one and six. Table 2.15 reproduces those tables and the percent ranges are numbered 1-6 depending on normal (1) or less than 60% of normal (6).

Percent weight loss was calculated as the real weight loss of the patient, determined from the patient's recall of their former weight when well. Weight and percent weight loss were not recorded or assessed when oedema or ascites were present.

Skin recall tests were performed by the intracutaneous injection of 0.1 ml. each of mumps (Eli Lilly), Candida (Bencard), trichophyton rubrum (Bencard) and PPD 1:1000 antigen at separate sites into the volar surface of one forearm. Repeat tests were performed on the opposite forearm. Measurement was carried out at 48 hours of the mean of two diameters of

TABLE 2.15

MAMC AND TSFT MEASUREMENTS BY PERCENT
OF NORMAL ASSIGNED VALUES OF 1 TO 6

(From Jelliffe 1966)

MAMC (cm)

	1	2	3	4	5	6
Sex	Standard	90%	80%	70%	60%	<60%
Male	25.3	22.8	20.2	17.7	15.2	
Female	23.2	20.9	18.6	16.2	13.9	

TSFT (mm)

Sex	Standard	90%	80%	70%	60%	<60%
Male	12.5	11.3	10.0	8.8	7.5	
Female	16.5	14.9	13.2	11.6	9.9	

the area of induration using a ball point pen as advocated by Sokal (1975).

The methods used for the biochemical tests are documented in Table 2.16a, together with the normal ranges and standard deviation. All biochemical tests were undertaken by the Biochemistry Department, Gartnavel General Hospital/Western Infirmary, Glasgow. Blood was taken from a forearm vein after an overnight fast so that blood for amino acid analysis could be simultaneously collected. All blood samples were taken between the hours of 0830 and 0930.

Results

All the results are tabulated in Appendix II. Results were compared between three tumour groups: (1) lung carcinomas, (2) gut carcinomas, (3) other tumours as in the groups above.

Statistical analysis of the three tumour groups revealed no significant differences with respect to age, weight, weight loss (percent), MAMC and TSFT (using the grading system detailed above), total protein, albumin, transferrin, retinal binding protein, CRP, zinc, urea, vitamin A or survival. There were, in addition, no statistical differences between sex and any of these measurements.

Accordingly, further analyses were performed on the groups as a whole because of the apparent uniformity of the nutritional deficits of the patients.

In this group of patients 75.5% had in excess of 15% weight loss, whilst 53.1% had greater than 20% weight loss. The mean weight loss was $21.2 \pm 8.53\%$ with a range of 5.0% to 38.6%. Mean survival of deceased patients was 3.23 months which is a reflection of the advanced nature of their disease. Survival exceeded 4 months in only 12 patients. Of 6 patients surviving more than 6 months, 3 had responded to therapy.

TABLE 2.16a

BIOCHEMICAL TESTS AND METHODS

TEST	NORMAL RANGE	S.D.	METHOD
Albumin	35-45 g/l	0.8	SMA 12/60 BCG dye binding
Total Protein	62-79 g/l	1.3	SMA 12/60 Biuret
RBP	40-80 mg/l	6	Electroimmunodiffusion Laurell rocket technique
PA	0.1-0.4 g/l	0.018	"
Transferrin	2.0-4.0 g/l	0.3	A.A II Autoimmunoprecipitation
CRP	0-4 mg/l	2.5	Electroimmunodiffusion Laurell rocket technique
Vit A	1.70-3.5 $\mu\text{mol/l}$	0.2	Carr Price colour reaction
Zinc	14-18 $\mu\text{mol/l}$	1.3	Atomic absorption

TABLE 2.16b

BIOCHEMICAL RESULTS

TEST	NO. ASSESSABLE	No. >2SD from mean normal	% LOW
Albumin	52	43	82.7
Total Protein	52	12	23.1
Transferrin	44	9	20.5
RBP	46	34	73.9
P.A.	3	11	33.3
Zinc	46	45	97.8
Vit A	38	4	10.5

Apart from one patient with a drug-related death at 2.3 months, these were the only treatment responses.

Figure 2.10 reveals that skin-fold thickness was markedly reduced (less than 60% normal) in 69% of patients whereas MAMC was less than 60% of normal in only 2.1% of patients, suggesting fat loss in excess of the reduction in lean body mass for most patients.

A multivariate analysis of variables (Table 2.17) revealed a significant correlation between weight and percent weight loss ($r = -0.508$, P less than 0.001), weight and MAMC ($r = -0.636$, p less than 0.001), weight and TSFT ($r = -0.568$, p less than 0.001), MAMC and TSFT ($r = 0.560$, p less than 0.001) and percent weight loss and MAMC ($r = 0.417$, p less than 0.01) (Figure 2.9). Thus, most of the anthropometric variables correlate significantly with each other although there is no significant correlation between percent weight loss and TSFT (Figure 2.10).

Of 19 patients in whom skin recall tests were performed using the four antigens PPD, mumps, trichophyton rubrum and candida, 13 patients were completely anergic. Only 7 patients had positive reactions, one with one antigen, one with two, three with three and one with four. The mean weight loss of all patients tested with skin recall tests was 19.93%. The mean weight loss of the patients with positive skin recall tests was 16.1%.

Some biochemical results are not available primarily related to difficulties with the assays, however, statistical analysis and calculation of data have been performed on the available results.

Table 2.16b documents the biochemical data and patient numbers assessable. Most patients had low serum RBP and serum albumin. Although the majority of patients with a low RBP also had a low albumin,

TABLE 2.17

MULTIVARIATE ANALYSIS OF NUTRITION DATA IN MALNOURISHED CANCER PATIENTS[@]

	WGT	LOSS	MAMC	TRIC	SKIN	ALB	TP	TF	RBP	PA	CRP	ZINC	UREA	VITA
LOSS	-0.508***													
MAMC	-0.636***	0.417**												
TRIC	-0.568***	0.221	0.560***											
SKIN	-0.045	-0.231	-0.021	0.152										
ALB	-0.102	0.024	0.000	0.098	-0.040									
TP	0.213	-0.081	-0.143	-0.103	0.179	0.147								
TF	-0.106	-0.089	-0.168	-0.123	0.230	0.197	0.180							
RBP	-0.028	0.027	-0.035	0.100	0.260 ^o	0.109	0.281	0.052						
PA	-0.143	-0.000	0.286	0.152	-0.106	0.324*	-0.153	-0.000	-0.119					
CRP	0.008	-0.100	0.234	-0.006	-0.136	0.132	0.105	-0.115	-0.197	-0.064				
ZINC	0.002	0.135	0.013	0.270 ^o	0.217	0.005	0.404**	0.041	0.011	0.046	-0.027			
UREA	0.008	0.137	0.177	0.008	-0.104	-0.144	-0.021	0.046	0.072	-0.027	0.575***	0.066		
VITA	0.012	-0.128	0.132	0.017	0.078	0.178	0.151	0.058	0.235	-0.036	0.378**	0.195	-0.043	
SURV	-0.050	-0.102	-0.167	0.135	0.004	0.005	0.037	0.192	0.120	-0.087	-0.232	-0.079	-0.115	0.062

*** P < 0.001

^o 0.1 < P < 0.05

** P < 0.01

* P < 0.05

@ WGT = weight. LOSS = % weight loss from normal weight. MAMC = mid arm muscle circumference as percentile of normal. TRIC = triceps skin fold thickness as percentile of normal. SKIN = graded skin recall tests. ALB = serum albumin. TP = total serum protein. TF = transferrin. RBP = retinol binding protein. PA = pre-albumin. CRP = C-reactive protein. ZINC = serum zinc. UREA = serum urea. VITA - serum vitamin A.

FIGURE 2.9

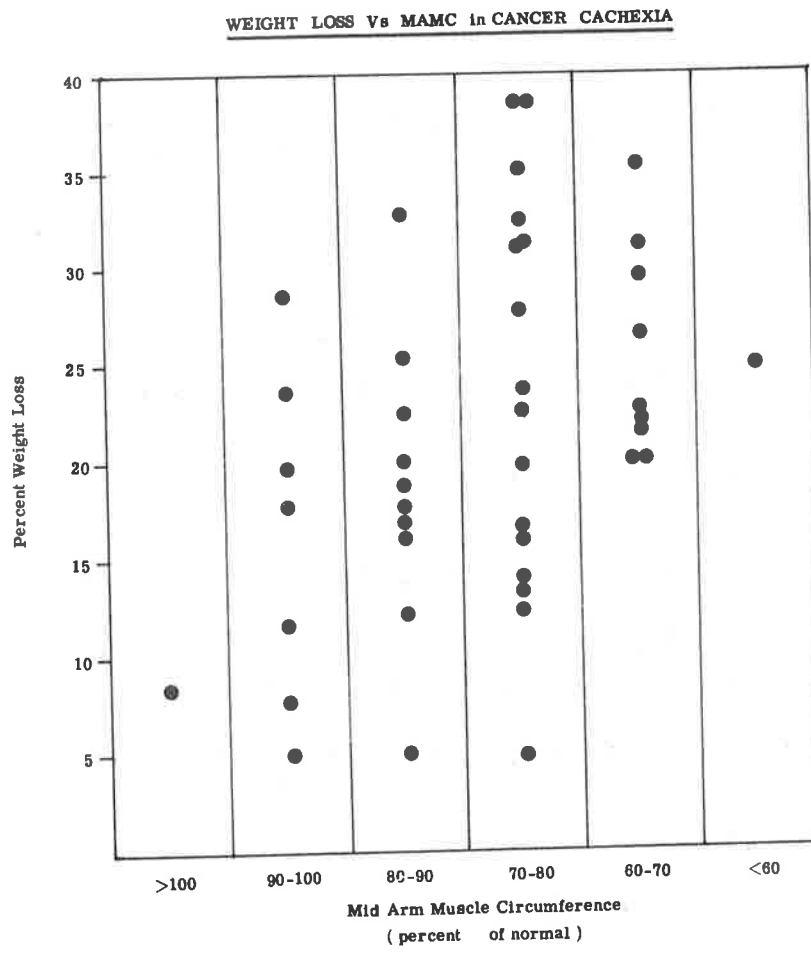
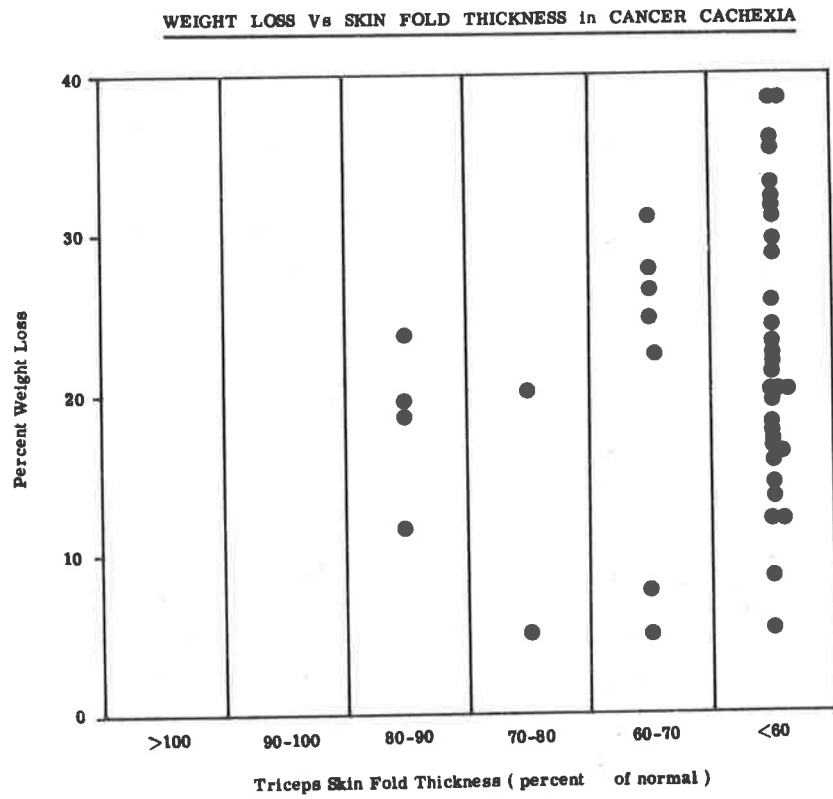


FIGURE 2.10



there were some who had normal levels of one but not the other protein (Figure. 2.11).

Mean value for plasma zinc was 9.5 $\mu\text{mol/l}$ with 84.8% less than 12 $\mu\text{mol/l}$ and 19.6% less than 8 $\mu\text{mol/l}$. There was no correlation with zinc and albumin ($r = 0.005$) but there was with total protein ($r = 0.404$ p less than 0.01). CRP was less than 10 mg/l in 83.3% and less than 50 mg/l in 50% of patients.

There were few correlations between individual plasma protein except for PA and albumin (p less than 0.05). None of the plasma proteins correlated significantly with the anthropometric data (example shown in Figure 2.12). Interestingly, CRP correlated with urea (p less than 0.001) and vit. A (p less than 0.01) and there was a barely significant correlation between TSFT and zinc (p between 0.1 and 0.05). Vit A did not correlate with its carrier protein RBP ($r = 0.235$).

The best correlation with survival was with CRP where $r = -0.232$. This does not quite reach statistical significance (P between 0.1 and 0.05).

Discussion

The results of this study suggest that there is little value in the use of serum protein data as a measure of nutritional status in the cancer patient with weight loss. As discussed in Section I, these tests of nutritional status have been widely used in PEM, and often applied to the nutritional evaluation of the cancer patient.

TSFT results were compared with the widely used standard tables of Jelliffe (1966) which were found easier to use than those of Durnin & Womersley (1964) compiled from data collected on a Glasgow population.

FIGURE 2.11

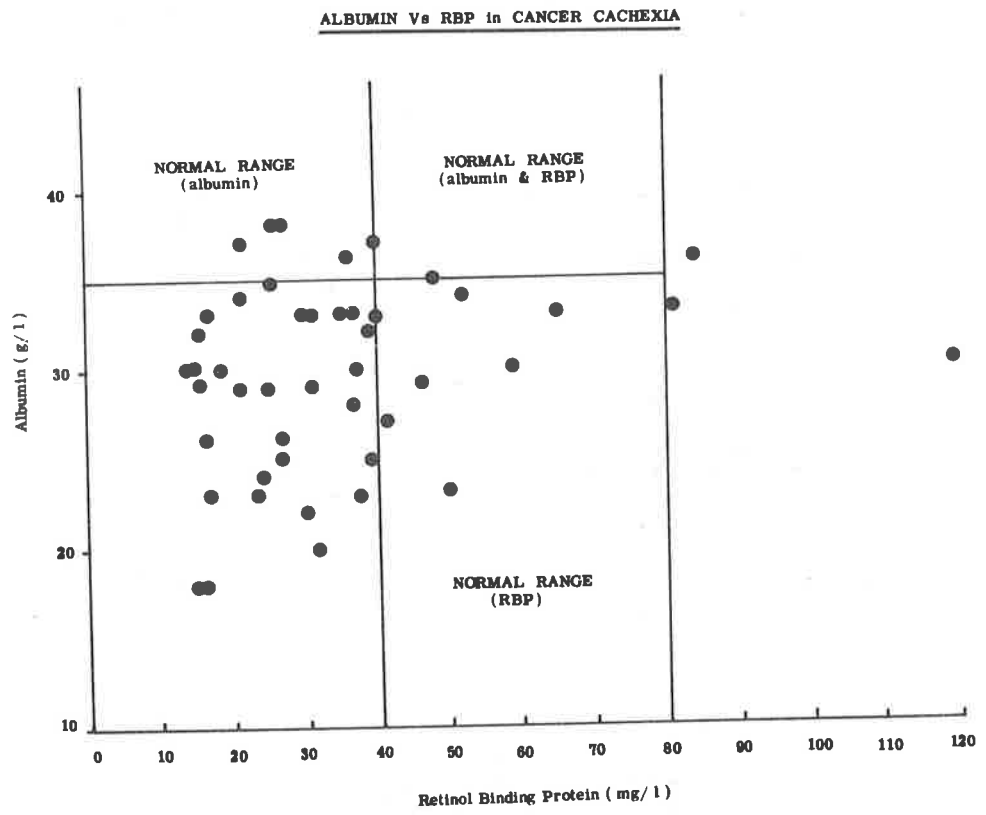
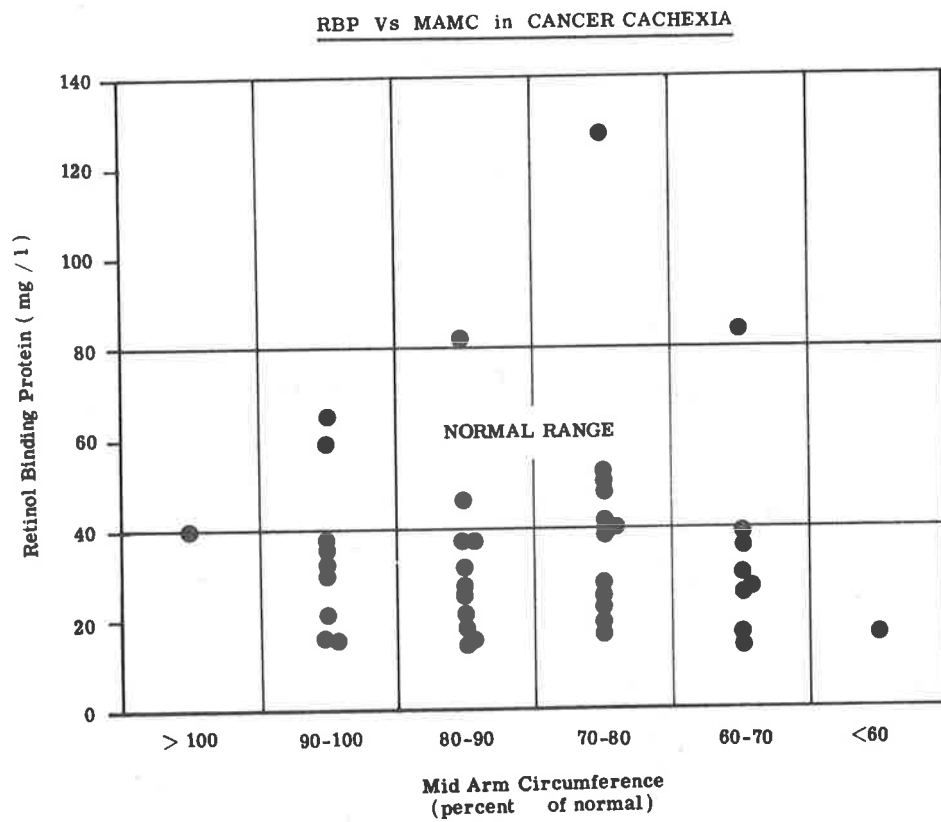


FIGURE 2.12



These latter tables gave higher means for females which implies that loss of fat would have been under-estimated. For males, the two standard tables are comparable. Frisancho (1974) provides results comparable with Durnin & Womersly but again without the advantage provided by the table of percentages of Jelliffe's.

No patient in this study was unable to recall his/her former weight. This figure was thought to be a truer indication of the effects of the tumour on the individual than the calculation of weight loss from standard tables of height and weight for age and sex, many of which are now outdated (including the 1959 Metropolitan Life Assurance Tables which have been widely employed in the past).

The high correlation between the different anthropometric tests suggests that these are relatively reliable indices of loss of fat and lean body tissue in patients with marked weight loss and that concurrent losses of fat and lean body tissue are usual. It is interesting to note, however, that more patients had triceps skin fold thicknesses less than 60% of normal than had mid arm muscle circumference less than 60% of normal. Cohn et al (1981) in their study of the compartmental body composition of cancer patients, showed that although significant amounts of muscle mass and body fat were lost (confirmed in this present study), it was the skeletal muscle which was "predominantly lost". It would appear that if this is a universal finding in malnourished cancer patients, that anthropometric measurements are unable to detect it reliably.

The high prevalence of anergy to standard skin recall testing is common in malnourished cancer patients but does not necessarily mean that the malnutrition is the cause. Malignancy, especially the lymphomatous neoplasms, are well known to cause anergy. It seems reasonable to

assume that malnutrition was the principal cause of the anergy in this group of patients but separation from the effects of the neoplasm (which is more likely to be advanced in the malnourished patient) does not seem feasible with this approach. These results are consistent with the recent report of Twomey et al (1982) which concluded that "skin testing in nutritional assessment remains unproved".

It is clear that for the cancer patient, plasma protein data often does not correlate with anthropometric data, and the possible reasons for this are many. Albumin, for instance, has a complex metabolism and, as discussed in section 3, this is particularly so in cancer. Albumin has, however, been widely used as an index of nutritional status in cancer (e.g. Milano et al 1978) despite evidence from uncomplicated PEM that it is a poor index and with minimal falls even in moderately severe PEM (Keyes et al 1980). The fall in serum albumin concentration is a late event in cancer and often accompanied by a rise in C-reactive protein. The possible association of the CRP rise with a change in metabolic rate is discussed in a later section (p.175).

Significant falls in transferrin and pre-albumin occurred less often than for retinol-binding protein and would appear to be less sensitive indices of visceral protein status. This concurs with data on these proteins described by Shetty et al (1979) and Ingenbleek (1975). Transferrin production is reduced by iron deficiency. Neither plasma iron nor latent and total iron binding capacities were measured in these patients and haemoglobin concentration is not a reliable index of available iron. Transferrin, retinol-binding protein and pre-albumin concentrations fall slightly following an acute phase response in association with trauma (see p. 75). This is a result of a temporary fall in synthesis. It would seem that this does not account for the

lack of correlation between anthropometric data and these plasma proteins. It is possible that the falls in serum concentration of these proteins with stress may be nutritionally induced. There are no data on the synthesis rates of these proteins in either situation.

As 50-60% zinc is bound to albumin in plasma, the lack of correlation with albumin levels is interesting, particularly since a statistically significant correlation was found between total protein and zinc concentrations. Although zinc is also bound to an alpha 2-macroglobulin (20-30%) (Fell and Burns 1978), any correlation would be more likely expected with albumin in view of the greater amount of bound zinc it carries. Zinc concentration also falls with an acute phase response. The lack of a demonstrated correlation however between zinc and CRP does not mean this does not exist. It may simply be that acute phase effects on zinc can occur with mild elevations of CRP and that maximal responses occur early in the course of an acute phase response. More likely, however, is that the modest effects on zinc concentration by CRP are masked by nutritional changes affecting zinc and tumour-host responses affecting CRP. This latter effect is discussed in more detail later.

Vit. A, unlike RBP, correlates with CRP and this cannot be readily explained and may be simply coincidental. Vitamin A storage in the liver occurs with acute phase responses as a result of a fall in RBP and zinc, both of which are important for serum vitamin A levels.

None of the tests of nutritional status, including albumin, correlated with survival.

Conclusion

Cancer patients with significant weight loss have been shown to have frequent and compound nutritional deficiencies. The majority of cancer

patients studied had significant and often marked deficiencies of body fat, protein (lean body mass and visceral protein), zinc and vitamin A. Anthropometric data alone provide the simplest and probably best evaluation of nutritional status. The lack of correlation of plasma proteins with the anthropometric measurements suggests they are of limited use for overall nutritional assessment. The lack of correlation may be related to alteration of the host metabolic response by the tumour in some patients which, indirectly via mediators, alters visceral protein metabolism. If so, there may be two or more types of metabolic response to malignancy, e.g. normometabolic, hypometabolic and hypermetabolic. Each may be expected to produce differing patterns of nutritional deficit. This concept is discussed further in later sections. These data suggest, however, that standard biochemical tests of nutritional deficiency used for uncomplicated protein-energy malnutrition, particularly plasma protein measurements as an index of whole body protein status, are less applicable in malignant disease.

6. ENTERAL HYPERALIMENTATION IN CANCER PATIENTS WITH WEIGHT LOSS

Our body is a machine for living.

It is organised for that, it is its nature.

Let life go on in it unhindered and let it defend itself, it will do more than if you paralyse it by encumbering it with remedies.

Leo Tolstoy (1828-1910)

War and Peace bk X, ch.29

Introduction

The previous studies have established that there is a high incidence of nutritional problems in cancer patients and have defined some of the nutritional deficits. Because anorexia is a significant factor in the development of malnutrition in the cancer patient, it was decided to investigate whether some of the nutritional deficits of cancer patients with advanced disease could be reversed by nasogastric tube feeding and to evaluate the tolerance and side effects of this form of nutritional support.

Because of the potential effects of cytotoxic chemotherapy on nutrition, patients who had received chemotherapy within three weeks of the study were excluded. This study was not designed to examine the role of enteral nutrition in reducing chemotherapeutic toxicity or improving response rates in malnourished cancer patients. These aspects and the results of other studies have been discussed in detail in Section I.

Methods and Patients

The criteria used to select patients for this study were the same as

those used in the previous study. All patients remained in hospital for the two weeks of the study to allow optimal data collection and nutritional support. A total of 28 studies were undertaken on 27 patients. One patient was studied twice with an interval of eight weeks between studies.

Nutritional support was provided in two ways. Firstly, a dietitian obtained a dietary history from the patient, discussed food preferences and attempted to supply all requested foods from the hospital kitchen. Dietary supplements were provided to every patient, selected from the products tested in palatability study discussed above (p.100). In most instances, as might be anticipated from results of the palatability study, the products provided were Build-Up, Complian or Triosorbon. These products were supplied regularly from the diet kitchen on a daily basis and patients were encouraged to take them in addition to their normal daily food intake. The dietitian visited patients regularly during their inpatient stay and provided a pre-study and thereafter weekly dietary recall history with assessment of oral protein and energy intake.

Secondly, a fine-bore naso-gastric tube with 1 mm. internal diameter (Clinifeed system 1, Roussel Laboratories) was used to administer liquid nutritional supplements (Clinifeed 400, Roussel Laboratories Ltd. or Isocal, Mead-Johnson Ltd.). Insertion of these tubes required the use of an introducer. Tube position was checked in the stomach by instillation of air and auscultation or by x-ray (the tubes were impregnated with barium sulphate to render them radiopaque). The nasogastric tubes were fixed in position with adhesive tape to the nose and cheek, a method found to be more satisfactory than fixation to the forehead.

A continuous 24 hour drip feeding technique was used, either by gravity or with the use of peristaltic pump (Clinifeeding Pump, Roussel Laboratories Ltd.). An attempt was made to supply at least 2,500 Kcal/day of energy with a N:Calorie ratio of between 1:150 and 1:200 to all patients. Concentrations of tube feeds were introduced at half strength for 24 hours and increased to full strength in the absence of side effects such as abdominal fullness, nausea or diarrhoea.

In patients where nausea or cough was a problem, a weighted mercury tipped naso-enteric tube (Dobhoff Enteric Tube, Vygon) was inserted. This tube was of larger bore than the Clinifeed tube and was therefore not used in the first instance.

Nutritional status was monitored by measuring the parameters listed in Table 1.9 (see Section I) on all patients, where possible, on at least two occasions: (1) prior to commencement of nutritional support ("baseline" data); (2) after two weeks of nutritional support. Electrolytes, liver and renal function tests, serum proteins and anthropometry were performed at least weekly. Skin recall testing and hair root morphology were examined in a small group of patients prior to commencement of the study and after 2 weeks. Nitrogen excretion was measured in continuous daily 24 hour urinary collections. Urinary creatinine was used as a guide to the accuracy of the daily collections. Apparently incomplete collections were excluded from analysis. Nitrogen balance was calculated by subtracting estimated nitrogen losses (24 hours urinary nitrogen + 2 G) from estimated intake (nasogastric feeds and oral intake). Two grams nitrogen loss was allowed for loss from the bowel, skin, hair, etc. (see p.70). Although urinary zinc measurements were undertaken, the results were subsequently found to be valueless due to contamination of the specimens by zinc from the collection receptacles.

Anthropometric tests were performed by the author and biochemical tests were performed by the Department of Biochemistry, Gartnavel General Hospital as described in the previous study.

Skin recall tests were performed as discussed previously (p.124). Repeat tests were performed on the opposite forearm at the completion of two weeks of enteral nutrition.

Hair root morphology is discussed separately (p.162).

Data was collected on the results sheets reproduced in appendix IV.

Statistical analyses were undertaken on the University of Glasgow ICL computer using the Minitab Package: Statistics Dept.: Penn. State University.

Results

28 studies were available for analysis on 27 patients. There were 59 attempts to complete the enteral feeding protocol, but 31 studies (52.5%) were incomplete. Incomplete studies were the result of patients declining to continue the study (6), intolerance of the nasogastric tube (3), premature patient discharge (3), death (6) and inadequate laboratory data despite completing 2 weeks of tube feeding (13).

Patient statistics are detailed in Table 2.18. The study group comprised: 7 lung cancer patients, 12 gastro-intestinal cancer (stomach 5, colon 4, oesophagus 3) and 8 others (lymphoma 3, kidney 1, maxillary antrum 1, postcricoid 1, ovary 1). One patient with a malignant lymphoma was studied twice. Mean age of the patients was 56.6 years (range 37-81). Male:female ratio was 21:7 (3:1), with a mean survival of 4.56 months (range 0.5 - 14.5)

Extent of disease was graded 1-4 on the following basis [1 : regional disease, 2 : bulk regional (mass greater than 4 cm. diameter), 3 : metastatic, 4 : bulk metastatic (masses greater than 4 cm.

TABLE 2.18
PATIENT STATISTICS

Patient	Primary Tumour type	Age	Sex	Stage**	Performance Status (ECOG)	Response to therapy***	Survival (months)
1	Lung	63	M	2	3	-	0.5
2	Stomach	64	M	4	3	-	2.2
3	Oesophagus	45	F	3	3	NR	3.75
4	Lung	60	F	4	1	SD	3.0
5	Stomach	57	M	1	2	*CR	3.0
6	Lymphoma	45	M	4	2	PR	3.0
7	Lung	52	M	2	1	NR	5.0
8	Lung	62	M	2	3	-	0.5
9	Kidney	37	M	4	2	NR	4.5
10	Colon	51	M	4	2	NR	4.5
11	Ovary	43	F	2	3	NR	2.0
12	Lymphoma	46	M	4	2	PR	3.5
13	Lymphoma	46	M	4	3	PR	2.5
14	Colon	54	M	2	2	NR	6.0
15	Postcricoid	44	F	1	3	-	1.25
16	Stomach	65	M	4	3	NR	2.0
17	Lung	72	M	2	2	-	7.0
18	Colon	63	F	2	2	NR	11.0
19	Stomach	64	M	4	3	NR	5.0
20	Maxillary ant.	50	M	4	2	NR	11.25
21	Mesothelioma	68	M	4	3	-	1.5
22	Lymphoma	70	F	3	2	PR	14.5
23	Lung	66	M	2	1	NR	1.0
24	Oesophagus	81	F	3	3	NR	5.0
25	Lung	50	M	2	1	NR	6.5
26	Oesophagus	58	M	3	1	-	6.0
27	Colon	61	M	3	2	NR	2.0
28	Stomach	45	M	2	2	NR	0.75

Mean survival
4.56

*Cause of death - drug toxicity

**Stage: 1 Regional
 2 Bulk regional
 3 Metastatic
 4 Bulk metastatic

***Response to therapy: NR No response SD Stable disease
 PR Partial response CR Complete response

diameter)]. Differences in staging methods for different tumours led to this attempt to simplify extent of disease by this means. Most patients (Table 2.18) had extensive tumour. Performance status was assessed using the ECOG (Eastern Co-operative Oncology Group) Criteria (Table 2.19). No patient was bed-bound and most were ambulant. Response to therapy, in all instances, refers to response to chemotherapy subsequent to the tube feeding. Six patients (Numbers 1, 2, 8, 15, 21, 26) received no cytotoxic chemotherapy and in this group of patients with advanced disease most of those treated with cytotoxics failed to respond (Table 2.18). One patient (5), who achieved a complete response, died from drug toxicity (sepsis secondary to pancytopenia).

Insertion of the Clinifeed System 1 nasogastric tubes proved relatively simple in most patients and was tolerated in all but three of 59 patients. Insertion of tubes into the bronchial tree occurred on two occasions, both of which were detected by chest x-ray before instillation of any liquids. The most frequent untoward effects which limited delivery of adequate feed were dislodging of the tube (usually by vomiting or being inadvertently pulled out) and abdominal fullness, bloating and nausea. These latter symptoms were common and tended to be recurrent in individual patients and resulted in less than optimal delivery of nutritional supplement. Recurrent vomiting or coughing of tubes could be reduced by using a mercury weighted tube but this did not reduce the incidence of nausea and abdominal fullness.

Diarrhoea in four patients did not occur with any clear relationship to tube feeds with either the milk-based product (Clinifeed) or the lactose-free product (Isocal). Cessation of feeds in the presence of diarrhoea in 3 patients produced no clear temporal benefit. Clinical

TABLE 2.19

E.C.O.G. PERFORMANCE STATUS

- 0 Fully active, able to carry out all pre-disease activities without restriction and without the aid of analgesia.
- 1 Restricted in strenuous activity but ambulatory and able to carry out light work or pursue a sedentary occupation. Patients who are fully active but require analgesia.
- 2 Ambulatory and capable of all self care but unable to carry out any work. Up and about more than fifty per cent of waking hours.
- 3 Capable of only limited self care, confined to bed or chair more than fifty per cent of waking hours.
- 4 Completely disabled. Unable to carry out any self care and confined totally to bed or chair.

evidence of oedema did not develop during tube feeding where none existed at the baseline assessment.

Table 2.20 presents the dietetic and nitrogen balance data on the 26 studies for which adequate data is available. Dietetic data was inadequate for two patients (subjects 10 and 12). Total nitrogen urinary excretion can be calculated from the respective columns by applying the formula: nitrogen excretion = mean daily nitrogen intake -2- mean daily nitrogen balance. It can be seen that all but one patient were in negative nitrogen balance at commencement of the study and all but 6 patients achieved a positive nitrogen balance of greater than 1.0 g/day which is probably the limit of accuracy of dietetic evaluation. Eighteen of the 26 assessable patients had a basal nitrogen loss of greater than 8 g/24 hours which, in the presence of a negative nitrogen balance, is abnormal except in situations of acute stress (e.g. trauma, burns, surgery, shock). One of these patients was in positive nitrogen balance but only by consuming 12.8 g. nitrogen daily. Eight patients (30.7%) failed to achieve an on-study energy intake of greater than 2500 k.cal/day. In all instances this was the result of an inability to tolerate the volume (2500 ml/day) of tube feed required because of abdominal fullness and bloating. Nevertheless, all patients in this sub group were keen to persevere with their tube feedings. Six of this group had mean nitrogen balances of less than 1.0 g/day. All but one of these patients had primary lung or bowel carcinoma. One patient (no. 7) had a net negative nitrogen balance despite receiving more than the target on study energy intake.

Table 2.21 documents the mean energy and nitrogen intakes for the three groups and for the whole. There is no significant difference

DIETETIC AND NITROGEN BALANCE DATA : ENTERAL NUTRITION STUDY

Patient	Daily Energy (k.cal.)		Mean daily nitrogen intake (g)		Mean daily nitrogen balance (g)	
	Baseline	During feeding	Baseline	During feeding	Baseline	During feeding
1	1300	2110	6.4	10.2	-4.4	+0.4
2	1430	2640	7.8	15.2	-3.2	+1.0
3	440	1600	1.5	10.0	-5.0	0.0
4	1100	2700	4.6	14.2	-4.5	+3.6
5	2500	4200	4.7	15.4	-0.5	+7.8
6	780	3345	2.9	13.6	-5.8	+2.2
7	1150	2750	5.2	14.8	-9.3	-0.1
8	800	1280	6.1	8.1	-1.0	+0.9
9	1500	2890	5.4	10.5	-3.7	+1.4
10						
11	2036	2800	12.8	19.2	+0.6	+11.6
12						
13	1180	2500	1.0	13.4	-9.5	+0.6
14	950	1750	4.8	9.6	-2.6	0.0
15	650	3325	3.4	12.6	-5.1	+1.6
16	1060	2600	7.0	17.6	-4.0	+5.2
17	638	3300	3.4	20.8	-2.4	+9.0
18	1310	2040	7.7	12.4	-1.3	0.0
19	1640	3950	6.7	13.6	-2.2	+4.4
20	720	2271	3.2	11.5	-6.6	+0.1
21	650	2250	3.0	13.6	-7.0	+3.1
22	973	3860	6.4	24.2	-0.6	+12.0
23	1400	2700	5.8	15.0	-3.2	+4.3
24	580	2950	2.1	14.4	-4.0	+5.4
25	1539	2900	9.6	14.8	-1.2	+2.8
26	1010	3300	5.7	17.4	-1.1	+4.7
27	1130	2330	5.8	13.3	-3.8	+3.7
28	1950	4140	9.6	18.2	-1.0	+6.3

TABLE 2.20

TABLE 2.21

ENERGY AND NITROGEN INTAKES. MEAN VALUES FOR 26 PATIENTS, BEFORE AND DURING ENTERAL HYPERALIMENTATION.

Group	No.	Energy (k.cal)		Nitrogen (g)	
		Baseline	During Feeding	Baseline	During Feeding
All patients	26	1170	2788	5.48	14.37
Lung	7	1072	2500	5.51	13.94
Gut	11	1273	2864	5.76	14.28
Miscellaneous	8	1120	2999	5.01	15.0

TABLE 2.22

ANTHROPOMETRIC DATA

RESPONSE TO NUTRITIONAL SUPPORT	* WEIGHT NUMBER (%)	MAMC NUMBER (%)	TSFT NUMBER (%)
INCREASE	22/26 (84.6)	3/28 (21.4)	9/28 (32.1)
NO CHANGE	-	10/28 (35.7)	14/28 (5)
DECREASE	4/26 (15.4)	12/28 (42.9)	5/28 (17.9)

* 2 PATIENTS WITH CLINICAL OEDEMA NOT INCLUDED.

between the groups with respect to energy and nitrogen intakes and the mean energy intakes for the groups met, or exceeded, 2500 k.cal. per day. In all groups baseline nitrogen and energy consumption was more than doubled during feeding. The mean baseline energy intake of all patients combined was 1169.9 ± 493 Kcal/day (range 440-2500 kcal/day) which increased to 2787.7 ± 754 kcal/day (range 1280-4200 kcal/day) during feeding. The mean daily nitrogen intake of the whole group increased from a baseline of 5.48 ± 2.68 g/day to 14.4 ± 3.64 g/day following enteral nutrition. Overall mean daily nitrogen balance also improved from a baseline of -3.55 ± 2.61 g/day to $+3.54 \pm 3.5$ g/day following feeding. All these values represent significant improvements (paired t tests).

Patients who failed to meet an intake of 2500 k.cal and/or achieve positive nitrogen balance had a mean weight gain of +0.77 kg. as opposed to the patients with an adequate energy intake whose mean weight gain was +2.1 kg. This difference also applied to mean changes in MAMC (-0.15 cm. vs +0.27 cm.) and TSFT (+0.02 mm. vs +0.2 mm.) respectively. In 11 of the 20 patients who achieved the target calorie intake the MAMC and/or TSFT fell or did not change during the study period.

The anthropometric data and biochemical data is listed in full in Appendix III. Computer analysis of this data was undertaken to compare changes in the anthropometric and biochemical data over the two weeks of study. No significant differences in the baseline data were noted between the three tumour groups in any of the anthropometric or biochemical tests. In addition, no sexual differences were evident. The total group was therefore presumed to be nutritionally homogeneous and further analyses were performed on the group as a whole.

Table 2.22 documents the changes in the anthropometric data with

feeding. Most patients (84.6% of those without oedema) gained weight during the study and 15.4% lost weight. MAMC (changes of greater than ± 0.3 cm.) was noted as increased in 21.4% and decreased in 42.9%). For TSFT (changes of greater than ± 0.3 mm.), increases were noted in 32.1% and reductions in 17.9% of patients. MAMC and TSFT remained the same (i.e. ± 0.3 mm. for TSFT) in 35.7% and 50% of patients respectively. An error of $\pm 3.5\%$ in predicting body fat from skinfolds was shown by Durnin and Rahaman (1967) and TSFT changes of ± 0.3 mm. were therefore considered within experimental error. The use of ± 0.3 cm. for MAMC was considered reasonable in the absence of the known experimental error.

Similar findings can be noted in the plasma transport protein data (Table 2.23) where the number of patients in whom increases of albumin, transferrin and RBP were noted were exceeded by those in whom these proteins decreased or remained within ± 1 S.D. (classified as no change). Increases in RBP, reputedly the most sensitive of the plasma proteins to nutritional change (Shetty et al 1979, Ingenbleek 1975), had the highest (35.7) percentage of increases. Serum albumin concentrations fell over the 2 weeks by a mean of -1.0 g/l in the under-repleted group and by -2.1 g/l in the adequately repleted group. These reductions may in part be dilutional due to expansion of the intravascular compartment.

Zinc (Table 2.24) rose by greater than 1 S.D. in 28% of patients but fell in 36.0%. Vitamin A had the greatest number of increases (60.0%) but this figure was obtained from results from only 20 patients, due to turbidity which interfered with the interpretation of the Carr Price colour reaction in the remaining patients.

Analysis of the results of the tests of nutritional status revealed that there was good correlation between changes in MAMC and weight before

TABLE 2.23

PLASMA PROTEINS

RESPONSE TO NUTRITIONAL SUPPORT	ALBUMIN NUMBER (%)	TRANSFERRIN NUMBER (%)	R.B.P. NUMBER (%)
INCREASE	5/28 (17.9)	4/23 (17.4)	10/28 (35.7)
NO CHANGE	12/28 (42.9)	14/23 (60.9)	11/28 (39.3)
DECREASE	11/28 (39.3)	5/23 (21.7)	7/28 (25.0)

TABLE 2.24

ZINC AND VITAMIN A

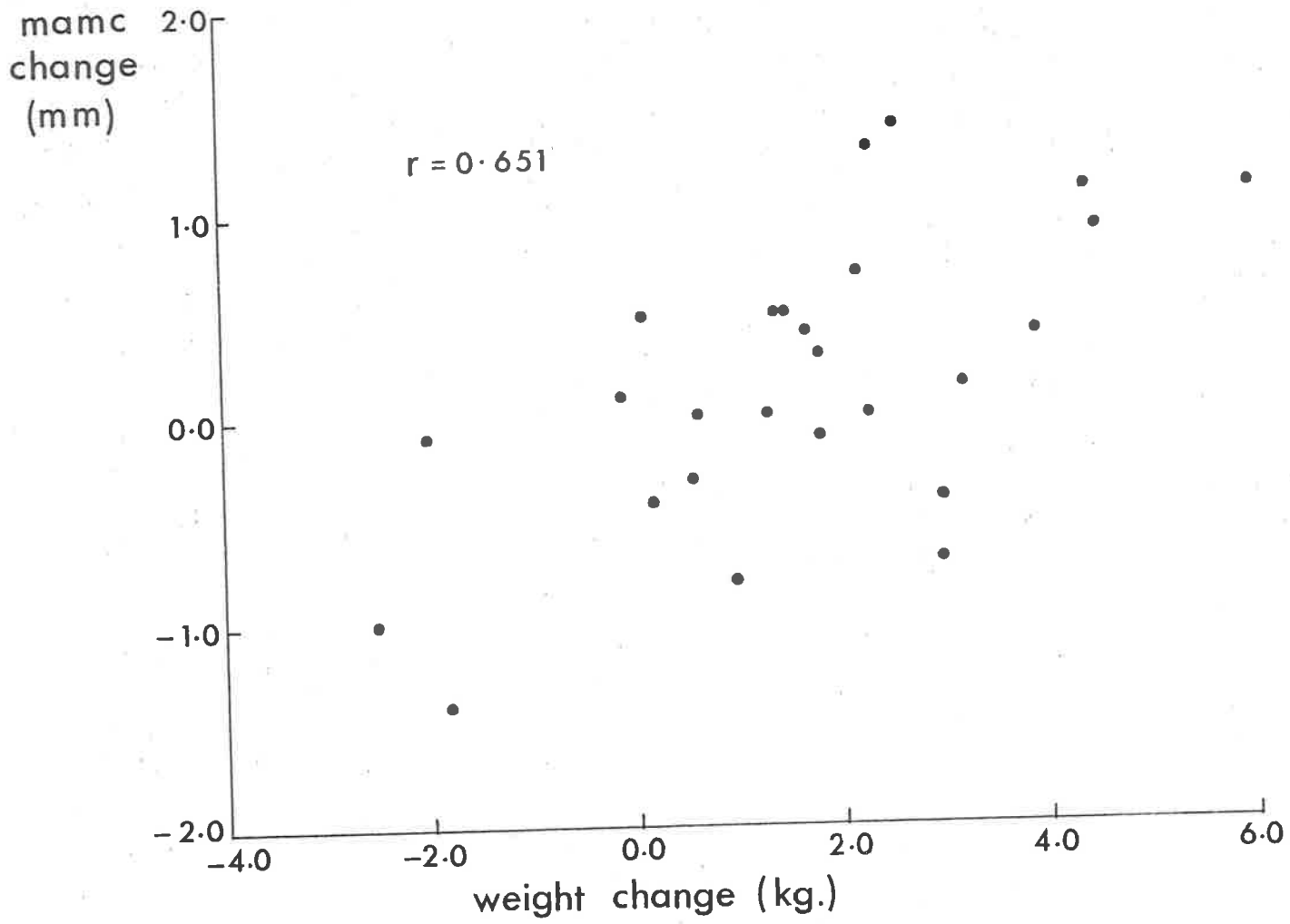
RESPONSE TO NUTRITIONAL SUPPORT	ZINC NUMBER (%)	VITAMIN A NUMBER (%)
INCREASE	7/25 (28.0)	12/20 (60.0)
NO CHANGE	9/25 (36.0)	6/20 (30.0)
DECREASE	9/25 (36.0)	2/20 (10.0)

and after nutritional support ($r = 0.651$, p less than 0.001) (Figure 2.13). There was no correlation ($r = 0.222$) between changes in MAMC with nutritional support and % weight loss changes, as distinct from the correlation of these measurements in the baseline data discussed in the previous study. There was also a lack of correlation between TSFT and MAMC with feeding ($r = 0.075$). In addition, there was no correlation between changes in the anthropometric data and serum protein data.

A moderate correlation was evident between changes in RBP and albumin ($r = 0.354$ p between 0.1 and 0.05) and between Vit. A and its carrier protein RBP ($r = 0.437$ p less than 0.05) (Figure 2.14). No other correlations were evident (e.g. albumin vs vitamin A ($r = 0.299$, Figure 2.15) although pre-albumin data could not be adequately assessed due to inadequate data. There was no correlation between plasma zinc and albumin ($r = 0.233$) despite the fact that 30% of plasma zinc is albumin bound.

Table 2.24a documents the results of skin recall tests in ten patients. No patient demonstrated any significant improvement with nutritional support. Negative baseline skin recall tests became positive on only 4 occasions but were offset by reduced or absent reactions with other of the skin recall tests in the same patients.

The CRP results are listed in Appendix III and presented in detail separately (see p.175). Of the 8 patients with daily nitrogen loss of less than 5 g., 7 had a CRP of less than 40 mg/l but only 6 of the other 18 assessable patients had CRP values of less than 40 mg/l. Further analysis of this group of 8 patients (nos. 3, 5, 8, 14, 17, 22, 24, 26) reveals that 3 failed to reach an intake of 2000 k.cal during nutritional support and two of these failed to improve or maintain MAMC or TSFT



MID-ARM MUSCLE CIRCUMFERENCE VS. WEIGHT
 CHANGES IN ANTHROPOMETRIC DATA FOLLOWING ENTERAL
 NUTRITIONAL SUPPORT IN MALNOURISHED CANCER PATIENTS

FIGURE 2.13

FIGURE 2.14

CHANGES IN BIOCHEMICAL TESTS FOLLOWING ENTERAL
NUTRITIONAL SUPPORT IN MALNOURISHED CANCER PATIENTS

RETINOL BINDING PROTEIN VS. VITAMIN A.

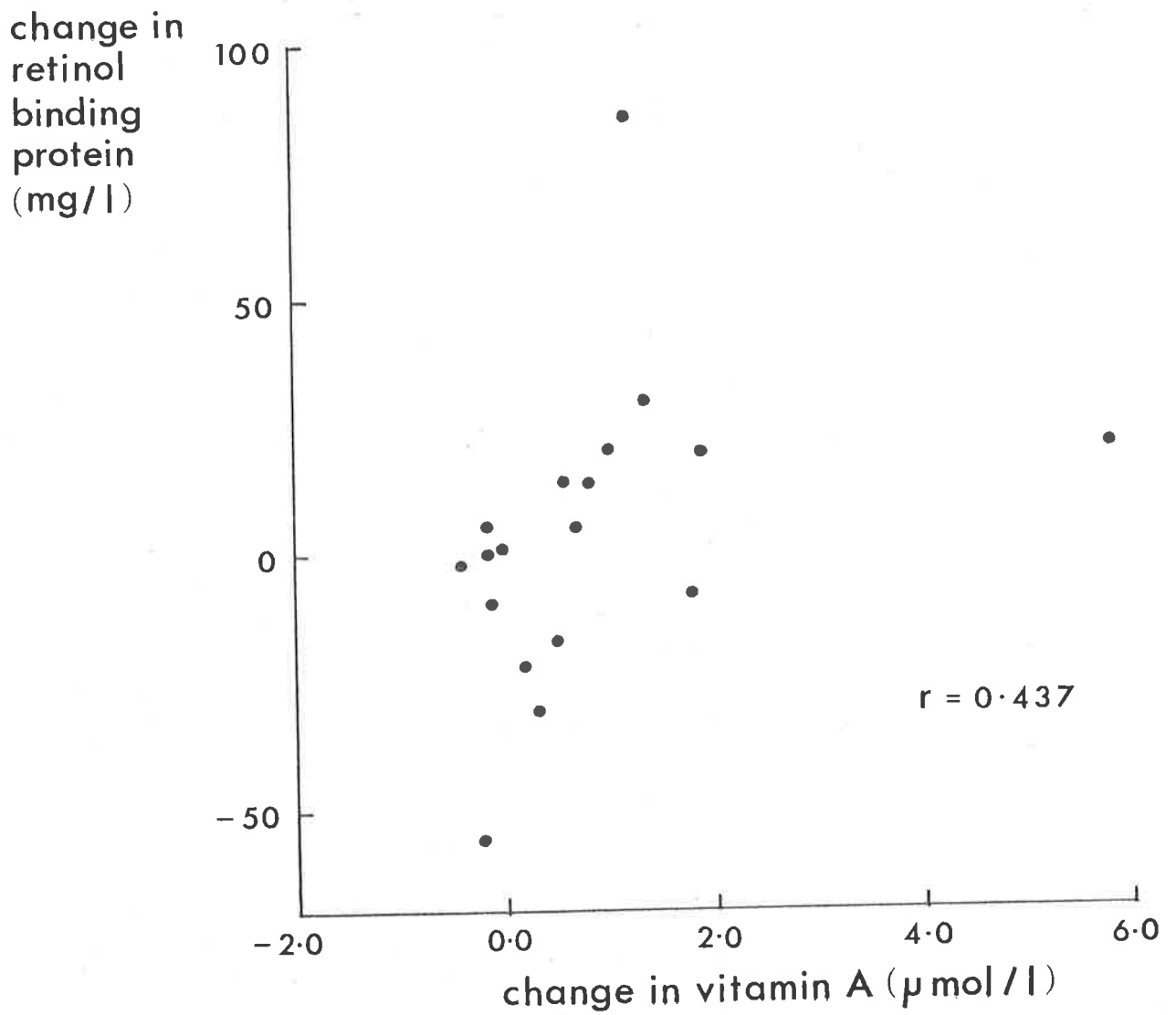


FIGURE 2.15

CHANGES IN BIOCHEMICAL TESTS FOLLOWING ENTERAL
NUTRITIONAL SUPPORT IN MALNOURISHED CANCER PATIENTS

CHANGE IN SERUM ALBUMIN VS. VITAMIN A.

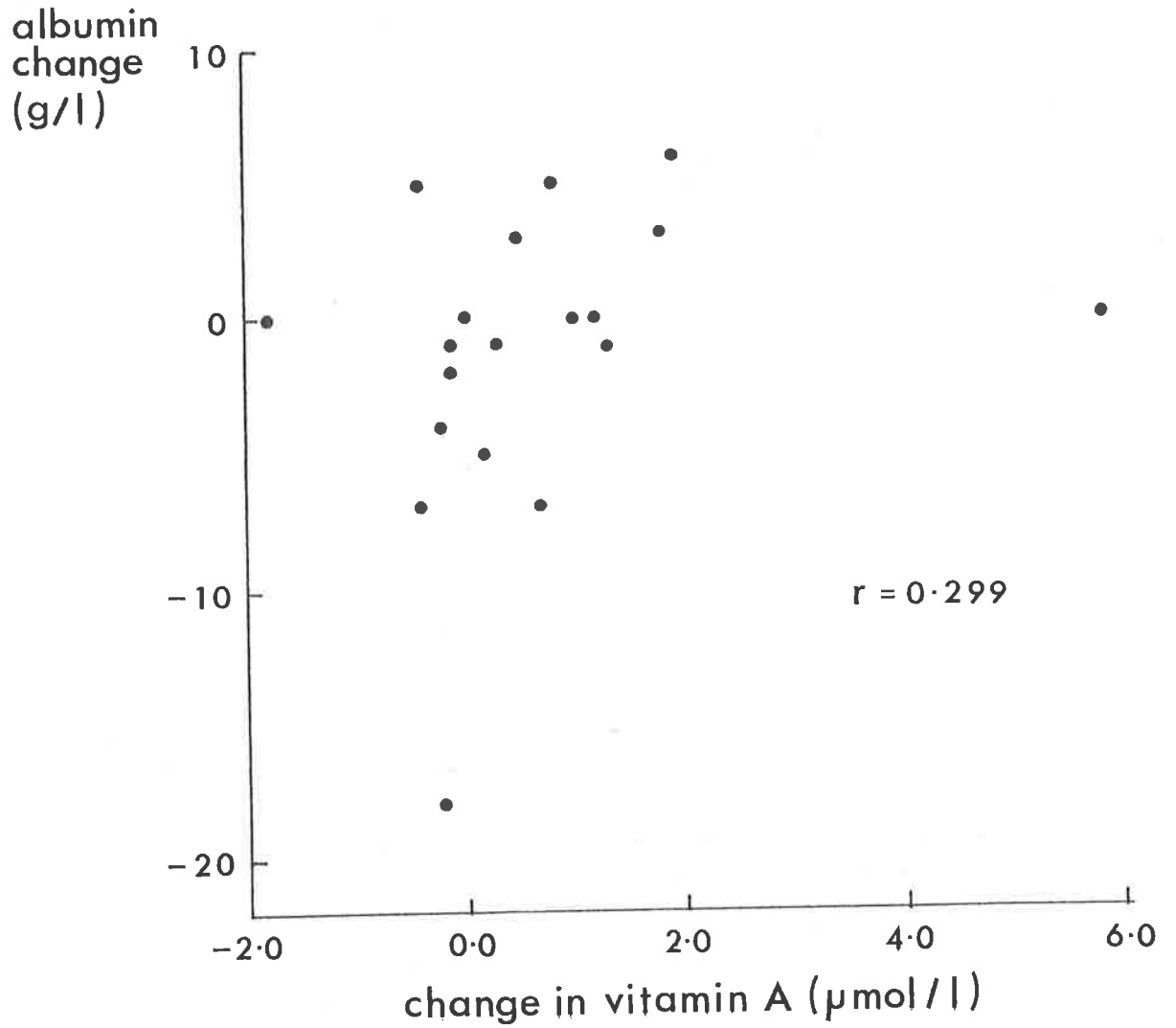


TABLE 2.24a

SKIN RECALL TEST RESULTS : ENTERAL NUTRITION STUDY*

Antigen Tested

Patient Study No.	PPD 1:1000		Mumps		Candida		T. rubrum	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
4	2	0	0	0	4	15	0	0
7	0	0	0	0	0	3	0	0
13	0	0	0	0	0	0	0	0
14	0	23	25	7	0	0	24	0
17	0	0	0	0	0	0	0	0
19	0	3	0	0	5	7	0	0
22	4	2	0	0	0	0	5	5
23	3	12	4	2	11	8	10	5
25	22	26	5	5	32	38	8	8
27	0	0	0	0	0	5	0	0

*PPD 1:1000 = Tuberculin. T. rubrum = Trichophyton rubrum.
 Diameter of skin reaction measured in mm.
 Pre- = baseline results prior to nutritional support.
 Post = results after 2 weeks of enteral nutritional support.

during feeding and body weight fell in one. All other patients in this group had weight gain and improvement in MAMC and TSFT.

Discussion

The baseline nitrogen excretion for many patients in this study was high. Normal adaptation to PEM results in conservation of lean body mass and utilization of fat stores as the main energy source, with consequent reduction in nitrogen excretion to below 5 or 6 g. per day and usually 3 or 4 g/day (see Section I). These results suggest, therefore, that many cancer patients have a hypercatabolic response to their disease which may contribute to the cancer cachexia syndrome. Many other authors have suggested that a hypermetabolic state (increased protein synthesis and catabolism) frequently co-exists with malignancy (see Section I). Such a hypermetabolic state may be chronic and low grade which would be expected to produce a gradual wasting of lean body mass such as occurs commonly in the wasting syndrome of cancer patients.

The catabolic state which usually accompanies acute stress is associated with a rise in the serum concentrations of acute phase proteins such as C-reactive protein (see Section I). Patients with low CRP levels tended to have the lowest nitrogen excretion which suggests that the two might be used as indices of the underlying metabolic response. This subject is discussed later (see p.175).

In this group of cancer patients, most of whom had advanced disease, there was very little success in reversing established malnutrition as indicated by the frequent lack of improvement in the anthropometric and biochemical parameters, despite significant improvement in energy and protein intake and the establishment of positive nitrogen balance. This applied to all the patient groups analysed. However, many patients had stable tests of nutritional status during nutritional support as

evidenced by no change or a slight rise in individual parameters. This suggests that nutritional support prevented further nutritional depletion in some patients for at least the two weeks of the study.

Changes in the albumin and plasma protein data did not correlate with changes in the anthropometric data perhaps because of changes in intravascular fluid volume as a result of the increased fluid load of nutritional support. The weight gain of most patients, therefore, in the absence of improvement in other nutritional parameters, probably reflects fluid retention during feeding. Others (Hill et al 1978) have shown this to be the case with parenteral nutrition and Nixon et al (1979) with enteral nutrition.

The lack of correlation of RBP levels with albumin levels is important because of the purported sensitivity of RBP concentration to changes in nutritional status. Indeed, once serum albumin concentration falls in PEM, one would expect RBP concentration to be universally low and if albumin rises, that RBP should follow. This is not the case in this study and suggests that plasma protein changes do not accurately reflect nutritional status or response to nutritional support in the majority of patients with advanced cancer. These results also suggest that the metabolic responses of cancer patients to feeding may differ, even with the same tumour type. Anthropometric data (with the exception of weight) and nitrogen balance data appear to be the best of the simple tests of nutritional status for monitoring response to nutritional support.

Unexpected changes in the plasma transport proteins may be a reflection of reduced availability of co-factors such as zinc which is essential for RBP production in liver. Zinc deficiency per se will cause a fall in RBP and of vitamin A (Atukorala et al 1979) (see Section

I). The fact that zinc fell in 36.0% of patients during nutritional support has important implications for vitamin A transport and protein synthesis. Although plasma zinc does not necessarily reflect whole body and tissue zinc levels, low plasma levels probably indicate low total body stores in most instances. There is little data at present to determine the validity or otherwise of this assumption. Although urinary zinc levels were monitored in patients, these proved difficult to interpret due to the discovery of contamination of the urine by trace amounts of zinc in the collecting receptacles.

The lack of improvement in skin recall tests is also in keeping with failure to achieve nutritional repletion although effects of disseminated malignancy on immunological function may have masked any change (see Section I).

Delivery of adequate nutrition was a problem for almost a third of patients due to inability to tolerate the planned volume of tube feed. Use of the larger duodenal tubes did not obviate the problem of abdominal fullness and/or nausea and nine patients had a mean negative nitrogen balance during the study. This problem in food delivery via the enteral route was not confined to patients with gastro-intestinal cancer and occurred as often in patients with lung cancer. It is of interest that malignant cachexia is commonly associated with lung and bowel malignancies suggesting a fundamental difference in the metabolic consequences of the malignancy compared with primary sites such as breast, kidney and melanoma. The majority of patients, however, tolerated the nutritional support sufficiently to enable maintenance of a positive nitrogen balance. Forty per cent of patients felt subjectively better as a result of the feeding and performance status improved in all these patients.

The theoretical risk of acceleration of tumour growth has been discussed in Section I. There was no suggestion that this occurred in the patients under study, with one possible exception. This patient, who had a carcinoma of the lung, had a visible and measurable increase in the size of a supraclavicular node mass during the nutritional support but which interestingly subsequently subsided spontaneously. Oedema may have been the cause.

Although subsequent definitive therapy of cancer was planned for all patients receiving nutritional support, only 20 survived or were well enough to receive any treatment following feeding and of those only 4 responded. All but one of these had lymphoma. The short survival in this group is an indication of the advanced nature of their disease. The lack of objective response to nutritional support suggests the need for earlier intervention in providing this support.

It is clear from this study that, in contradistinction to patients with uncomplicated PEM, most cancer patients with significant malnutrition and advanced disease cannot be nutritionally repleted with enteral hyperalimentation alone. However, stabilisation of nutritional status is possible in many patients and this might be a useful adjunct to definitive treatment in some patients who have potentially treatable malignancies. The short survival of most patients in this study reflects the fact that most tumours were non-responsive to therapy. For these reasons, nutritional support cannot be recommended for cancer patients who have tumours resistant to conventional therapies.

The reasons for the inability to nutritionally replete patients includes an inability to deliver adequate food and a probable hypermetabolic state which prevents adequate utilization of protein despite a sustained positive nitrogen balance. Evidence for a

hypercatabolic state includes the nitrogen balance data and possibly the CRP data. The results of the hair root analysis (see overleaf) also indicate that nutritional support of the cancer patient with advanced disease does not usually result in net protein synthesis.

7. HAIR ROOT MORPHOLOGY AS AN INDEX OF
NUTRITIONAL STATUS IN CANCER PATIENTS

There are spread
On the blue surface of thine aery surge,
Like the bright hair uplifted from the head.....
P.B. Shelley (1792-1822)
Ode to the West Wind

Introduction

The use of hair root morphological assessment and protein content as a measure of P-E malnutrition was discussed in pages 72-74. Hair roots from normal subjects, cancer patients recently on chemotherapy and those cancer patients on enteral nutritional support were examined in order to evaluate the usefulness of hair analysis as a measure of PEM and to determine if nutritional support could be demonstrated to improve the bulb diameter of the hair root in cancer patients as suggested by the studies of Bradfield in PEM patients (1971, 1972). Jourdan (1980) noted protein changes in hair roots within 10 days of surgery, which suggests that a study period of 14 days should be adequate to demonstrate any changes with nutritional repletion.

Method

Hair roots were extracted from the occiput of subjects as described by Bradfield (1972). An attempt was made to obtain 50-100 hairs in 2-3 pulls. The hairs were then cut and the proximal 1 cm. of shaft with integral bulb placed in air tight sterile glass containers and frozen at -70°C until examined. For examination, hairs were placed on glass slides and examined under 100x magnification by a light microscope using subdued substage and added supra-stage lighting.

Hairs were morphologically separated into anagen (growing) and telogen (resting) hairs, and the anagen hairs subdivided into normal and atrophic. The ratio of atrophic anagen hairs to total anagen hairs was determined as well as the percentage of anagen and telogen hairs. In addition, the mean bulb and shaft diameters of at least 10 anagen and 10 atrophic hairs were determined with the use of a Huygens measuring eyepiece (x10) with graticule 10:100 (16 mm.) which was calibrated using a stage micrometer scale. Mean values were calculated.

Four groups were studied: normal subjects, post-chemotherapy cancer patients; malnourished cancer patients; and cancer patients receiving enteral hyperalimentation. In this latter group, hair roots were examined before, and at completion of two weeks of naso-gastric tube feeding.

Hair root protein was determined in the group of malnourished cancer patients using the Lowry method for protein determination (Lowry et al 1951), and adapted by Jordan (1976). All anagen hairs were cut at 1 cm. from the tip of the bulb and homogenized in a ground glass homogenizer for 5 minutes in 1 ml. of 1 N NH_4OH . Alkaline copper solution was prepared from 2 per cent Na_2CO_3 , and 0.5 per cent $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in 1 per cent NaK tartrate as described by Lowry. Standard curves were prepared using 1 mg/ml bovine serum albumin. To 200 μl of protein solution, 1 ml of copper reagent was added, mixed and left for 10 minutes, then 100 μl of Folic reagent (diluted 1 in 2.5 with water) was added, mixed and left 30 minutes. The optical density was read at 750 nm. on a spectrophotometer.

Results

Individual results are shown in Tables 2.25 - 2.27 and summarised in Table 2.28. Statistical evaluation is presented in Table 2.29 and

sexual comparison in Table 2.30.

An average of 82.0 hairs (range 40-148) were analysed per patient on each occasion which ensured a minimum of 10 anagen hairs available for protein measurement. A total of 70 samples were assessed with a total of over 5,500 hairs morphologically classified.

Table 2.25 shows that for a group of normal subjects aged 23-37 there is a wide variation in the mean diameter of the anagen hair bulb and that for only 3 of the 7 does the diameter of the bulb exceed 11×10^{-2} mm which is the normal suggested by Bradfield (1972) for a group of children. Anagen bulb diameter was 25.8×10^{-2} mm for a group of elderly American subjects examined by Jordan (1976) who also reported that the percentage of anagen hairs was only 45.5% with a range of 3-86%.

Table 2.25 shows hair profiles in a group of cancer patients all with active hair regrowth following chemotherapy-induced alopecia. Anagen counts are high, indicative of active hair growth but atrophic counts are also high for some patients. Anagen bulb diameters are not significantly different from the normal subjects.

Table 2.26 documents the hair root profiles of 17 studies in 16 patients in the enteral feeding study (see p.139) who had hair analysis before and after 2 weeks of tube feeding. During 2 weeks of feeding, anagen counts fell by more than 10% in 5, remained the same ($\pm 10\%$) in 8 and rose by more than 10% in 4 (in two of those the rise was predominately atrophic hairs with a fall in mean bulb diameter). Telogen counts varied from 1.3% to 72.1%, and in 5 patients rose by greater than 10% in association with a fall in anagen count during feeding.

TABLE 2.25

HAIR ROOT MORPHOLOGYNORMAL SUBJECTS

Subject	% Anagen	% Atrophic	<u>Atrophic Anagen</u>	% Telogen	Shaft diameter x 10 ⁻² mm.	Bulb diameter x 10 ⁻² mm.
1	84.2	10.6	0.13	15.8	4.83	16.0
2	78.9	12.5	0.16	21.1	5.54	13.78
3	55.2	20.0	0.33	40.0	5.92	10.18
4	76.6	7.8	0.11	23.4	4.95	8.57
5	89.7	21.2	0.23	10.3	6.08	12.09
6	70.7	15.5	0.22	29.3	4.46	6.39
7	94.2	36.0	0.38	5.8	5.43	6.42
8	85.7	38.0	0.44	14.3	6.21	6.6

CANCER PATIENTS RECENTLY ON CHEMOTHERAPY

1	90.2	23.0	0.25	9.8	6.26	9.72
2	91.7	61.1	0.67	8.3	6.79	8.91
3	89.7	37.9	0.42	10.3	4.54	7.59
4	89.7	17.9	0.20	10.3	4.89	12.44
5	89.3	17.9	0.20	10.7	3.56	9.90
6	90.5	45.2	0.50	9.5	3.48	6.85

TABLE 2.25

TABLE 2.26

HAIR ROOT MORPHOLOGY IN CANCER PATIENTS
PRE AND POST ENTERAL NUTRITIONAL SUPPORT*

Subject**	% Anagen	% Atrophic	Atrophic Anagen	% Telogen	Shaft diameter x 10 ⁻² mm.	Bulb diameter x 10 ⁻² mm.
1a	89.0	69.9	0.79	11.0	5.64	6.10
b	78.1	49.0	0.63	21.9	5.22	4.09
2a	78.0	13.7	0.18	22.0	5.07	7.8
b	95.9	32.0	0.33	5.1	5.3	10.5
3a	71.4	14.3	0.20	28.6	5.87	8.31
b	72.3	34.0	0.47	27.7	5.80	9.20
6a	49.4	31.3	0.63	50.6	4.05	5.62
b	49.2	23.8	0.48	50.8	4.28	4.32
7a	40.3	11.0	0.27	59.8	5.17	7.34
b	27.9	26.0	0.93	72.1	5.45	3.22
8a	60.2	17.3	0.29	39.8	6.88	9.88
b	78.6	10.0	0.13	21.4	6.88	13.57
9a	88.8	65.4	0.74	11.2	4.5	4.72
b	92.9	65.6	0.71	7.1	4.16	4.46
11a	83.7	63.5	0.76	16.3	4.77	4.68
b	77.5	45.2	0.58	22.6	4.14	6.03
12a	43.5	25.3	0.58	56.5	5.23	8.10
b	82.7	46.7	0.56	17.3	6.37	6.17
13a	75.4	73.9	0.98	24.6	6.36	3.69
b	40.0	38.6	0.97	60.0	5.37	3.24
15a	67.2	26.2	0.39	32.8	5.46	5.29
b	76.6	49.3	0.64	24.7	6.51	3.87
16a	97.0	28.7	0.30	3.0	5.16	7.20
b	57.1	20.6	0.36	42.9	5.24	8.56

* Subjects for whom both pre and post treatment data available.

** a = pre nutritional support (baseline). b = post 2 weeks nutritional support.

TABLE 2.26

TABLE 2.26 CONTINUED

Subject**	% Anagen	% Atrophic	<u>Atrophic</u> Anagen	% Telogen	Shaft diameter x 10 ⁻² mm.	Bulb diameter x 10 ⁻² mm.
17a	63.4	39.0	0.62	36.6	6.20	7.45
b	80.8	40.4	0.50	19.1	6.55	7.30
22a	93.9	26.8	0.29	6.1	7.4	10.38
b	98.7	34.2	0.34	1.3	6.3	8.79
23a	71.1	26.5	0.37	28.9	4.76	7.04
b	78.3	27.7	0.35	21.7	5.75	8.75
24a	76.8	40.6	0.53	26.1	6.0	8.73
b	53.9	25.3	0.47	41.7	7.15	7.20
25a	76.6	40.4	0.53	23.4	6.3	6.50
b	81.6	34.2	0.41	18.4	6.4	7.84

* Subjects for whom both pre and post treatment data available.

** a = pre nutritional support (baseline). b = post 2 weeks nutritional support.

TABLE 2.26 CONTINUED

TABLE 2.27

HAIR ROOT MORPHOLOGY AND HAIR ROOT PROTEIN CONTENT IN CANCER PATIENTS

Subject	% Anagen	% Atrophic	Atrophic Anagen	% Telogen	Shaft diameter x 10 ⁻² mm.	Bulb diameter [@] x 10 ⁻² mm.	Protein [@] ug/hair root
1	60.0	29.0	0.33	40.0	5.92	10.18	7.0
2	90.2	23.0	0.25	9.8	6.26	9.72	10.88
3	91.7	61.1	0.67	8.3	6.79	8.91	10.64
4	71.7	31.7	0.44	28.3	4.96	6.04	5.17
5	89.7	37.9	0.42	10.3	4.54	7.59	5.46
6	71.4	42.9	0.42	28.6	4.88	6.80	6.58
7	57.1	25.3	0.44	42.9	4.84	8.78	11.11
8	61.8	30.9	0.50	38.2	3.77	4.48	9.28
9	31.4	15.7	0.50	68.6	3.95	5.80	10.97
10	90.5	45.2	0.50	9.5	3.48	6.85	5.82
11	70.7	15.5	0.22	29.3	4.46	6.39	5.12
12	56.3	9.2	0.16	43.7	3.65	5.70	3.49
13	48.8	26.7	0.55	51.2	3.75	3.42	2.62
14	53.2	30.4	0.57	46.8	4.16	6.12	4.41
15	45.5	31.8	0.70	54.5	3.58	3.63	1.62
16	63.8	49.5	0.78	36.2	3.84	4.11	4.23
17	77.2	40.6	0.53	22.8	3.93	7.38	11.11
18	49.4	31.3	0.63	50.6	4.05	5.62	11.06
19	21.5	15.7	0.73	78.4	3.41	4.43	14.4
20	92.7	63.5	0.69	7.3	4.23	6.52	14.71
21	61.4	61.4	1.0	38.6	3.79	2.68	10.93

@ No correlation by Spearman's Correlation Test.

TABLE 2.27

TABLE 2.28

HAIR ROOT MORPHOLOGY : COMBINED RESULTS

	Normal Subjects	Cancer Patients on Chemo-therapy	Mal-nourished Cancer Patients	Cancer Patients on enteral hyperalimentation	
				Baseline Data	After 2 weeks Nutritional Support
No. of subjects	8	6	21	17	17
Male/Female	5:3	2:4	12:9	11:6	11:6
Mean age (years)	30.1 ± 4.2	50.2 ± 18.9	56.81 ± 16.36	55.41 ± 12.7	55.41 ± 12.7
No. with weight loss	0	2	21	17	17
% anagen Mean ± S.D.	79.4 ± 12.39	90.2 ± 0.85	64.57 ± 19.81	72.10 ± 16.7	71.88 ± 19.73
% atrophic Mean ± S.D.	20.2 ± 11.31	33.83 ± 33.58	33.78 ± 15.77	36.11 ± 20.4	35.44 ± 13.27
Atrophic/ Anagen Mean ± S.D.	0.25 ± 0.12	0.37 ± 0.19	0.525 ± 0.06	0.498 ± 0.23	0.521 ± 0.30
% telogen Mean ± S.D.	20.0 ± 10.99	9.82 ± 0.85	35.47 ± 19.83	28.07 ± 16.7	27.99 ± 19.4
Shaft Diameter Mean ± S.D. x 10 ⁻² mm.	5.43 ± 0.65	4.92 ± 1.37	4.39 ± 0.85	5.58 ± 0.86	5.70 ± 1.44
Bulb Diameter Mean ± S.D. x 10 ⁻² mm.	10.00 ± 3.67	9.24 ± 1.97	6.53 ± 0.60	6.99 ± 1.84	6.88 ± 2.87
Protein/hair root : ug Mean ± S.D.	-	-	7.93 ± 3.85	-	-

TABLE 2.29
 STATISTICAL ANALYSIS OF HAIR ROOT DATA
 STUDENT'S t TESTS

	Normal subjects vs. Patients recently on chemotherapy	Normal subjects vs. Malnourished cancer patients	Baseline Enteral Hyperalimentation Patients vs.		
			Normal subjects	Malnourished cancer patients	Post-enteral nutrition patients*
Mean age	0.02 > p > 0.01	p < 0.001	p < 0.001	NS	-
% anagen	0.01 > p > 0.05 (NS)	0.1 > p > 0.05 (NS)	0.05 > p > 0.02	NS	NS
% atrophic	NS	0.05 > p > 0.02	p < 0.05	NS	NS
$\frac{\text{Anagen}}{\text{Atrophic}}$ ratio	NS	0.01 > p > 0.001	0.02 > p > 0.01	NS	NS
% telogen	0.05 > p > 0.02	0.05 > p > 0.02	NS	NS	NS
Shaft diameter	NS	0.01 > p > 0.001	NS	p < 0.001	NS
Bulb diameter	NS	p < 0.001	0.02 > p > 0.01	NS	NS
Hair root protein	-	-	-	-	NS**

* Paired t test.

** Spearman's correlation test.

TABLE 2.29

TABLE 2.30

HAIR ROOT DATA

COMBINED DATA TABLES 2.26 AND 2.27
COMPARING MALE AND FEMALE PATIENTS*

	FEMALES	MALES	P (t test)
TOTAL PATIENTS	15	23	
Mean Age \pm S.D.	61.67 \pm 11.59	52.61 \pm 12.74	0.05 p 0.02
% anagen Mean \pm S.D.	70.42 \pm 19.47	66.32 \pm 18.36	NS
% atrophic Mean \pm S.D.	31.9 \pm 15.57	36.72 \pm 19.16	NS
$\frac{\text{Atrophic}}{\text{Anagen}}$ ratio Mean \pm S.D.	0.47 \pm 0.185	0.54 \pm 0.229	NS
% telogen hairs Mean \pm S.D.	29.77 \pm 19.41	33.86 \pm 18.28	NS
Shaft diameter $\times 10^{-2}$ mm. Mean \pm S.D.	5.15 \pm 1.32	4.76 \pm 0.91	NS
Bulb diameter $\times 10^{-2}$ mm. Mean \pm S.D.	7.05 \pm 2.27	6.27 \pm 0.74	NS

*Female patients from table 2.26 are subject nos. 3, 8, 11, 15, 22, 24 and from table 2.27 are subject nos. 1, 3, 4, 5, 8, 10, 11, 15, 19.

All patients had mean anagen bulb diameters of less than 11×10^{-2} mm in diameter before feeding. One patient had an increase in mean anagen bulb diameter to greater than 11×10^{-2} mm post feeding but this rise did not match anthropometric and serum protein data.

Hair root protein analysis on 21 patients is listed, with their morphological data, in Table 2.27. There is no correlation between hair root morphology and hair root protein content (Spearman's Rank Correlation Test) and in the light of these data, further protein assays were not undertaken. In addition, there was no correlation between hair bulb diameter and dietary protein intake.

Tables 2.28 and 2.29 detail the mean values of the morphologic data and the statistical analysis of the study groups. Malnourished cancer patients and the enteral hyperalimentation patients both had statistically greater mean atrophic hair counts, lower mean anagen/atrophic ratio, and hence lower mean bulb diameters than normal subjects. Patients recently on chemotherapy had anagen bulb diameters not significantly different from normal subjects. There was no significant change in any of the hair root morphological characteristics following enteral nutritional support.

Comparison of male and female malnourished cancer patients was undertaken by combining the data in Tables 2.26 and 2.27 (Table 2.30). There is no statistical difference between the sexes with respect to any of the hair root morphological characteristics studied. The female cancer patients were significantly older than the male cancer patients, a finding which reflects the lower mean age of the male cancer population in general.

The technique of hair sampling was well tolerated by all patients and none refused on subsequent occasions.

Discussion

Although hair root data might potentially provide a relatively easy and cheap index of protein metabolism, it was found to be tedious to implement in practice. Previous chemotherapy, even some months before, seriously interferes with interpretation of the measurements and the use of hair root morphology in cancer patients is therefore limited to patients who have had no previous chemotherapy. In addition, the low bulb diameters in many normal subjects mean that Bradfield's criteria for malnutrition cannot be applied to this group of patients. The mean bulb diameter of the malnourished cancer patients was, however, significantly less than that of the normal subjects.

Unlike the study of Jourdan (1980), no correlation between hair bulb diameter and protein (nitrogen) intake could be demonstrated. This may reflect the different patient populations (Jourdan studied general surgical patients). In addition, cancer patients frequently do not have simple protein-energy malnutrition and some patients may have a high dietary protein intake but a low hair bulb diameter due to a hypercatabolic state. A combination of this group of patients with those with a low protein intake and low hair bulb diameter due to a hypocatabolic state may well mask any correlation.

There is no significant improvement in hair root morphology with enteral nutritional support over the two week study period. Improvement in anagen hair diameters in some patients may reflect sampling errors rather than true increases in protein synthesis and a significant number of patients continue to lose hair root protein during enteral nutritional support. The lack of change in mean values with nutritional support suggests an inability to replete protein with enteral nutrition in these patients and a stabilization of nutritional status during tube feeding.

These conclusions confirm those made on the same group of patients using different tests of nutritional status and described in the previous chapter. It would be interesting and useful to compare hair root profiles with in vivo protein turnover studies but this would be a very difficult study to undertake.

In conclusion, although the lack of change in hair root morphology with enteral nutritional support may reflect stabilization of whole body protein status during the study period, it also suggests the lack of benefit of nutritional support in improving lean body mass in this group of patients. Hair root morphology analysis was found to be too tedious to be used as a routine test of nutritional status, and did not clearly separate malnourished cancer patients from normal subjects.

8. C-REACTIVE PROTEIN

Introduction

C-reactive protein is an acute phase protein of unknown function (see Section I, p.75) which was first described by Tillett and Francis (1930) in febrile patients and infected rabbits. In common with other acute phase proteins, the serum concentration of CRP rises in response to physical stress, e.g. trauma and infections. Its association with malignancy was subsequently reported (Roantree and Rantz 1955, Comino et al 1961) but the reasons for the rise in cancer is not known. It is possible that its rise co-exists with other changes which occur concomitantly with hypermetabolic states in humans. C-reactive protein has been shown to be produced by lymphocytes (Ikuta et al 1986, Kuta et al 1986) although it is possible that it is also synthesized by other tissues. The serum CRP concentration is not a test of nutritional status but was measured as part of the nutritional studies in this thesis because of the serum protein changes which accompany an acute phase response. Such changes in serum proteins may mask or confuse the utilisation of such proteins as tests of nutritional status.

Method

C-reactive protein was assayed in serum samples obtained from all patients in study 5 and study 6 (nutritional abnormalities in cancer and enteral hyperalimentation studies). No patient had evidence of an infection. As for those studies, fasting specimens were collected between 0800 and 0900 hours. Assays were undertaken by the Department of Biochemistry, Gartnavel General Hospital using electroimmunodiffusion (Laurell rocket technique). The normal range for CRP is $0-4 \pm 2.5$ mg/l.

Results

The C-reactive protein (CRP) results are listed in full in

Appendices II and III.

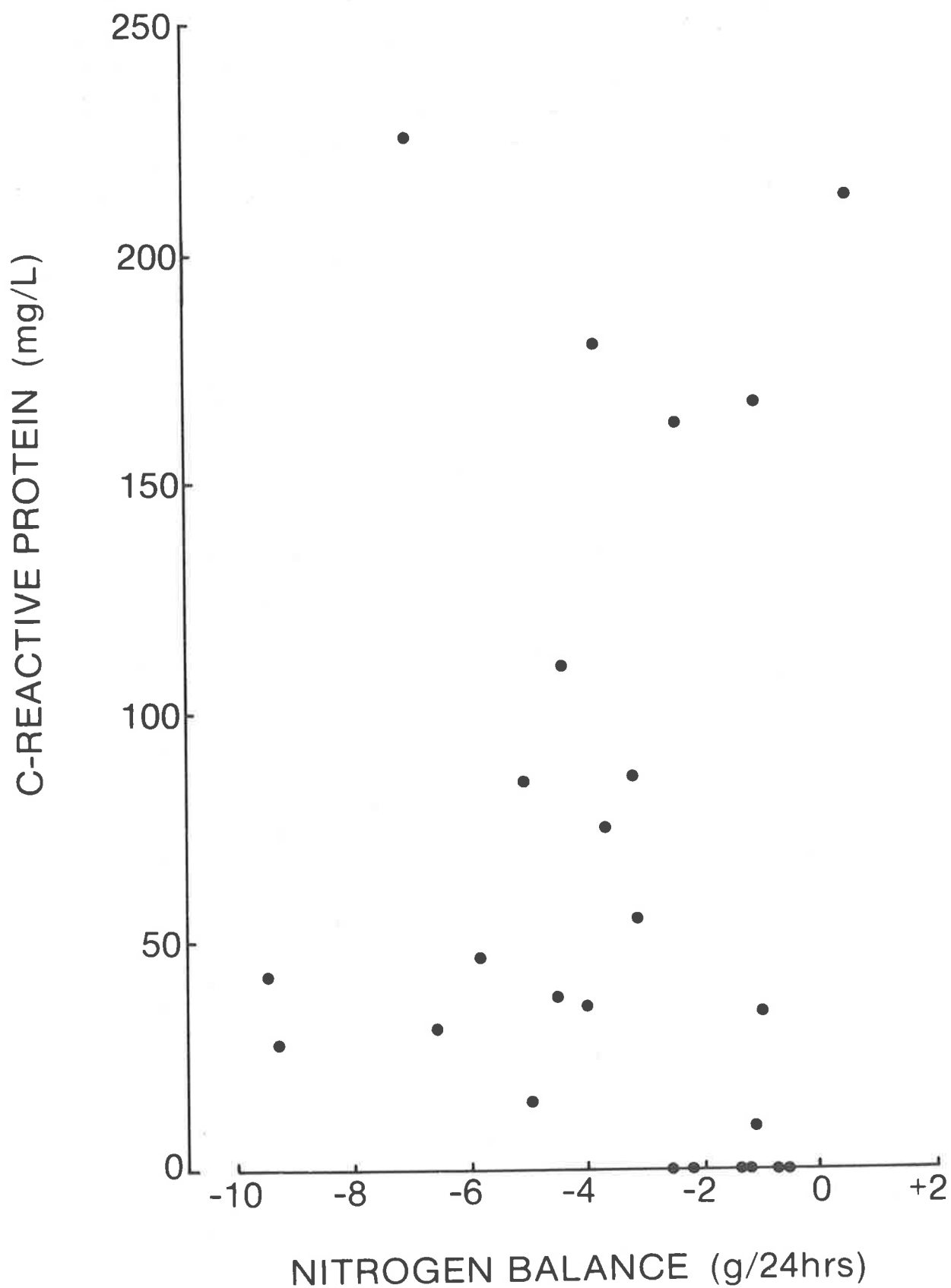
In study 5, a total of 48 assays were available for analysis in 52 patients studied. The CRP concentration was greater than 10 mg/l in 83.5% of the patients and greater than 50 mg/l in 50% of patients. In addition, there was a trend which did not reach statistical significance when CRP was correlated with survival ($r = -0.232$, P between 0.1 and 0.05).

In study 6, CRP levels fell in some patients during nutritional support and rose in others, but no reason for this is obvious except that these changes may have reflected intercurrent illness. Levels of CRP rose in 2 patients during episodes of pneumonia. One patient with an undetectable CRP died (in remission) of drug toxicity (overwhelming sepsis related to pancytopenia).

Comparison of baseline serum urea levels shows a highly significant correlation with C-reactive protein (p less than 0.001) (Table 2.17). It is also of interest that there is a modest negative correlation between CRP and nitrogen balance (p between 0.05 and 0.01, Spearman's correlation test) (Figure 2.16).

Discussion

The serum CRP level may be an important index of metabolic status of the cancer patient and an elevation may reflect a hypermetabolic state. In patients without evidence of infection, a high CRP and high urinary nitrogen excretion in the presence of a negative nitrogen balance may be indicative of hypermetabolism and useful as a guide to the likelihood of a response to nutritional support. The results in this study support this concept and a modest negative correlation of serum CRP concentration with nitrogen balance has been demonstrated. Milano et al (1978) have reported a rise in CRP occurring several months before death in patients

NITROGEN BALANCE vs. C-REACTIVE PROTEIN

with colo-rectal carcinoma. These data support the findings in this study of a poor prognosis in patients with a high serum CRP concentration and interestingly, this trend was almost of statistical significance.

A recent report by Darlington et al (1986) reported that tumour necrosis factor and interleukin I can induce an acute phase response in human hepatoma cells in vitro. If this is so, then it is possible that a rise in CRP is a reflection of a rise in tumour and/or host derived substances which may alter the host metabolic response. Such a change in metabolic rate to a hypercatabolic state is more likely to occur late in the course of the natural history of the cancer and account for the (often) late rise in CRP. It is postulated that patients with a low serum concentration of CRP are more likely to be hypo- or normometabolic and more likely to respond to nutritional support.

The concept of a differential response to nutritional support depending on metabolic rate is developed further in Section III of this thesis.

This is not the end. It is not even the
beginning of the end. But it is, perhaps,
the end of the beginning.

Speech at the Mansion House, 10 Nov. 1942

(Of the Battle of Egypt)

Sir Winston Churchill (1874-1965).

SECTION III

STUDIES IN AMINO ACID ABNORMALITIES AND
ALBUMIN METABOLISM IN MALNOURISHED CANCER
PATIENTS AND THE POTENTIAL USE OF PLASMA
EXCHANGE IN INVESTIGATING NUTRITIONAL
ABNORMALITIES.

It is a mistake to suppose, as it is so easy to do,
that science enjoins upon us the view that any given
idea is true or false and there is an end of it;
an idea may be neither demonstrably true or false,
and yet useful and interesting.

Wilfred Trotter

Observation and Experiment and their
use in Medical Sciences (1930)

The Collected Papers of Wilfred Trotter
FRS (1946)

PLASMA AMINO ACID PROFILES IN
CANCER PATIENTS WITH WEIGHT LOSS

INTRODUCTION

The plasma amino acid profile in protein-energy malnutrition (PEM) has been well established (Editorial 1973, Berry, H.K. 1970, Felig, P. et al 1969, Holt, L.E. et al 1963, McLaren et al 1965, Ittyerah et al 1965, Weller et al 1973, Smith et al 1974) and has been suggested as a useful marker of the nutritional status of the patient (Holt, L.E. et al 1963). In established and uncomplicated PEM there are significant reductions in the plasma concentrations of the branched-chain amino acids, leucine, isoleucine and valine. In addition, the plasma concentration of tyrosine is usually reduced. Restoration of these abnormalities to normal usually occurs rapidly with nutritional support. Indeed, refeeding of patients with PEM usually results in the rapid restoration of a normal clinical state (Smith et al 1974), a situation which, as studies in this thesis have shown, rarely pertains to cancer patients. In addition to the above plasma amino acid changes in PEM, plasma essential amino acids are usually low and plasma glycine concentration may be normal or high. Plasma alanine concentration is usually low because branched-chain amino acid concentrations control the production of alanine and glutamine by skeletal muscle.

After 3-5 days of fasting, normal subjects have aminograms with high branched-chain amino acid (BCAA) concentrations. In these patients, the elevated concentrations reflect gluconeogenic activity with hepatic release of BCAA, tyrosine and lysine for peripheral metabolism.

The situation in malignant disease is less clear, and most early publications did not consider nutritional status (Okada and Hayashi 1922, Eades, C.H. and Pollack, R.L. 1954, Waisman et al 1952, Kelly and Waisman 1957, Brackenridge 1959, Nixon, D. et al 1980, Wannemacher, R.W. et al 1976). In some of these studies the possible effects of cytotoxic chemotherapy on plasma amino acid concentration were neglected. Clarke et al (1978) measured plasma amino acid levels by gas chromatography in a small group of malnourished cancer patients and concluded that the rate of gluconeogenesis was increased.

It is important to know the prevalence of uncomplicated protein-energy malnutrition (P.E.M.) in malignant disease as distinct from the hypermetabolic state of true cancer cachexia, as these factors may influence the response to nutritional support in different ways and could also affect the response to cancer therapy.

As part of the larger study investigating nutritional parameters in cancer patients with weight loss, fasting peripheral venous plasma amino acid profiles were determined by ion exchange chromatography. The aim was to determine if the fasting plasma amino acid profile in malnourished cancer patients was consistent with protein-energy malnutrition, or whether there were differences sufficient to indicate a distinct metabolic response to protein-energy deprivation.

METHOD AND PATIENT SELECTION

Thirty-nine patients (26 male : 13 female), of mean age 57.0 years (range 21-81), and with histologically confirmed cancer were studied. All had weight loss either in excess of 10% over the preceding 6 months or 5% over the preceding 4 weeks. No patient had received chemotherapy, radiotherapy or had surgery within the preceding 3 weeks. The

malignancies studied were gastrointestinal (15), lung (5), ovary (1), breast (4), larynx (4), testis (2), lymphomata (3), renal (2), melanoma (2) and sarcoma (1). All the cancer patients were anorectic at the time of the study and were considered to require nutritional support.

A group of 13 patients admitted for elective eye surgery, but without systemic disease, malignancy or weight loss, had fasting plasma amino acid profiles determined pre-operatively for comparison.

Blood was obtained between 0830 and 0930 from a forearm vein after an overnight fast and transported to the laboratory in a heparinised tube where the plasma was separated within an hour, deproteinized with sulphosalicylic acid and stored at -25°C .

Thawed samples were later analysed by ion exchanged chromatography on a Locarte amino acid analyser (Moore, Spackman and Stein 1958).

RESULTS

The mean plasma amino acid concentrations are listed in Table 3.1a. The mean amino acid concentrations for the control group were comparable with published ranges for normal values. Plasma levels of the essential amino acids, threonine and methionine were all significantly reduced in the cancer population compared to the control subjects. Although the mean plasma levels of the branched-chain amino acids isoleucine, leucine and valine in cancer patients were not significantly different from control subjects, there was a much wider scatter of individual values (Figs. 3.1, 3.2, 3.3).

Examination of these scattergrams reveal a number of patients with elevated plasma levels of branched-chain amino acids (i.e. valine, leucine, isoleucine) who had had an acute reduction in protein and energy intake over the preceding one or two weeks (Table 3.1b). The causes of

TABLE 3.1a
PLASMA AMINO ACID PROFILES

AMINO ACID	CONTROL PATIENTS MEAN (umol/L) \pm SEM*	CANCER PATIENTS MEAN (umol/L) \pm SEM	P
Alanine	349.8 \pm 20.3	223.2 \pm 17.0	<0.001
Arginine	104.7 \pm 5.4	65.6 \pm 5.5	0.01>p>0.001
Asparagine	59.1 \pm 0.5	53.4 \pm 3.5	N.S.
Aspartic Acid	4.8 \pm 3.1	9 \pm 1.5	N.S.
Citrulline	38.3 \pm 4.0	16.9 \pm 2.1	<0.001
Cystine	110.8 \pm 7.7	77.9 \pm 5.2	0.01>p>0.001
Glutamic Acid	44.9 \pm 3.0	79.5 \pm 7.3	0.05>p>0.02
Glutamine	395.2 \pm 19.4	326.6 \pm 20.7	N.S.
Glycine	175.5 \pm 11.0	180.6 \pm 9.3	N.S.
Histidine	87.4 \pm 8.5	51.9 \pm 4.5	<0.001
Isoleucine	65.2 \pm 3.0	62.0 \pm 4.8	N.S.
Leucine	130.7 \pm 5.8	117.4 \pm 7.7	N.S.
Lysine	167 \pm 12.1	140.1 \pm 8.5	N.S.
Methionine	24 \pm 1.5	17.9 \pm 1.2	0.02>p>0.01
Ornithine	130 \pm 15.6	78.1 \pm 5.5	<0.001
Phenylalanine	57.8 \pm 2.8	63.2 \pm 3.6	N.S.
Serine	93.7 \pm 4.5	93.4 \pm 4.2	N.S.
Threonine	112 \pm 6.1	92.7 \pm 5.1	0.05>p>0.02
Tyrosine	63.8 \pm 4.0	56.7 \pm 2.6	N.S.
Valine	200.5 \pm 8.0	171.5 \pm 10.6	N.S.

* SEM = Standard error of the mean.

FIGURE 3.1

ISOLEUCINE

PLASMA
ISOLEUCINE
($\mu\text{mol/l}$)

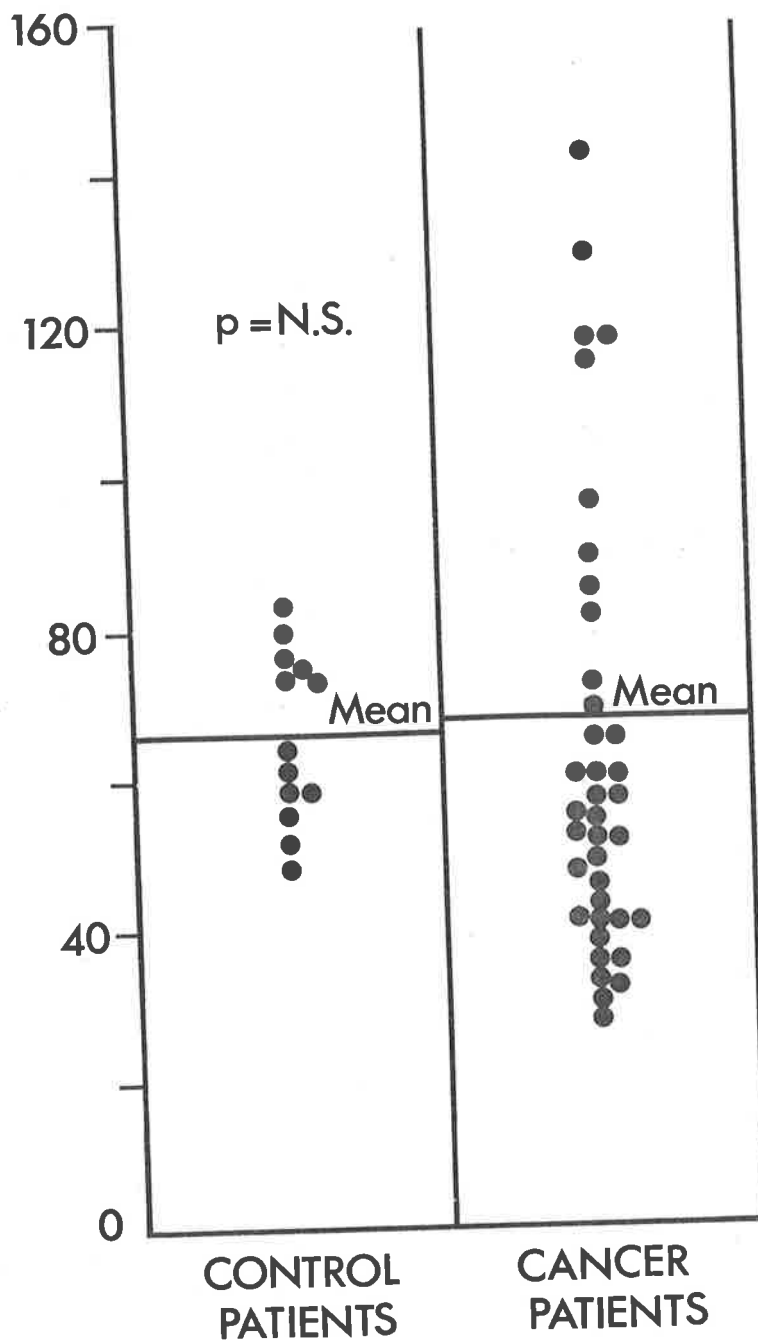


FIGURE 3.2

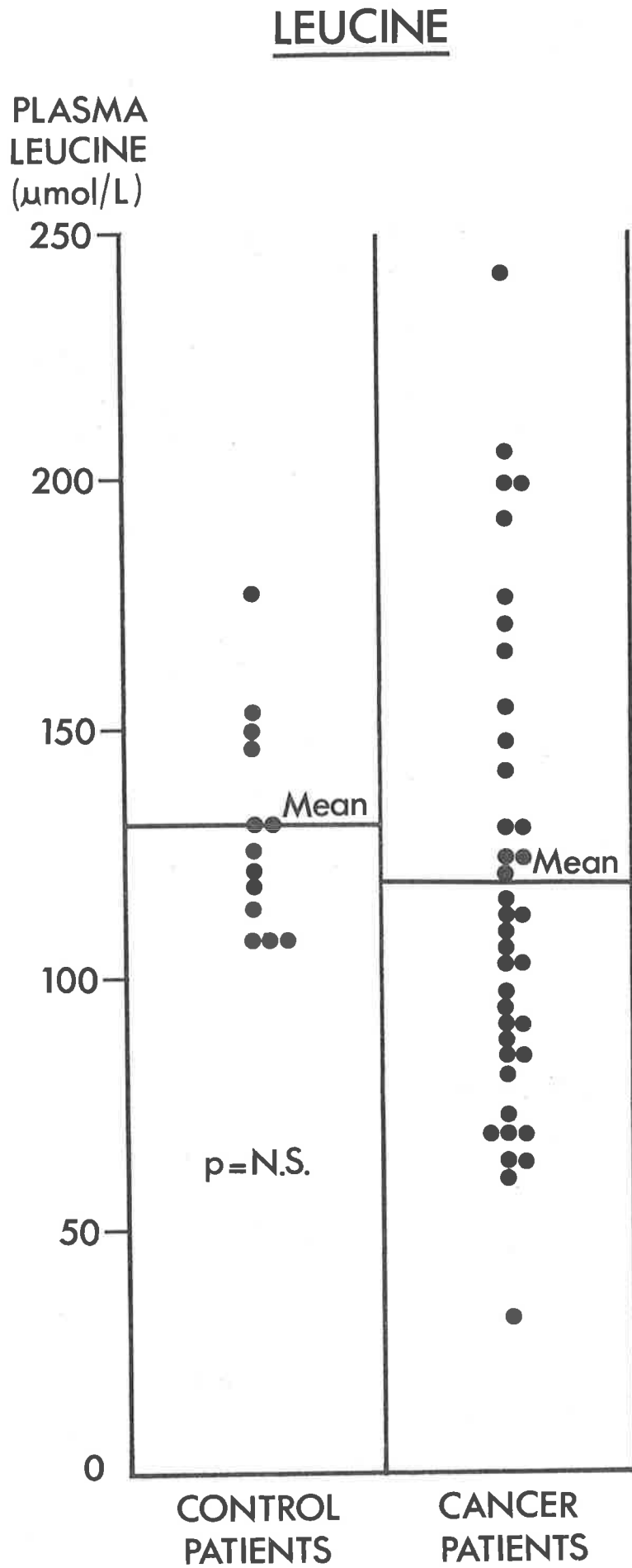


FIGURE 3.3

VALINE

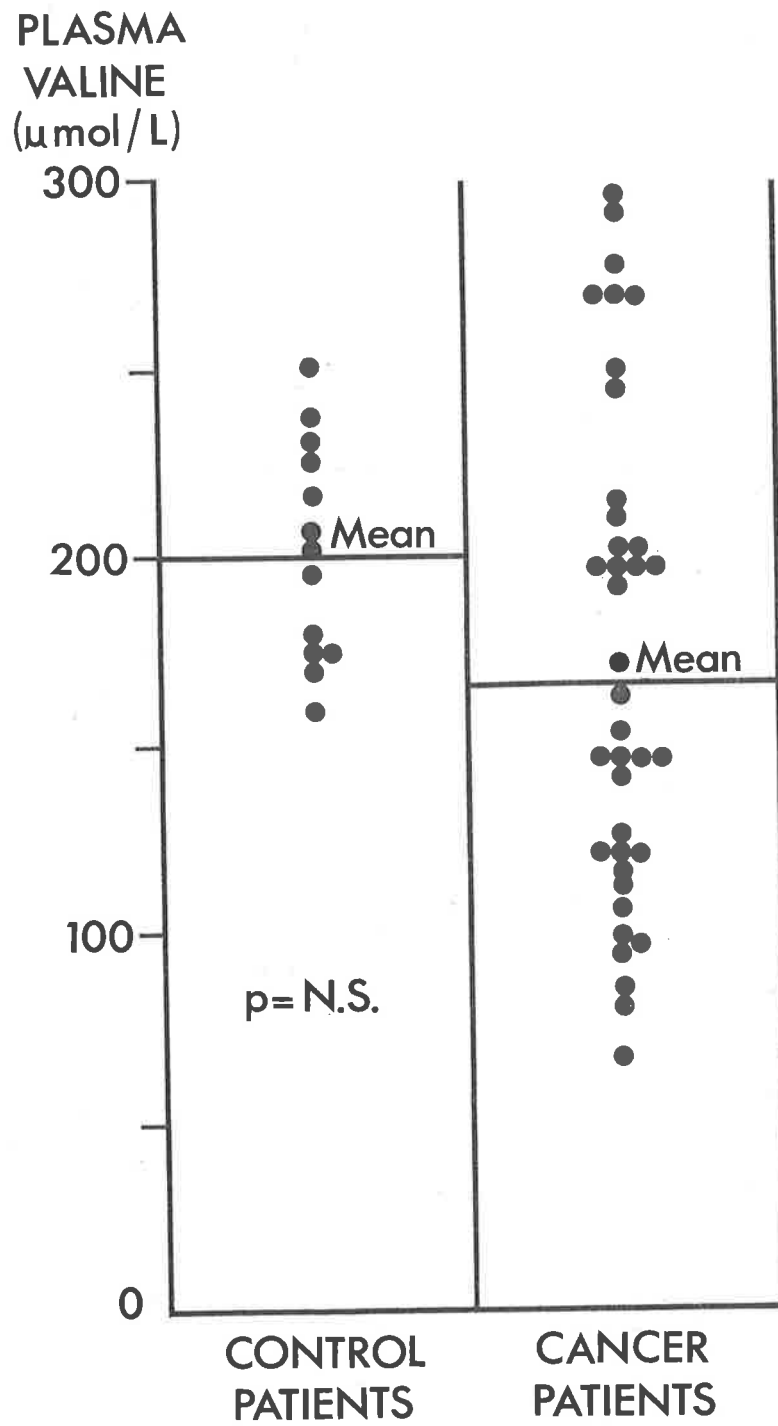


TABLE 3.1b

Patients with elevated branch-chain amino acids
(Valine, Leucine, Isoleucine)

Tumour Type	Weight Loss (% of normal)	Onset of weight loss and duration	Reason for acute weight loss
Carcinoma of larynx	20.6	Acute on chronic 2 weeks	Dysphagia
Carcinoma of colon	8.3	Early chronic 8 weeks	Anorexia, hepatic secondaries
Renal cell carcinoma	15.0	Acute on chronic 4 weeks	Anorexia
Carcinoma maxillary antrum	17.9	Acute on chronic 2 weeks	Radiation mucositis
Carcinoma of oesophagus	25.2	Acute on chronic 3 weeks	Post-operative anorexia and depression
Carcinoma of lung	12.0	Acute 3 weeks	Hemiparesis due to cerebral metastases

the "acute starvation" in these patients included depression, radiotherapy-induced oral mucositis, dysphagia due to laryngeal carcinoma and swallowing difficulty due to cerebral metastases resulting in a hemiparesis and facial nerve palsy.

Low values of a branched-chain amino acid usually occurred in association with low values of other branched-chain amino acids.

There was no correlation between the degree of weight loss, plasma amino acid values, tumour type or duration of anorexia. The mean plasma values of alanine, citrulline, cystine, ornithine, arginine and histidine were significantly lower in the cancer patients than in the control group (Figures 3.4-3.9). Mean levels of glutamic acid and aspartic acid were higher in the cancer patients than in the control group; the latter did not reach statistical significance (Figure 3.10). A number of patients also had elevated levels of phenylalanine, but the mean level in the cancer group did not differ significantly from the control group (Figure 3.11).

DISCUSSION

There has been increasing emphasis in the literature on the possible value of nutritional support in cancer patients prior to, and during, therapy with surgery, cytotoxic chemotherapy and radiotherapy (Copeland, E.M. et al 1977, Greenberg, G.R. et al 1976, Serrou, B. et al 1981, Valerio, D. et al 1979). However, the studies reported in this thesis and those of others (Nixon, D. et al 1980, Nixon, D. et al 1981) have shown that not all cancer patients respond to conventional nutritional support. Differences in responses between studies may reflect differences in patient selection, but it is most likely that the cancer population is heterogeneous with respect to the metabolic response that

FIGURE 3.4

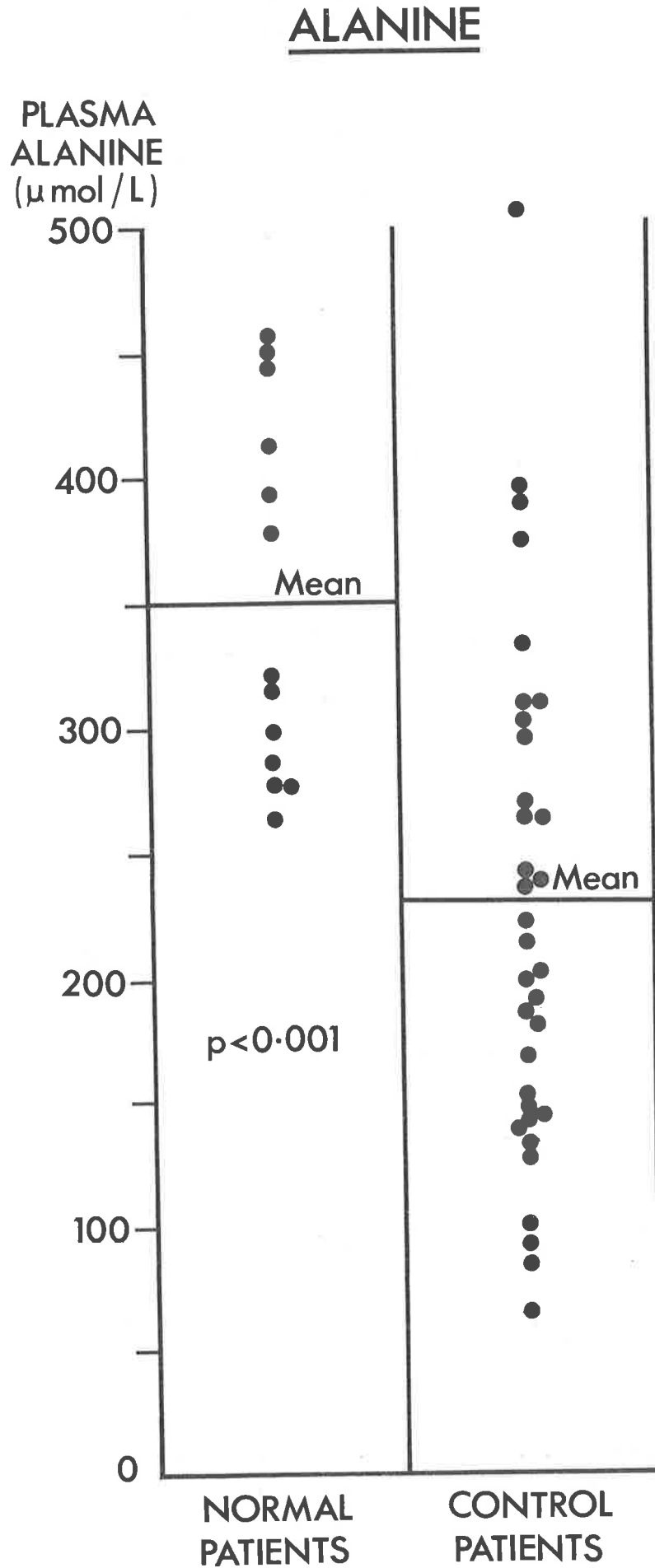


FIGURE 3.5

CITRULLINE

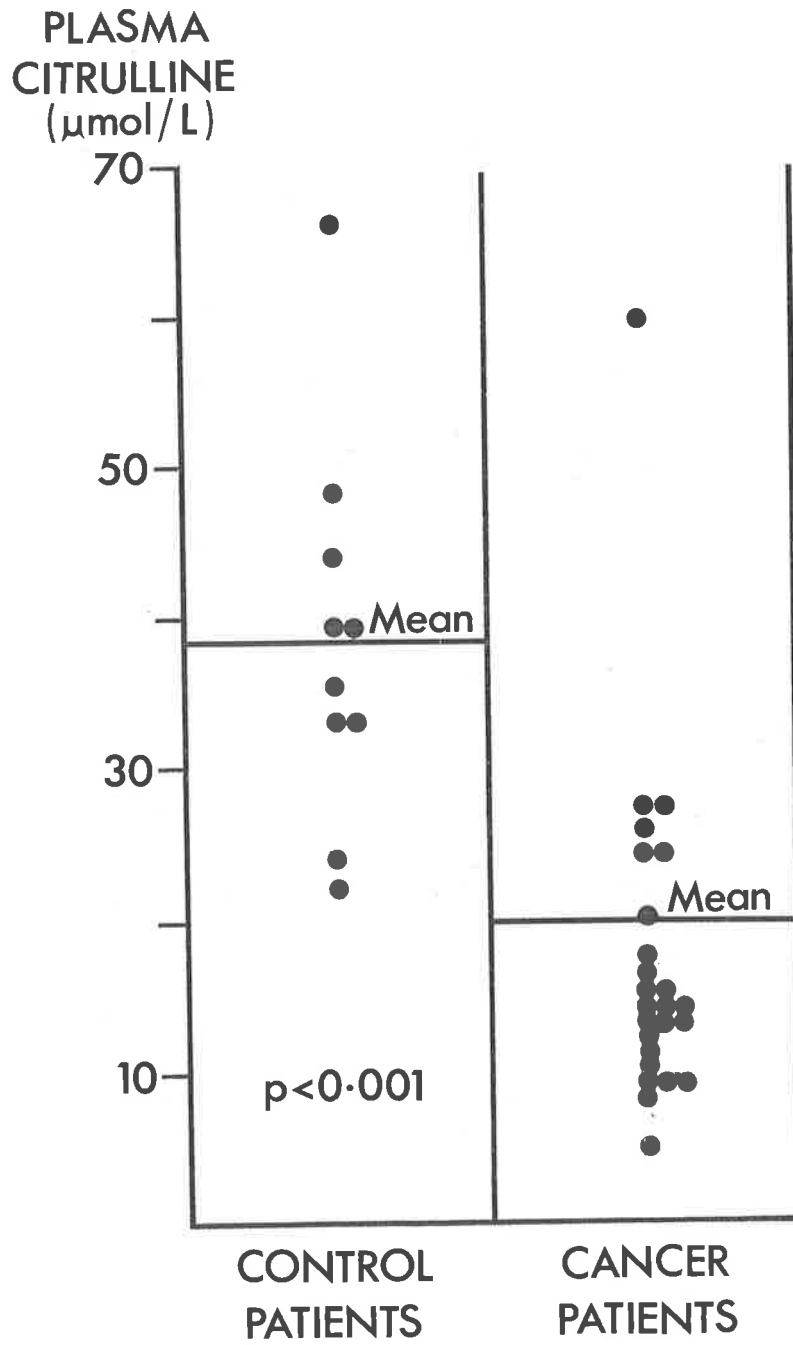
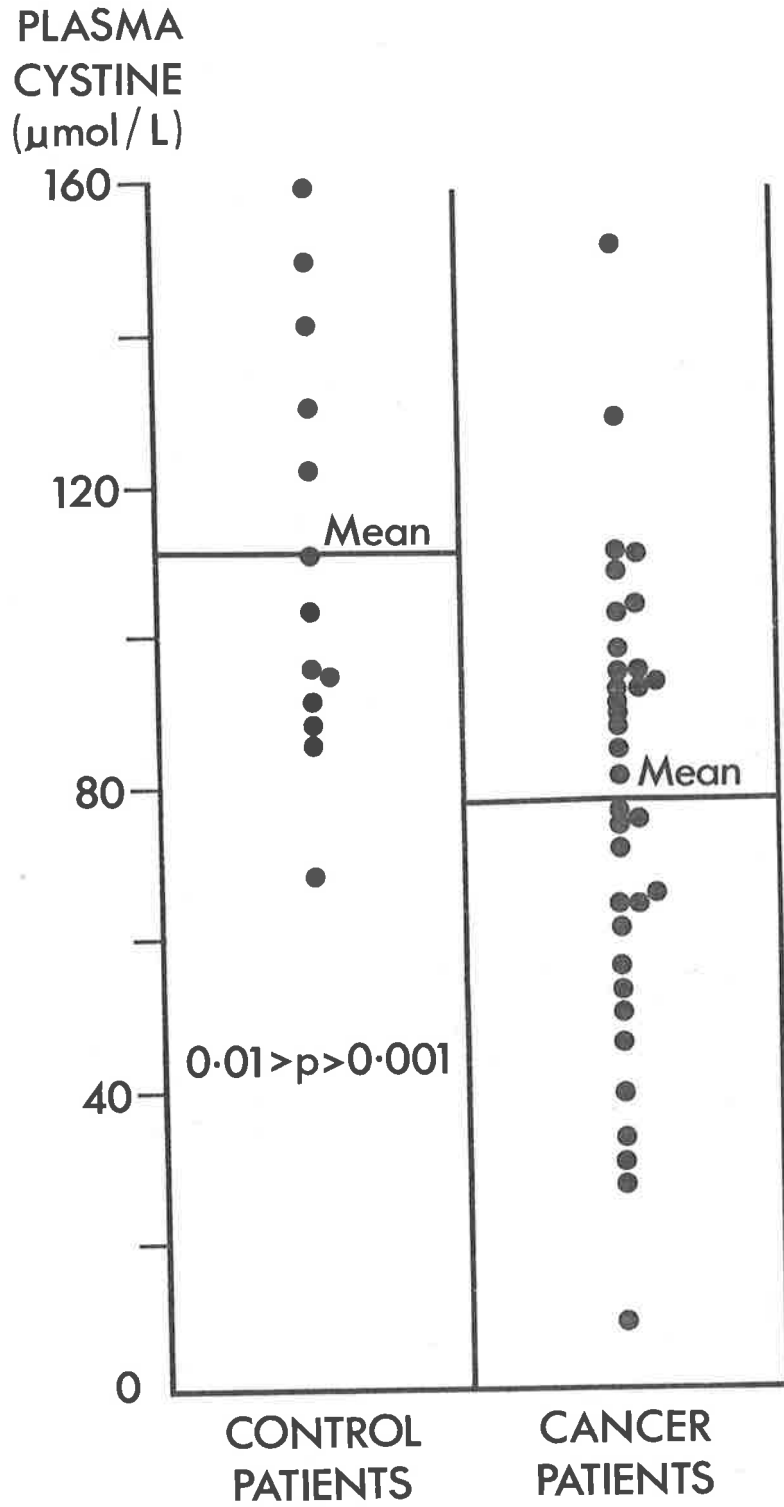


FIGURE 3.6

CYSTINE



ORNITHINE

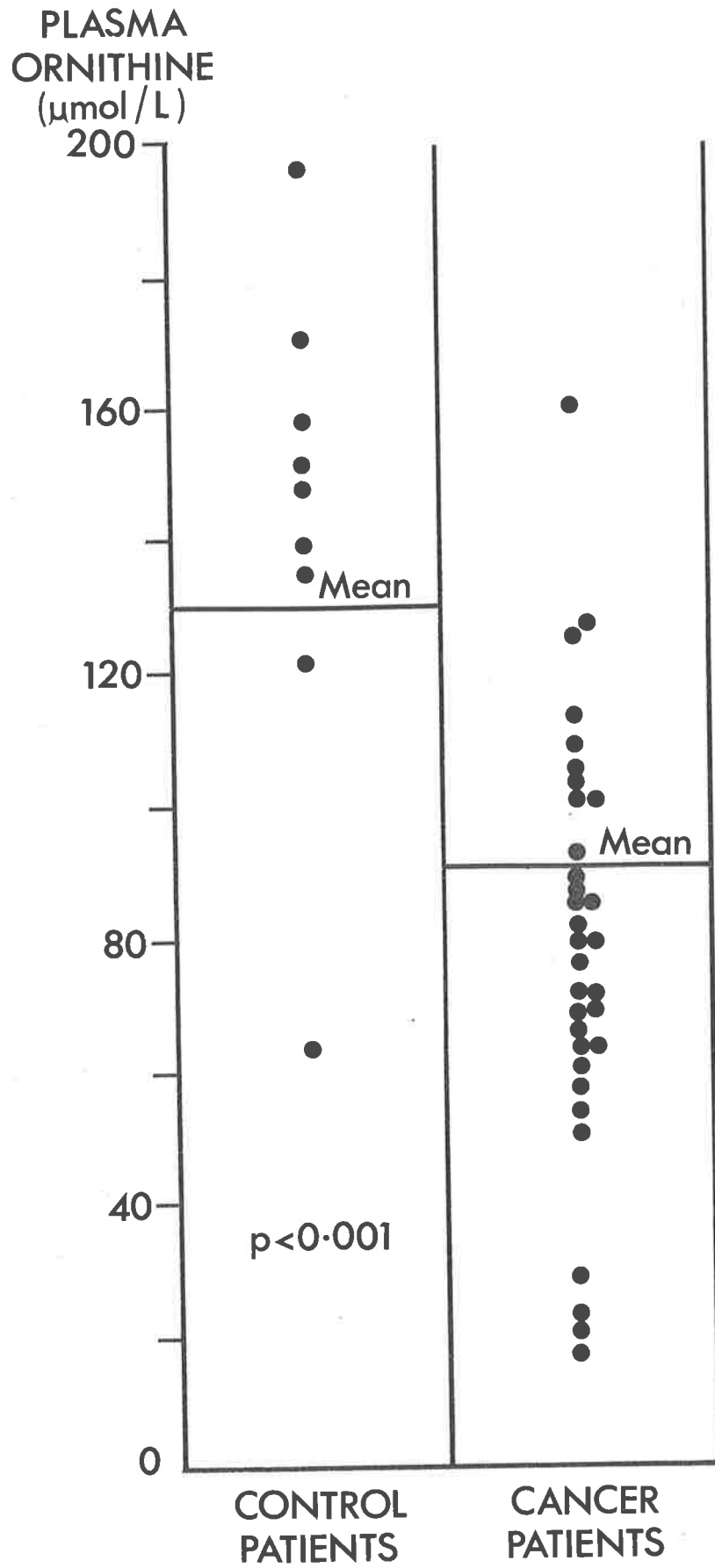


FIGURE 3.8

ARGININE

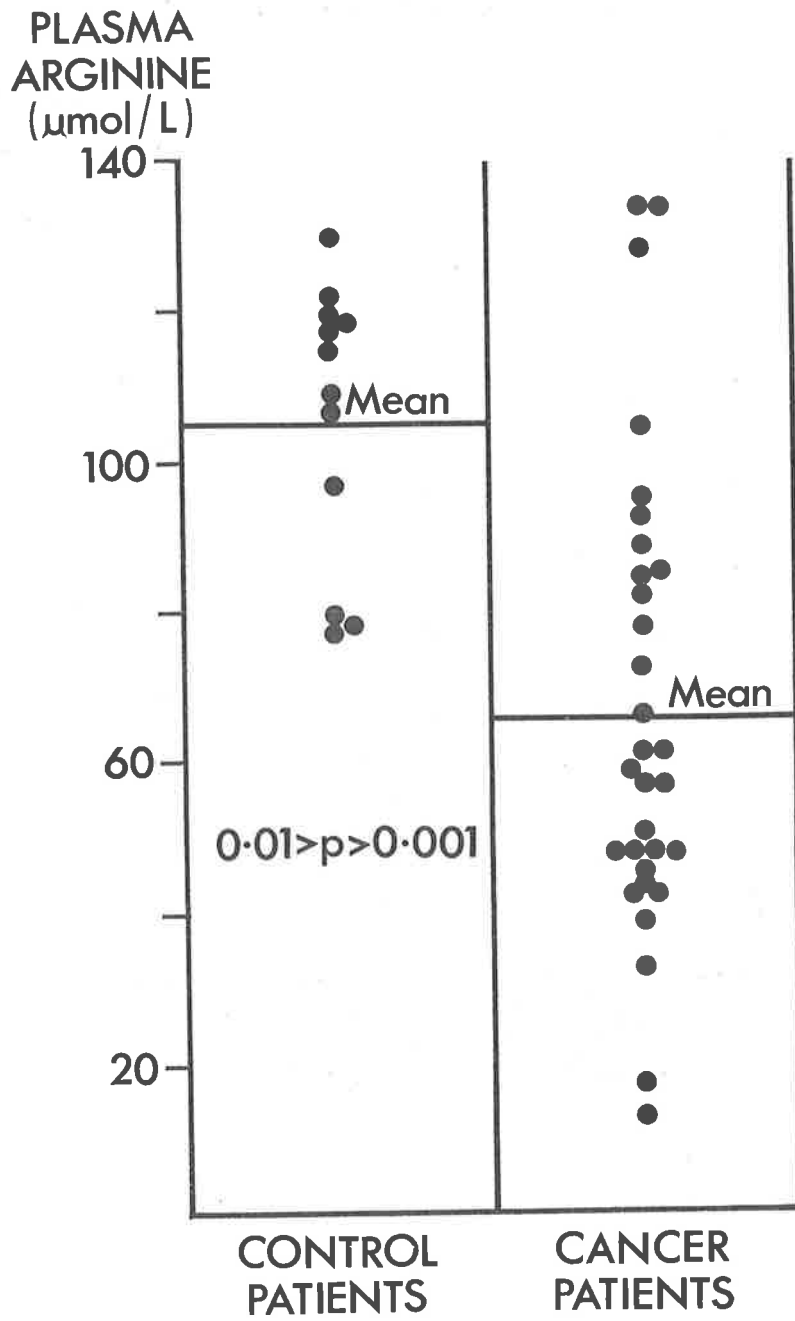


FIGURE 3.9

HISTIDINE

PLASMA
HISTIDINE
($\mu\text{mol/L}$)

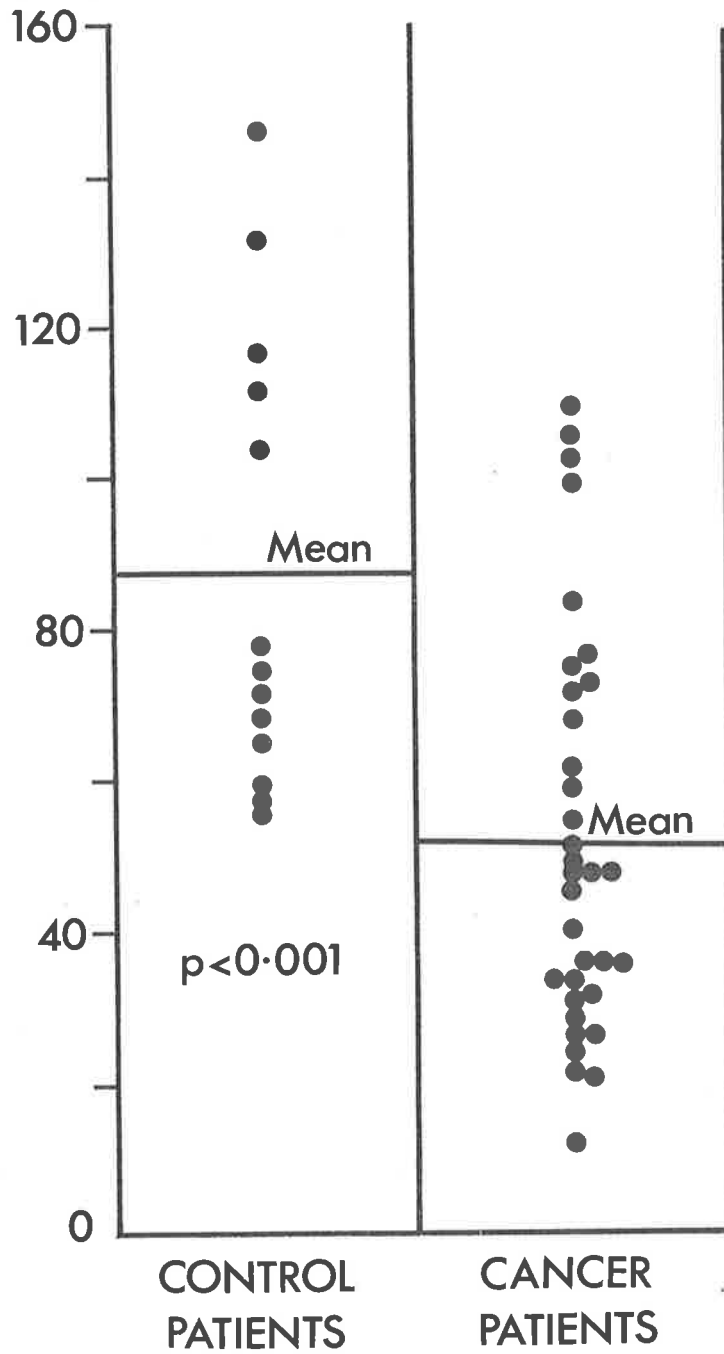


FIGURE 3.10

GLUTAMIC ACID

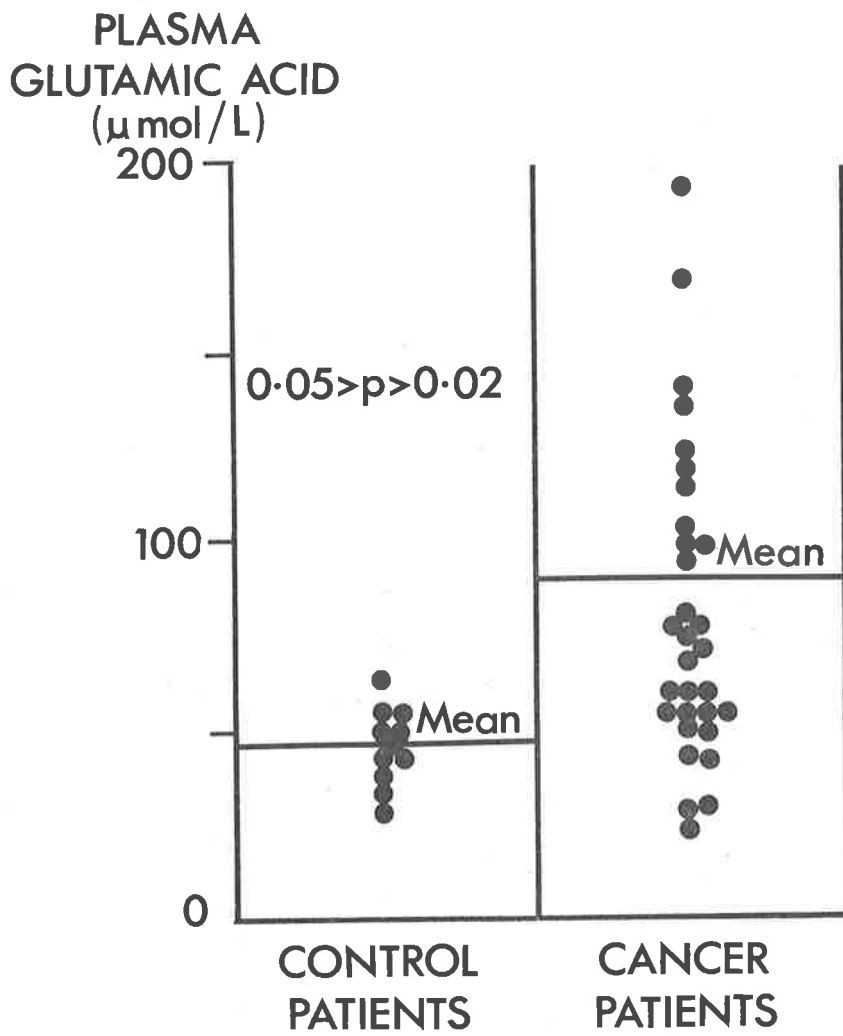
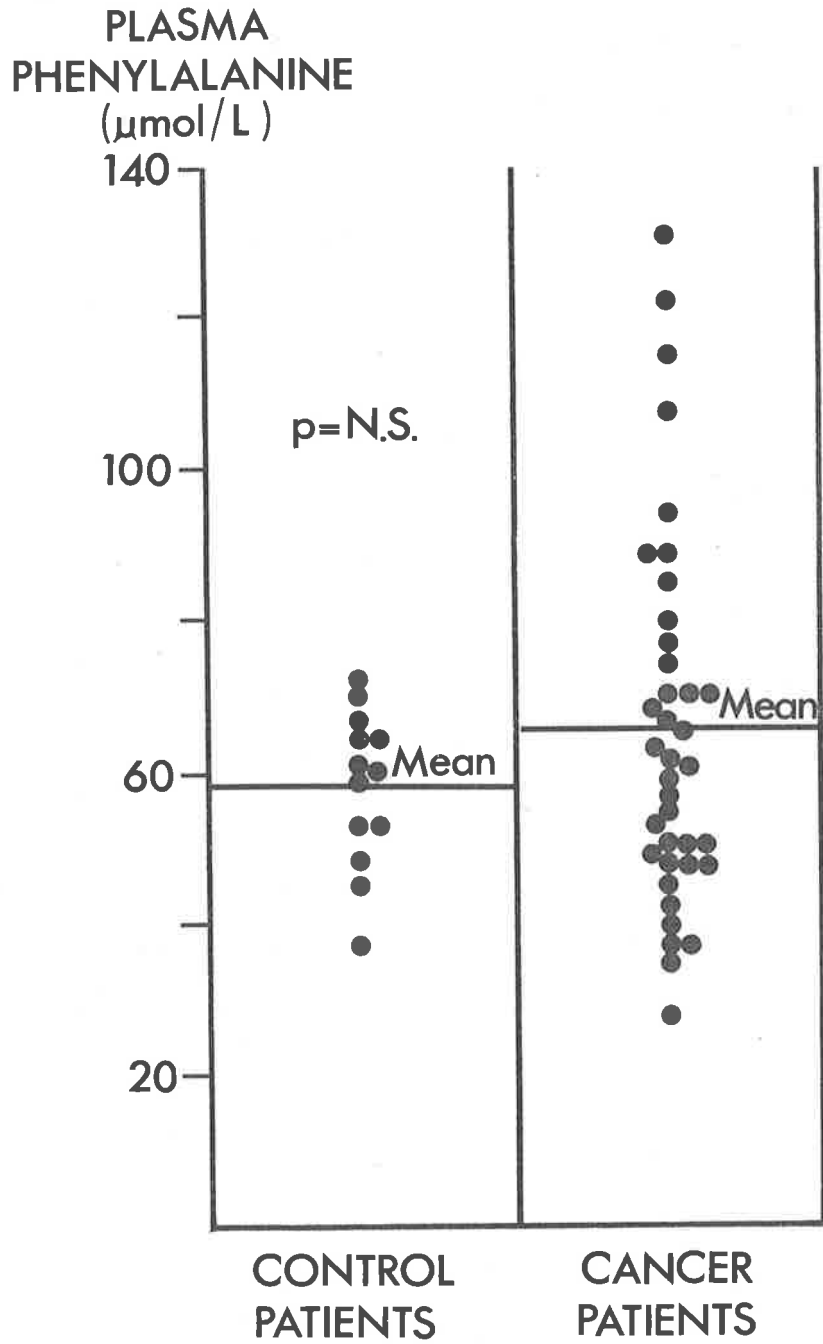


FIGURE 3.11

PHENYLALANINE



the malnourished cancer patient develops. The amino acid data presented here would lend support to the concept suggested by previous studies in this thesis that cancer patients may be hypocatabolic or hypercatabolic.

It has been reported that the plasma concentrations of branched-chain amino acids in malignancy are normal (Clarke, E. et al 1978). These authors suggested that the absence of significant arterio-venous differences in the amino acid concentrations excluded excessive muscle protein catabolism. They deduced that increased gluconeogenesis accounted for the normal branched-chain and reduced glycine, alanine and threonine concentrations in the malnourished cancer patients. Whilst this may be so for some cancer patients, our data would suggest that there may be two other groups of cancer patients. In one, elevated levels of branched-chain amino acids imply acute muscle catabolism for the purpose of gluconeogenesis. Such increases are seen in acute starvation (Felig, P. et al 1969) and in some patients with acute leukaemia (Waisman, H.A. et al 1952). In this study, a recent acute reduction in food intake was usually the cause for this plasma amino acid pattern, and represents a normal response to such a situation.

In the other group, low levels of branched-chain amino acids may reflect a normal metabolic response to starvation. It might be anticipated that such patients would be more likely to respond to nutritional repletion. It can be argued that "normal" plasma levels of branched-chain amino acids are inappropriately elevated in relation to reduced protein and energy intake, and may reflect an elevated catabolic rate for the nutritional state of the individual. This "low grade" hypercatabolic state may be the result or cause of the acute phase response often seen in cancer patients.

Serum levels of CRP were elevated in all but five patients in this study. None of the five patients with a normal C-reactive protein had elevated branched-chain amino acids, and their mean plasma concentrations were not significantly different from the mean values of the whole group.

The normal values for histidine, arginine, lysine and glutamic acid in the patients with leukaemia mentioned above (Waisman, H.A. et al 1952) imply that these patients had a better nutritional state than those in the present study.

The fall in the plasma levels of urea cycle amino acids citrulline, ornithine and arginine and the rise in glutamic acid levels in some patients suggests a reduction in urea synthesis as a result of substrate deficiency. These effects are comparable to those of uncomplicated starvation. The increased glutamic acid (and perhaps aspartic acid) are consistent with increased gluconeogenesis as reported by Clarke et al (1978).

The increased plasma levels of phenylalanine and unchanged or reduced tyrosine levels may reflect inadequate conversion by phenylalanine hydroxylase following increased muscle catabolism (Smith et al 1974). This mechanism has been postulated to account for increased plasma phenylalanine levels in viral or bacterial infections in man (Wannemacher 1977). Wannemacher, R.W. et al (1976), studying metabolism of ^{14}C -phenylalanine, found that increased serum phenylalanine levels were more likely a reflection of increased striated muscle catabolism rather than reduced hydroxylation.

In conclusion, these data suggest that the metabolic response to protein-energy depletion in the cancer patient varies between individuals, even those with apparently the same tumour type and extent of disease. Some cancer patients respond to protein-energy deprivation

in the normal way with appropriate changes in the plasma amino acid concentration. Other cancer patients have evidence from the plasma amino acid profile of a hypercatabolic state, despite malnutrition, which is presumably a consequence of a host response to humoral factors produced by the host or tumour. It is predicted that the patient's response to nutritional support depends upon the type of metabolic response produced by that patient.

SUMMARY

Fasting plasma amino acid profiles were determined by ion exchange chromatography in a group of 39 anorectic malnourished cancer patients, most with weight loss in excess of 10% of normal body weight. Comparison of these values with a control group revealed significantly low values for the urea cycle amino acids citrulline, ornithine and arginine with an increase in glutamic acid. In addition, mean values for the branched-chain amino acids were normal but there was a wide scatter of values, suggesting that cancer patients can be divided into three groups:

- (1) Those with high plasma levels of branched-chain amino acids due to an acute or acute on chronic catabolic phase.
- (2) Those with low plasma levels of branched-chain amino acids indicating a normal response to protein-energy depletion, and
- (3) Those with "normal" but inappropriately high levels of high branched-chain amino acids, representing a hypercatabolic response in relation to the state of nutrition of the individual (i.e. a failure of normal adaptation to starvation). It is suggested that patients with fasting amino acid profiles of the type seen in

uncomplicated protein-energy malnutrition should respond best to nutritional repletion.

The abnormal metabolic response to malnutrition demonstrable in "group 3" patients may be the result of a humoral factor of either host or tumour derivation.

ALBUMIN METABOLISM AND DISTRIBUTION
IN CANCER PATIENTS WITH CACHEXIA

All human things must decay

And, when fate summons, monarchs must obey.

John Dryden

MacFlecknoe l.l.

INTRODUCTION

The cachexia associated with malignant disease is commonly associated with hypoalbuminaemia (Mider 1951), but the causes of the fall in plasma albumin concentration have not been fully elucidated (Lundholm, K., Karlberg, I. and Schersten, T. 1978). In the cachexia of protein-energy malnutrition, both albumin catabolism and synthesis are reduced (Rothchild, M.A. et al 1977, James, W.P.T. and Hay, A.M. 1968, Picou, D. and Waterlow, J.C. 1962). Several studies have suggested that reduced albumin synthesis is the predominant cause of the hypoalbuminaemia in cancer and that this may be associated with a low rate of albumin catabolism (Steinfeld, J.L. 1960, Waldmann, T., Trier, J. and Fallon, H. 1963, Costa, G., Bernbeck, P. 1966, Mariani, G. et al 1976). However, others have reported an increased rate of albumin catabolism (Rossing, N. 1968). In some of these studies, however, a commercial albumin preparation was used, which might have been partially denatured. This could give rise to a falsely high estimate of fractional catabolic rate.

There are at least four possible mechanisms for the hypoalbuminaemia which occurs in patients with cancer. Firstly, the basal metabolic rate (BMR) may be increased, leading to increased albumin catabolism which exceeds increased synthesis (Mider 1951, Warnold, I. et al 1978,

Waterhouse, C., Fenninger, L.D., Keutmann, E.H. 1951). In hyperthyroid patients with increased BMR, albumin catabolism is increased and hypoalbuminaemia occurs (Waldmann, T.A. 1977). Secondly, a malignancy may be associated with an acute phase response, which in turn leads to a decreased albumin concentration with possibly an increased fractional catabolic rate. In recent years there has been increasing evidence that cancer is associated with an acute phase response with elevation of acute phase reactants such as C-reactive protein (CRP) (Coombes et al 1977) and fibrinogen (Huggins, C. 1949). This acute phase response is often associated with a fall in the concentration of some plasma proteins, e.g. albumin (Fleck, A. 1980). Hepatic synthesis of albumin may be impaired in association with the acute phase response (Darlington et al 1986). In addition, a change in capillary permeability may cause an increase in the extravascular to intravascular (E/P) ratio of albumin, perhaps an increased fractional catabolic rate, and a reduced plasma albumin concentration. In contrast, protein-energy malnutrition is associated with a reduction in the catabolic rate of albumin and a reduction in the E/P ratio (Rothchild, M.A. et al 1977).

Thirdly, there may be direct losses of albumin from the gut in patients with alimentary tract cancer (Mariani, G. et al 1976, Wadmann, T.A., Wochner, R.D., Strober, W. 1969, Werdegarr, D. et al 1963, Wangel, A.G., Deller, D.J. 1965). Fourthly, protein-energy malnutrition may contribute to the hypoalbuminaemia. In some patients this may be the result of mechanical obstruction to the gut, as in oesophageal cancer, or in others due to anorexia in the absence of significant host metabolic derangement induced by extensive or bulky tumour. In such patients there might be no increase in metabolic rate and minimal acute phase response.

In order to determine which of these mechanisms is responsible for hypoalbuminaemia in cancer patients, the metabolism and distribution of albumin were studied in malnourished cancer patients with a serum albumin concentration of less than 30 g/l. It was planned to determine the fractional catabolic rate (FCR), transcapillary escape rate (TCER) and extravascular to intravascular ratio (E/P) of albumin and the fractional synthesis rate from the distribution and rate of excretion or synthesis of the appropriate radio-active products following injection of ^{131}I -albumin, Na^{125}I and $\text{Na}_2^{14}\text{CO}_3$ (see Methods).

Albumin synthesis is normally in equilibrium with catabolism. This has been shown by others using similar methods to those in the present study (Tavill, A.S. et al 1968, Wochner, R.D. et al 1968).

METHODS

1. Patient Selection

Eligible patients for the study had histologically proven malignancy, plasma albumin concentrations of less than 30 g/l and weight loss in excess of 10% of normal body weight over the preceding six months. Patients were excluded from the study if there was clinical or radiological evidence of pleural effusion, ascites or peripheral oedema, congestive cardiac failure, hypertension, diabetes mellitus, known inflammatory disease, or diarrhoea. Also excluded were those who had received cytotoxic chemotherapy either within the preceding four weeks, or radiotherapy or surgery within the preceding three months. Patients on corticosteroid therapy were excluded from the study.

Ten patients (6 male : 4 female) were studied, most of whom had metastatic disease (Table 3.2). The bulk of metastatic disease was small in patient 3 and the only known metastatic disease (a cutaneous

TABLE 3.2
PATIENT DATA AND TUMOUR CHARACTERISTICS

NO.	PATIENT	SEX	AGE	PERF.STATUS	TUMOUR TYPE	EXTENT OF DISEASE	PREVIOUS THERAPY	SURVIVAL TIME (DAYS)
1.	T.C.	M	64	3	Gastric adenocarcinoma	Disseminated bone metastases	Partial	47
2.	J.L.	M	64	2	Adenocarcinoma of unknown origin	Metastatic hepatic disease	None	56
3.	M.S.	F	81	2	Adenocarcinoma oesophagus	Local recurrence : stricture June 1974 pulmonary metastases	Oesophago-gastrectomy 1976 5-FU 1976-77	150
4.	J.C.	F	45	2	Adenocarcinoma	Local disease stricture Cutaneous metastasis	Celestin tube	115
5.	J.M.	M	72	2	Squamous cell ca. lung	Local	Nil	330
6.	D.F.	M	62	3	Oat cell ca. lung	Local	Nil	12
7.	J.O.	M	68	3	Pleural mesothelioma	Widely metastasising	Nil	45
8.	M.L.	F	59	3	Ca breast	Extensive bone/soft tissue metastases	Chemotherapy Hormone Px	13
9.	M.M.	F	61	3	Ca breast	Extensive bone metastases	Chemotherapy On hydrocortisone	400
10.	J.A.	M	45	3	Gastric adenocarcinoma	Bulk intra-abdominal	Surgery	17

TABLE 3.2

nodule) excised in patient 4. Patients 5 and 6 had local disease only and no evidence of metastatic disease on chest x-ray, hepatic ultrasonogram or bone isotope scan and had normal serum 'hepatic' enzymes. There were two patients with each of gastric, oesophageal and breast adenocarcinoma, three primary intrathoracic malignancies and an adenocarcinoma of unknown origin. Only patients 8 and 9 with breast carcinoma had previously received cytotoxic chemotherapy. Patient 9 was commenced on aminoglutethimide 250 mg. four times a day and hydrocortisone 20 mg. twice a day four days prior to commencement of the albumin studies. Hydrocortisone in this situation is necessary as adrenal replacement therapy for the aminoglutethimide induced adrenal suppression.

Survival ranged from 12 days to in excess of 400 days following the study. The longest surviving patient (patient 9) had a carcinoma which responded well to the hormone therapy documented above. This latter patient remained well with stable bone metastases for over 15 months. Patients 1, 2, 3 and 4 all had chemotherapy subsequent to the albumin metabolic studies but failed to respond. Patient 6 died at 12 days of an intercurrent bronchopneumonia, patient 8 at 13 days of a probable stroke due to severe thrombocytopaenia and extensive bone marrow replacement by tumour and patient 10 at 17 days following surgery for an acute bowel obstruction.

The performance status of patients ranged from 2 to 4 (Criteria of the Eastern Co-operative Oncology Group) (Table 2.19). In general the short survival times reflected the poor performance status of patients at the beginning of the study.

Reference ranges were determined from the results of albumin metabolism studies in seven control subjects using these methods in the same laboratory. The normal ranges for FCR were calculated to be

0.085 -0.11 of the total albumin pool per day; for TCER, 4-7% per hour; and the E/P ratio, 1.3 - 1.5. There was good agreement between FCR and FSR measurements (unpublished work, A. Fleck, G. Raines, S. Caine). These results are similar to those reported in the literature.

2. Nutritional Management and Data Collection

All patients were admitted to hospital and commenced on a ward diet at least 5 days prior to the start of the albumin studies to collect baseline nutritional data and allow time for stabilisation after commencement of enteral nutritional support. A careful dietetic history was obtained from each patient by a senior dietitian on admission and twice weekly thereafter. Nutritional supplementation was provided by oral liquid supplements of high energy and protein content or by nasogastric fine bore tube (Clinifeed System 1, Roussel Laboratories Limited, Middlesex) drip feeding in an attempt to provide minimum daily requirements of protein and energy as calculated from tables of recommended intake. An attempt was made to provide a steady nutritional intake during the study period. Continuous daily urine collections were made for measurement of total urinary nitrogen, urea and creatinine measurements, and nitrogen balance was calculated. Weight was measured on an Avery beam balance. Mid-upper arm circumference was measured with a tape measure and triceps skin-fold thickness was assessed using a Harpenden skin-fold caliper (British Indicators Limited). These measurements were repeated weekly.

3. Biochemical and Haematological Monitoring

The following parameters were measured at commencement of the studies of albumin metabolism and at least weekly during the studies: haemoglobin, haematocrit (Coulter Model S, Coulter Electronics, Luton, Bedfordshire), alkaline phosphatase, bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), albumin,

total protein, IgG, IgA, IgM, retinol binding protein (RBP), pre-albumin (PA), transferrin, C-reactive protein (CRP), alpha₁-antitrypsin (α_1 AT), urea, creatinine and electrolytes.

4. Studies of albumin metabolism

(a) Clinical procedure.

To block the thyroid uptake of radioactive iodine, potassium iodide tablets were given, 60 mg. tablet tid., three days before and one week after the injection. Thereafter the dose was reduced to 60 mg. bd. and continued for at least one month.

On the day of injection, 50-60 μ Ci sterile Na¹²⁵I was added to about 100 μ Ci ¹³¹I-HSA (¹³¹I-human serum albumin) and administered together with about 100 μ Ci Na₂¹⁴CO₃. A Cathlon intravenous plastic cannula (Johnston and Johnston, 260 Bath Road, Slough, Buckinghamshire) was inserted into a forearm vein to facilitate frequent blood sampling and a weighed amount of the radioactive ¹³¹I-HSA/Na¹²⁵I mixture was injected with the Na₂¹⁴CO₃ into a vein in the opposite arm making sure "washing in" was as complete as possible. In order to determine the dose, the residue (I.R.C. = injection residue counts) left in the syringe and needle was made up to a standard volume with bovine serum albumin (BSA) - (1 g/l in 10% Teepol with KI (1 g/l) to prevent adsorption of iodide and protein to glass). Venous blood samples were taken at 10, 20, 30, 45, 60 minutes; 2, 3, 4, 5, 6, 8, 10, 12, 24, 30, 36, 48, 56 hours; 3, 4, 5 etc. days up to 14-21 days. From these samples the fractional catabolic and synthesis rates of albumin were calculated as well as the transcapillary escape rate and extravascular to intravascular ratio as described below. Single samples of urine were collected for the first 3 days; thereafter 24 hour collections were made until the end of study, using 10% Teepol in KI (1 g/l) as a preservative. Faecal samples were

collected for the first week. (See Appendix V for abbreviated flow chart).

(b) Laboratory procedure for the preparation of ^{131}I -HSA

Sterile precautions and pyrogen free solutions were used throughout. Sterile gloves were worn. All glassware used was rinsed with pyrogen-free water and autoclaved prior to use. The apparatus which could not be autoclaved was sterilised using ethylene oxide. Dispensing of reagents was carried out in a laminar flow cabinet (Microflow pathfinder Limited, Fleet Mill, Minley Road, Hampshire, England).

MATERIALS USED FOR THE PREPARATION OF ^{131}I -HSA.

All reagents were Analar unless otherwise stated.

^{131}I -Sodium Iodide (^{131}I -NaI)-code no. IBS 30 and ^{125}I -NaI-code no. IMSIP was obtained from the Radiochemical Centre, Amersham, Bucks.

Buffers - (a) 1.0 M. Glycine/0.25 M NaCl at pH 8.5 and 9.1, (b) 1.0 M NaOH at pH 8.5 and 9.1, (c) 1.0 M glycine 0.1 M NaCl at pH 1.5 and 11.5, (d) 0.1 M NaOH at pH 1.5 and 11.5. The glycine NaCl was autoclaved prior to the addition of filtered NaOH. The latter must not be autoclaved.

Neutralised Saturated Ammonium Sulphate $[(\text{NH}_4)_2\text{SO}_4]$. 200 ml 1 M NaOH was added to 100% saturated $(\text{NH}_4)_2\text{SO}_4$ after the latter was autoclaved.

R Sephadex G10. (R Pharmacia Fine Chemicals, Paramount House, 75 Uxbridge Road, London) - swollen in sterile isotonic NaCl (9 g/l) and then autoclaved.

Columns. Brunswick 10 ml syringes with central aperture (Sherwood Medical Industries Limited, Crawley, Sussex, England) were used as columns. "Vyon" porous polythene (Porvair Limited, Estuary Road, King's Lynn, Norfolk, PE3 2HS) and nets (Pharmacia, Code No. 19-0652-01) were cut to size using a No. 11 cork borer. Each set including a rubber

plunger was sterilised by ethylene oxide.

0.9% W/V NaCl for injection (Travenol Laboratories Limited, Caxton Way, Thetford, Norfolk).

Dried Fresh Human Plasma. Scottish National Blood Transfusion Service, Regional Blood Transfusion Service, Law Hospital, Carlisle.

Human Albumin. 15% W/V salt-poor human albumin solution (Scottish National Blood Transfusion Service, Protein Fractionation Centre, Ellen's Glen Road, Edinburgh) was diluted 1 in 3 with sterile isotonic saline.

METHOD USED FOR THE PREPARATION OF ^{131}I -HSA.

Human Plasma Albumin (HPA). Autologous plasma albumin was prepared by ammonium sulphate precipitation prior to iodination. Twenty (20) ml. blood was collected from each patient in a heparinised syringe and put into sterile universal containers. The plasma was separated and diluted 1 in 3 with isotonic saline and then 1 in 2 with neutralised saturated $(\text{NH}_4)_2\text{SO}_4$. Some plasma was retained at 4°C for later use as 'carrier'. After 2 hours at room temperature the mixture was centrifuged and the supernatant adjusted to pH 4.6 with glycine buffer pH 1.5. After 1 hour at 25°C , the mixture was centrifuged again, the supernatant discarded and the precipitate dissolved in as small a volume of glycine buffer, pH 11.5, as possible (not more than 1.0 ml). Ammonium sulphate was removed using a Sephadex G10 column equilibrated with isotonic saline. The albumin solution was then concentrated into a volume of 0.5 ml using a Minocon Macrosolute Concentrator. (Amicon Corporation, Lexington, Mass. U.S.A.). Autologous albumin prepared by this method was used in the first four patients studied.

The percentage recovery of albumin from plasma was about 30-40%.
The Scottish Antibody Production Unit, Carlisle, Lanarkshire, kindly

supplied albumin prepared from Australia Antigen free human pooled plasma using a chromatographic procedure (Curling, J.M. et al 1977). Albumin from this source was used for the albumin catabolism study in the final six patients studied.

Determination of Albumin Concentration. The concentration of albumin was estimated using Bromocresol Green (B.C.G.) which reacts specifically with albumin at pH 4.2 (Dumas, B.T., Straumfjord, J.V. 1973, Dumas, B.T. et al 1971). Working standards were made from stock standard (10 g/100 ml) Human Serum (Hoechst U.K. Limited, Hoechst House, Salisbury Road, Hounslow, TW4). Due to the water content of albumin, it was necessary to dry the protein at 100°C to constant weight before calculating the actual albumin content of the standards.

Twenty (20) μ l sample and 200 μ l water were dispensed into macro disposable cuvettes. 3 ml B.C.G. working reagent was added and cuvettes read at 620 nm on a spectrophotometer after 10 minutes. A reagent blank was included; all the reagents and readings were at 25°C.

Iodination. The albumin (autologous or SAPU) was labelled by the iodine monochloride (ICl) method of McFarlane (McFarlane, A.S. 1958). The albumin was not oxidised prior to iodination. For maximum efficiency, the molar ratio of ICl to albumin was made 2:1 to give between 0.5 and 1.0 atoms of iodine bound per molecule of albumin (Munro, H.N., Allison, J.B. 1964). After five minutes incubation with the labelling mixture, 20 μ l was removed to determine the percentage incorporation by precipitating the iodinated albumin with trichloroacetic acid (T.C.A.). After determining the radioactivity in both the precipitate and supernatant, 5 mg sodium iodide was added. The solution was passed through a Sephadex G10 column to remove free iodide and 2 ml "carrier" plasma, (or 2 ml reconstituted human plasma) was added to the eluate, and the albumin was purified by ammonium sulphate precipitation as before.

After dissolving the precipitate in glycine buffer pH 11.5, the labelled albumin was purified by passage through two Sephadex G10 columns. This gave a labelled albumin preparation with less than 0.5% free iodide as determined by T.C.A. precipitation.

After priming the Millipore filter (Millex TM Disposable Filter Unit, Sterile 0.22 μ m, Millipore U.K. Limited, Millipore House, Abbey Road, London) with a dilute solution of sterile albumin to prevent absorption of the labelled preparation, the latter was filtered into a sterile bijoux. Finally, 100 μ l was diluted to 10 ml. with phosphate buffer, pH 7.5, and tested for pyrogens using the Limulus Amoebocyte Lysate kit (Laboratory Impex Limited, Lion Road, Twickenham, Middlesex). The filter was washed through with 5 ml. "carrier" plasma or the diluted salt poor human albumin. To minimise self-irradiation damage, the specific activity was kept below 5 μ Ci/mg albumin (Munro, H.N., Allison, J.B. 1964). A sample was taken to check for sterility.

5. Analysis of Results

(a) Albumin catabolism.

Plasma and urine radioactivity was determined using a Packard autogamma counter (5230) (Packard Instruments Limited, Caversham Bridge House, 13-17 Church Road, Caversham, Berkshire). The activity of the samples was compared with that of a standard containing a known quantity of the preparation injected. Initial processing of data was carried out on a Wang 2200 desktop computer (Wang Electronics Limited, 40-44 High Street, Northwood, Middlesex).

The data was weighted using reciprocal values, and semi-log curves of P and I, the plasma protein and inorganic iodide (^{125}I) radioactivity respectively, against time were fitted using the Nottingham Algorithms Group (NAG) library subroutine E04 FAF (Peckham, G. 1970) on an ICL 2976 Computer (University of Glasgow). The initial approximations of the

intercepts and exponents were obtained by a "curve stripping" approach with a standard package single exponential curve-fitting programme on the Wang 2200 or Wang 600 6T desktop programmable calculator. Data was graphically represented by the package GHOST in the ICL 2976 (Calderbank, V.J., Prior, W.A.S. 1977).

Urine recovery of ^{125}I and plasma ^{125}I were measured to monitor the distribution and rate of excretion of the radioactive catabolic products. Faecal samples were counted for ^{131}I to check for gastrointestinal losses. Plasma albumin was measured using bromocresol green on the Greiner MK II Selective Analyser. (Greiner Electronics, Langenthal, Switzerland).

The following variables were calculated as follows:

Plasma Volume (P.V.): the known injected dose of radioactivity divided by the radioactivity per ml. at time zero. The latter was found by extrapolation of the time-concentrations curve (over 60 minutes) of the ^{131}I -HSA.

Iodide Space (I.S.): as for P.V. but using the plasma ^{125}I curve. The transcapillary escape rate (TCER) was determined over the first 60 minutes of the ^{131}I -HSA time-concentration curve as the percentage of the intravascular mass of albumin passing into the extravascular space per hour.

Lean Body Mass (L.B.M.) was determined by the method of Hume (Hume, R. 1966).

Fractional Catabolic Rate (F.C.R.), and Extravascular to Intravascular ratio (E/P) and rate constants were determined by compartmental analysis (Matthews, C.M.E. 1957). (See Appendix V). An experimental "short" method (24-30 hours) for determining the metabolic rate of albumin using a two isotope method (Na^{125}I and ^{131}I -HSA) was being concurrently investigated by Prof. A. Fleck using methodology

reported by Bianchi et al (1973 and 1976). The results using this method are not discussed further here.

Absolute Catabolic Rate (ACR) of Albumin

$$= \frac{\text{albumin} \times \text{P.V.} \times \text{F.C.R.}}{\text{L.B.M.}}$$

Theoretical P.V. = Blood Volume (1-*Haematocrit)

Blood Volume = $0.3669 H^3 + 0.3219W + 0.0641$ where H = height (metres) and W = weight (Kg) (Allen T.H. et al 1956).

(b) Albumin synthesis.

Albumin synthesis rate was determined by the ^{14}C -carbonate method originated by McFarlane (1963) and Reeve et al (1963). Since then the method has been subject to a number of modifications (McFarlane, A.S. et al 1965, Kaj, A., McFarlane, A.S. 1968, Jeejeebhoy, K.N. et al 1972). The method is based on the urea cycle of the liver. Following the intravenous injection of $\text{Na}_2^{14}\text{CO}_3$, $^{14}\text{CO}_2$ is incorporated into the guanidine carbon of arginine. The labelled arginine forms a common precursor pool for the synthesis of liver proteins and the production of plasma urea. By measuring the specific activity of ^{14}C in the plasma urea and in the guanidine carbon of the arginine in the plasma protein at various time intervals and correcting these values for losses from the intravascular compartment due to distribution, catabolism and excretion, it is possible to calculate the synthesis rate of the protein.

In the present study, blood samples were taken at frequent time intervals and the specific activity of plasma urea and the guanidine carbon of the arginine of albumin determined by the method of Tavill et al (1968). The specific activity of the arginine guanidine carbon was measured on four samples taken at 8, 9, 10 and 12 hours. A simplification of the manometric method as used by these workers for the measurement of specific activities was employed (Caine, S., Fleck, A.

1984).

Results were calculated according to Jeejeebhoy et al (1972).

RESULTS

Table 3.3 presents the nutritional data. Eight patients, on admission, were in negative nitrogen balance and were losing weight as a consequence. In two patients (8 and 9) nitrogen balance data was incomplete, but had weight loss and anorexia. Nutritional supplementation was provided in an attempt to achieve a steady state during the study. Some patients, however, were unable to tolerate adequate amounts of food, with consequent continued weight loss. Most patients had a weight gain (mean 1.4 kg) during the study but much of this gain represented an increase in total body water rather than protein or fat. The evidence for this is provided by the upper arm circumference and triceps skin folds measurements which had mean changes of -0.26% and +0.06% respectively. These changes are small and represent minimal changes in lean body mass and adipose stores during the study in those patients for whom measurements are available.

Plasma albumin ranged from 20 to 30 g/l (Table 3.4). The concentrations of the short half-life plasma proteins [retinol binding protein (RBP), prealbumin (P) and transferrin (TF)] were also reduced in most patients. There were no significant alterations in the immunoglobulins which were comparatively normal despite the reduction in the hepatic-produced plasma proteins mentioned above. Most patients demonstrated an acute phase response with elevation of CRP and alpha-1-antitrypsin. CRP was over 50 mg/l in 7 and alpha-1-antitrypsin was moderately elevated in 6 of 9 patients, high in two and normal in one.

Table 3.5 shows that the serum levels of hepatic enzymes were

TABLE 3.3
NUTRITIONAL DATA

NO.	PATIENT	HEIGHT (cm)	INITIAL WEIGHT (kg)	WEIGHT LOSS %	BASELINE NITROGEN BALANCE (g)	BASELINE		DURING STUDY (MEAN)		CHANGE IN WEIGHT (Kg)	CHANGE IN MID ARM MUSCLE CIRCUM. DURING STUDY(%)	% CHANGE IN TRICEPS SKIN FOLD THICKNESS
						Energy (Kcal)	Nitrogen (g)	Energy (Kcal)	Nitrogen (g)			
1.	T.C.	178	51.5	16.4	-3.2	1430	7.8	2860	15.4	-0.9	-1.0	-5.9
2.	J.L.	172	57.6	13.5	-4.0	1060	7.0	2060	14.1	+3.0	-5.0	+5.8
3.	M.S.	155	34.4	35.3	-4.0	600	2.1	2150	13.2	+2.8	+2.4	+4.7
4.	J.C.	172	41.8	14.1	-5.0	470	1.5	1600	10	+1.8	+1.8	0
5.	J.M.	177	50.0	19.8	-2.6	640	3.4	2600	14.6	+4.0	+4.6	+7.1
6.	D.F.	167	49.5	25.4	-1.0	800	6.0	1280	8.1	+0.5	-6.7	-6.2
7.	J.O.	164	49.4	17.5	-7.0	650	3.0	2100	14	-1.4	0	-10.0
8.	M.L.	162	46.3	15.0	-	-	-	-	-	-0.9	-	-
9.	M.M.	160	38.2	22.6	-	590	5.0	1900	11.8	+3.4	-	-
10.	J.A.	177	49.0	21.7	-0.5	1950	9.6	4100	18.2	+3.2	+1.8	+5.0
											Mean -0.26	Mean +0.06

TABLE 3.3

TABLE 3.4
PLASMA PROTEIN DATA

No.	Patient	Albumin (37-45) g/l	RBP (N40-80) mg/l	P.A. (N 0.1-0.4) g/l	Transferrin (2.0-4.0) g/l	IgG 7-19 g/l	IgA 0.9-4.5 g/l	IgM 0.4-2.7 g/l	CRP (0-4) mg/l	AT 2-4 g/l
1.	T.C.	20	20.4	0.05	1.3	10.0	2.4	1.6	77	4.4
2.	J.L.	23	38	0.06	3.2	7.6	2.7	1.0	136	11.0
3.	M.S.	29	30	0.1	3.1	16.0	6.0	0.6	28	5.2
4.	J.C.	27	37	0.13	3.2	14.0	3.0	1.6	32	4.5
5.	J.M.	24	36.9	0.09	1.8	21.5	2.9	1.2	58	5.2
6.	D.F.	28	37	0.16	-	14.8	4.4	1.2	31	3.8
7.	J.O.	22	16	-	1.9	13.6	3.3	0.1	255	-
8.	M.L.	26	69	0.21	2.0	8.8	1.4	0.4	258	10.1
9.	M.M.	29	47	0.1	-	8.8	4.4	0.6	64	6.1
10.	J.A.	30	26	0.1	1.8	13.2	2.8	1.0	64	5.3

TABLE 3.4

TABLE 3.5

LIVER AND RENAL FUNCTION DATA AT COMMENCEMENT OF ALBUMIN STUDY

No.	Patient	Alkaline Phosphatase (3-13) K.A. units	Bilirubin (3-31) $\mu\text{mol/l}$	SGOT (12-42) U/l	SGPT (8-55) U/l	Urea (2.5-7.5) mmol/l	Creatinine (35-130) $\mu\text{mol/l}$
1.	T.C.	45	12	60	49	5.9	80
2.	J.L.	60	15	95	70	4.1	89
3.	M.S.	12	13	32	20	6.7	67
4.	J.L.	8	5	16	10	2.5	61
5.	J.M.	14	5	28	25	5.9	88
6.	D.F.	12	6	28	15	2.8	51
7.	J.O.	15	10	18	13	4.7	71
8.	M.L.	45	9	26	7	9.3	99
9.	M.M.	27	12	24	8	3.8	67
10.	J.A.	19	10	50	30	4.3	81

TABLE 3.5

abnormal in patient 2 due to intrahepatic metastases. Patients 1, 8, 9 had elevated alkaline phosphatase as a consequence of bone metastases. No patients had significant impairment of renal function although patient 8 had some pre-renal azotemia which persisted throughout the study period and may account for the high value of RBP in this patient.

Gut loss of total ^{131}I radioactivity for the first seven study days in six patients (including those with gastric and oesophageal malignancies) was less than 0.1% of the administered dose. Incomplete faecal collections in four patients prevented a reliable assessment of loss of albumin from the gut.

Sample radioactive albumin decay curves are shown in Figures 3.12-3.14, illustrating high, normal and low fractional catabolic rates. The fractional catabolic rate of albumin was elevated in 7 patients (Table 3.6) and was low or low normal in three. The latter patients had oesophageal carcinoma (patients 3 and 4) or lung cancer (patient 5). All patients demonstrated an elevated TCER except patient 4 who had a lower than normal value. The E/P ratio was slightly elevated in two patients, very high in six and low in two.

Figure 3.15 shows the survival of patients plotted against their FCR. Patients with a low, or low normal FCR survived longer than patients with an elevated FCR. The exception was patient 9 who responded to therapy and, as a consequence, had an altered prognosis. If patient 9 is excluded, this survival difference is significant (P less than 0.001, t test). There is also reasonable correlation between TCER and prognosis (Figure 3.16) except for two of the three patients with low FCR values and for the patient who responded to therapy (patient 9).

Fractional synthesis rates of albumin were calculated for six patients (Table 3.6). Three patients had net albumin catabolism, two a net synthesis and one was in equilibrium. The two patients with the

FIGURE 3.12

RADIOACTIVE PLASMA ALBUMIN DECAY

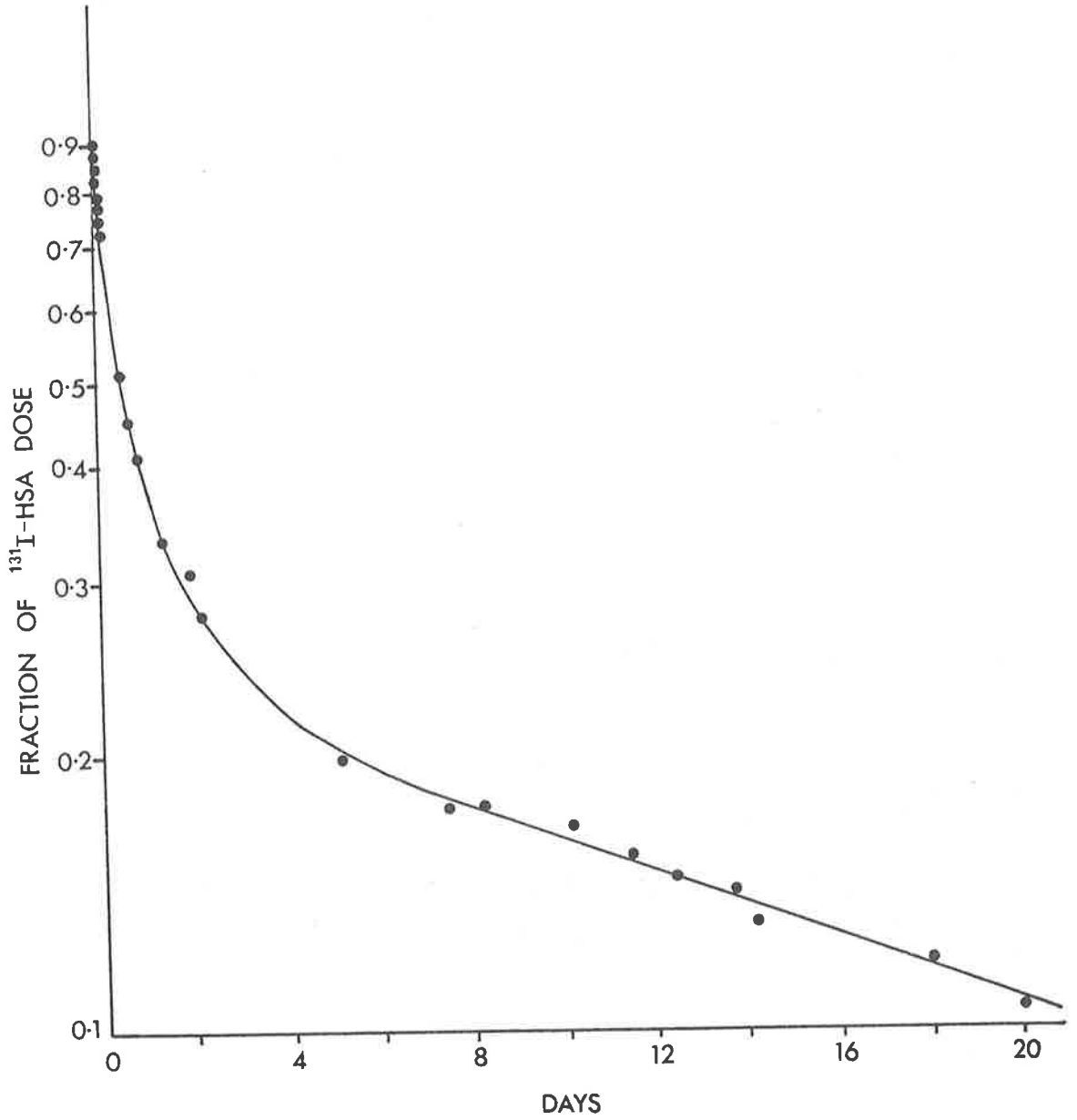


FIGURE 3.13

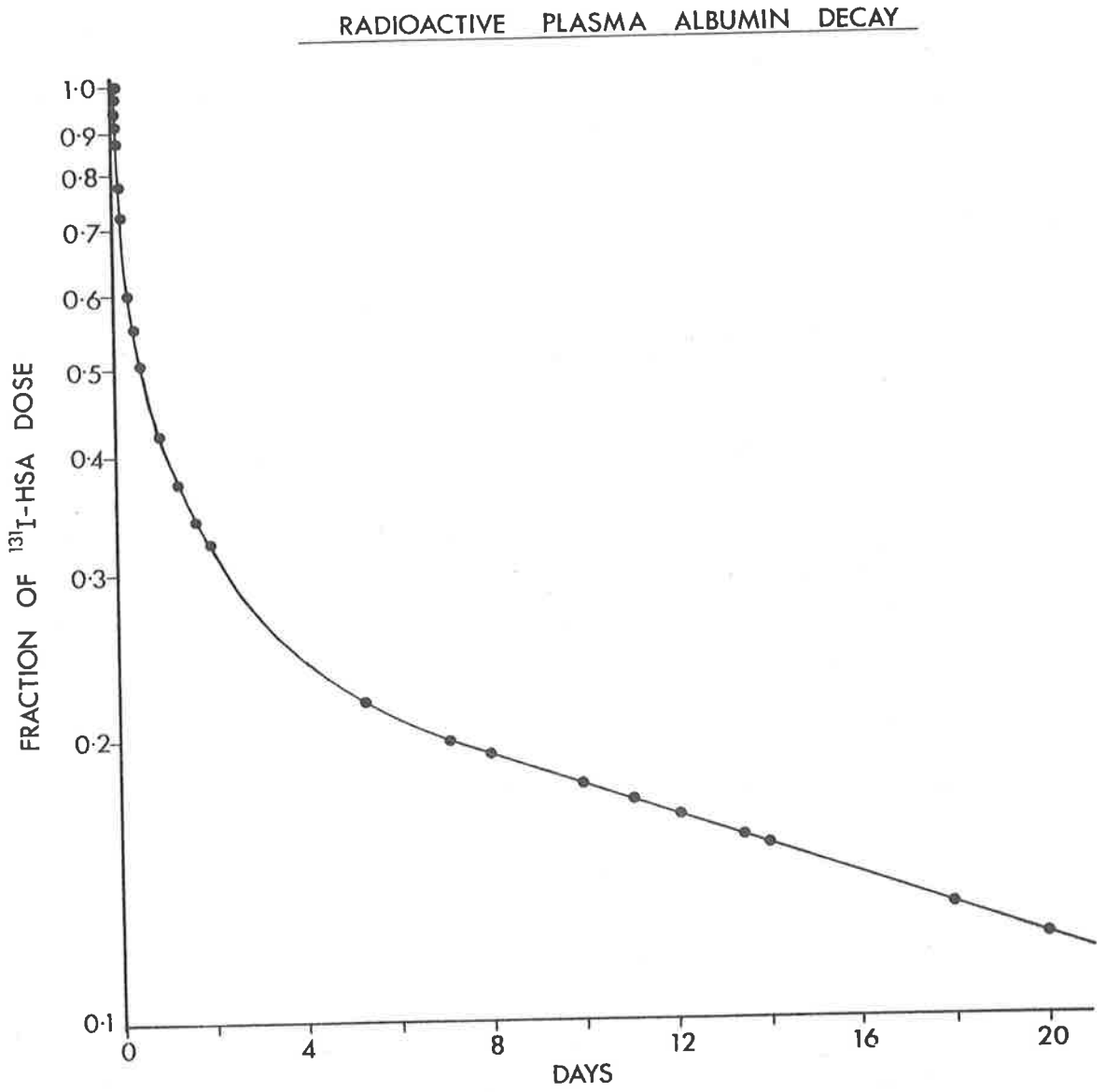


FIGURE 3.14

RADIOACTIVE PLASMA ALBUMIN DECAY

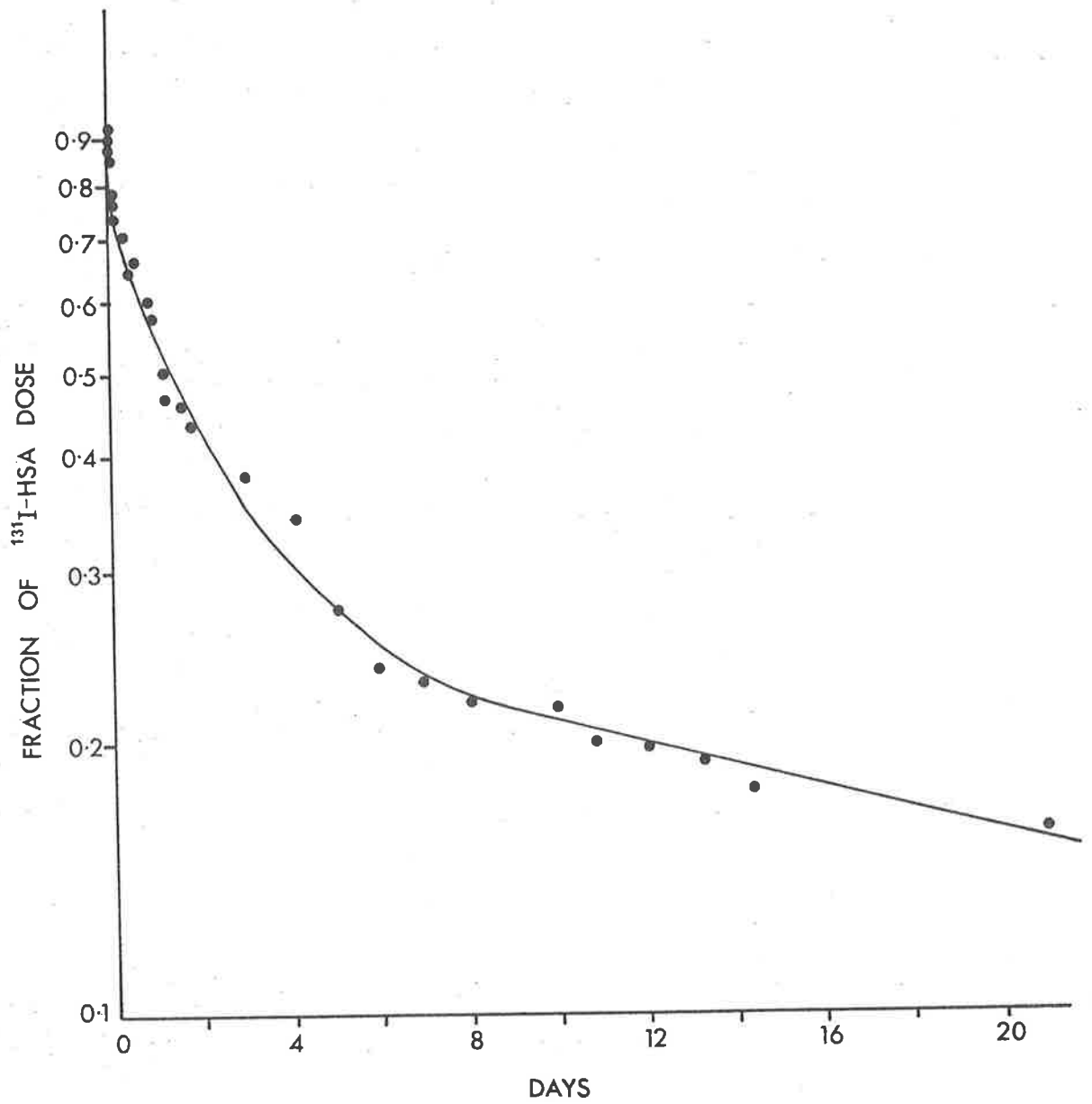


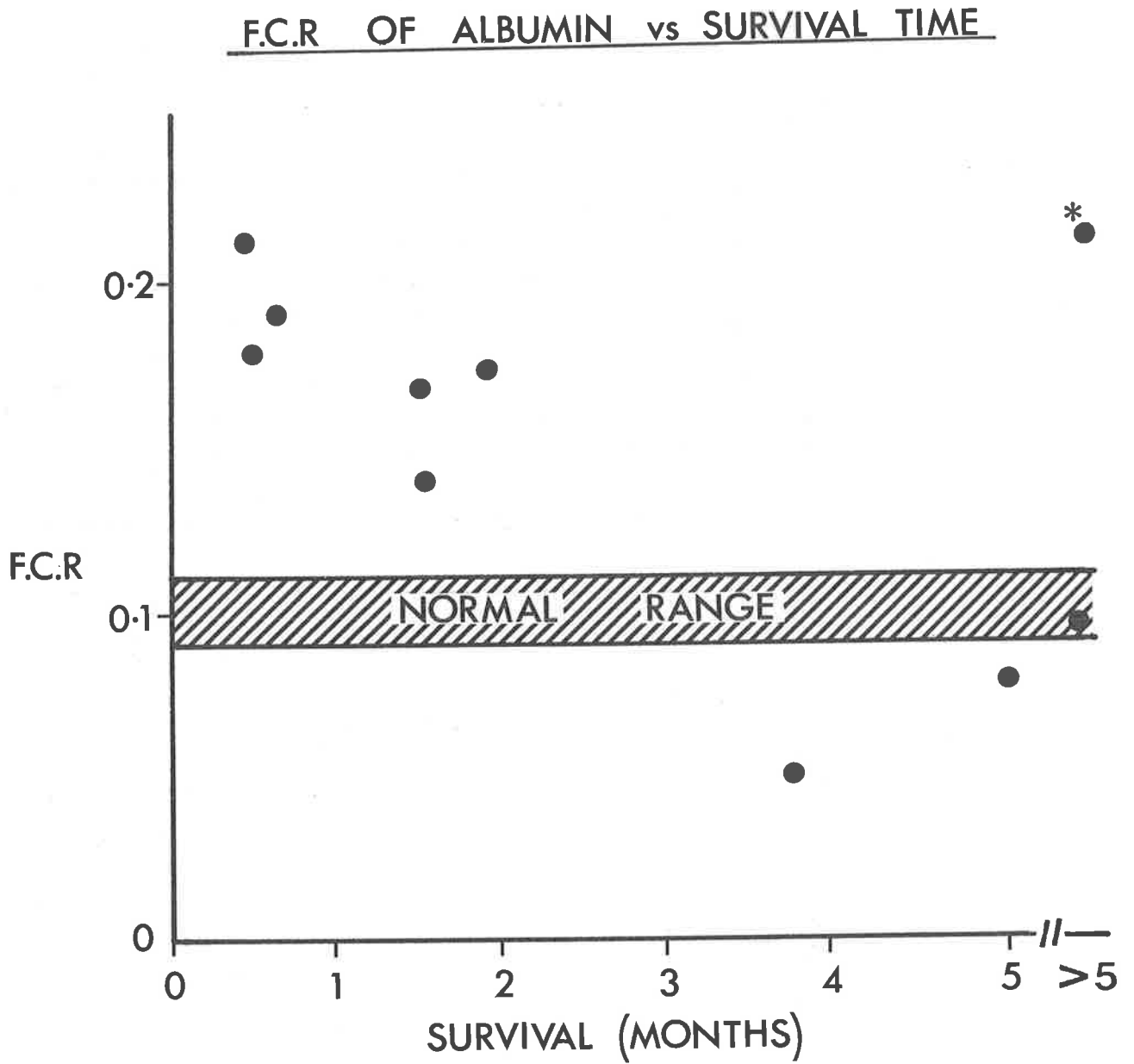
TABLE 3.6

ALBUMIN METABOLISM AND DISTRIBUTION DATA

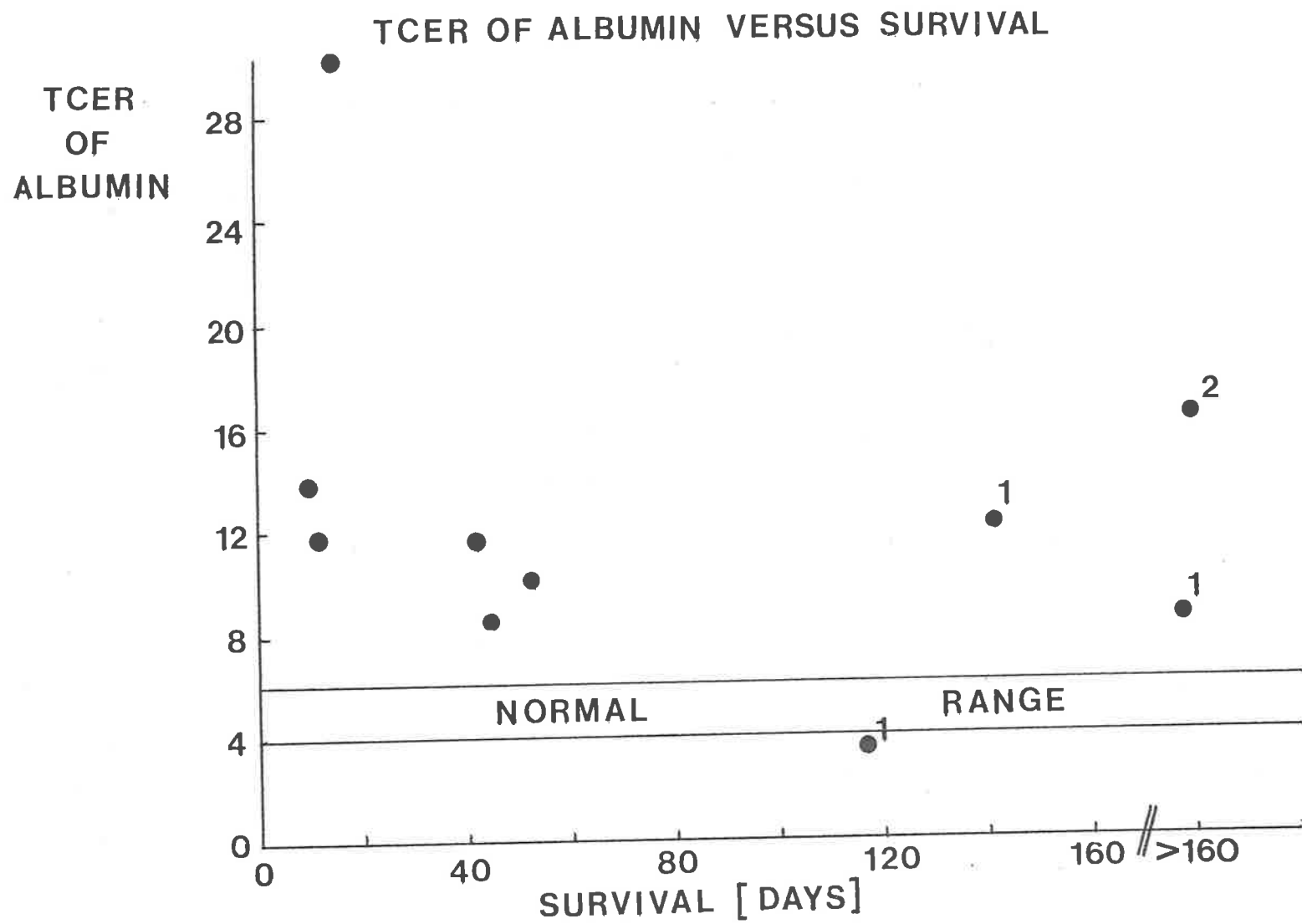
No.	Patient	Plasma Volume	FCR (0.085-0.11)	FSR	(FSR-FCR)	TCER (N4-7)	E/P (N 1.3-1.5)	Albumin Used A = Autologous B = SAPU	Gut Loss of 131Ib. for First 7 days (% of admin. dose)
1.	T.C.	3033	0.139	-	-	8.6	2.353	A	0.10
2.	J.L.	3035	0.173	0.135	-0.038	9.9	1.533	B	0.08
3.	M.S.	2104	0.077	-	-	11.9	2.478	A	0.09
4.	J.C.	2765	0.05	0.106	+0.0563	3.6	3.492	B	0.13
5.	J.M.	3116	0.093	0.158	+0.065	9.1	1.521	B	0.04
6.	D.F.	2885	0.211	0.103	-0.108	11.4	1.156	B	-
7.	J.O.	3275	0.166	-	-	11.3	2.465	A	-
8.	M.L.	2264	0.175	-	-	12.8	3.370	A	-
9.	M.M.	1585	0.212	0.215	+0.003	6.6	1.001	B	0.08
10.	J.A.	2828	0.187	0.128	-0.059	31.8	1.96	B	-

TABLE 3.6

FIGURE 3.15



* Responded to Anti-Cancer Therapy



1; LOW/NORMAL FCR 2; RESPONSE TO THERAPY

FIGURE 3.16

lowest FCR were those who had net albumin synthesis. Patients with elevated catabolic rates all had net catabolism, despite nutritional support, except patient 9. This latter patient was responding to anti-tumour therapy and was taking 40 mg. cortisone daily as adrenal replacement therapy, both of which may have contributed to the elevated FSR. Serum albumin concentrations rose a mean of 2 g/l during the two weeks of nutritional support in patients 3 and 4 and 4 g/l in patient 5 but remained the same or fell in all other patients.

DISCUSSION

One of the important questions facing the cancer nutritionist is whether the malnourished cancer patient can respond with an appropriate metabolic response to protein-energy deprivation. This topic has been reviewed by Brennan (Brennan, M.F. 1977). In uncomplicated PEM, substrate deficiency causes a fall in protein synthesis which occurs within days of dietary protein deprivation (Rothchild, M.A. et al 1977, James, W.P.T. 1977). Later, protein (and albumin) catabolism falls to conserve body protein with a concomitant fall in urinary nitrogen excretion. Uncomplicated PEM is also accompanied by a reduced BMR (Keys, A. et al 1950). In contrast, it is not uncommon for the patient with cancer to exhibit evidence of an "inappropriate" hypermetabolic state in the presence of cachexia, with elevated basal metabolic rate (Mider, G.B. 1951, Waterhouse, C. et al 1951, Warnold, I. et al 1978). In this study we have shown that in a population of malnourished cancer patients there is a group with low or normal albumin catabolic rates and a group with high albumin catabolic rates.

Protein-energy malnutrition, uncomplicated by infection, leads to only a slight fall in plasma albumin concentration even with 25% loss of body weight (Keys, A. et al 1950). The concentration of albumin in

plasma is therefore a late and rather insensitive index of malnutrition compared with the rapid turnover transport proteins such as RBP, PA and transferrin (Shetty, P.S. et al 1979b, Ingenbleek, Y. et al 1975). Therefore, cancer patients who develop hypoalbuminaemia more rapidly than would be usual for PEM presumably have mechanisms other than reduced substrate deficiency (and hence reduced catabolism) as a cause. The results of this study confirm that this is so. An elevated FCR was a common finding in the study population and closely correlates with a poor prognosis unless there is a response to cancer therapy. The response to nutritional support in this patient sub-group would be expected to be poor because of the hypercatabolic state. The poor prognosis presumably reflects this fact as well as the probability that the hypercatabolic state of malignancy is frequently a pre-terminal event. This latter view is supported by the CRP data discussed previously and by results published by Milano et al (1978) demonstrating a rise in CRP (and hence the possible development of a hypermetabolic state) several months before death in patients with colo-rectal carcinoma. It would be anticipated that patients with a low FCR (suggesting a normal metabolic response to malnutrition) should respond better to nutritional support than patients with an elevated FCR of albumin. Patients with uncomplicated PEM respond rapidly to nutritional repletion. As a consequence, it may be appropriate to alter the therapeutic approach by preceding chemotherapy with nutritional support in the patient with low or low normal catabolic rate, but withholding nutritional support until the tumour is controlled with therapy in those patients with a high catabolic rate.

It is assumed that there is a correlation between an elevated FCR of albumin, increased catabolism of lean body tissue and increased basal metabolic rate. In this study, those patients responding best to nutritional support with the greatest increases in upper arm

circumference, triceps skin fold thickness and improved performance status were those with low-normal or low FCR of albumin (patients 3, 4 and 5). Patients 1, 2, 6, 7 who also had nasogastric feeding, failed to demonstrate the significant improvement in these variables even where it was possible to achieve comparable energy and protein intake. In this latter group of patients nausea and abdominal fullness often prevented further increases in the volume of nasogastric feeds.

The FSR data reveals that net albumin synthesis is possible during nutritional support if the FCR of albumin is normal or low, or there is a response to anticancer therapy. That patients with elevated FCR failed to demonstrate a net synthesis may have reflected either the inability to provide adequate nutritional support or, more likely irreversible metabolic events preventing appropriate utilization of nutrients.

Anthropometric data can provide a fairly reliable index of body fat and lean tissue mass. Skinfold thickness can provide an assessment of body fat stores with an error of $\pm 3\%$ or less (Durnin, J.V.G.A. & Rahaman, M.M. 1967). Mid arm muscle circumference can provide an estimate of lean body mass (Jelliffe, D.D. 1966). The lack of improvement in skinfold thickness and mid arm muscle circumference in this study is consistent with the poor response to enteral or parenteral hyperalimentation which other authors have reported in surgical patients using the technique of neutron activation analysis (Hill, G.L. et al 1978). It is also possible that chemotherapy can alter protein synthesis and results from other studies, e.g. Rossing, N. 1968, where these drugs were used during the study period, need to be viewed with caution. In addition, it can be very difficult to maintain the steady state in a cancer patient with progressive disease. Some authors have relied on constant weight and haemoglobin as implying a stable nutritional state. This is frequently not so.

The preponderance of patients with advanced disease in this study with elevated FCR of albumin implies that an elevation of catabolic rate is often a late event in the natural history of malignant disease. It therefore seems reasonable to postulate that patients with early cancer or with a small bulk of tumour are more likely to respond normally to protein and caloric deprivation with a fall in FCR. Progression of disease may result in an increase in FCR which could rise from low, through the normal range to high. A normal FCR, such as patient 5, could therefore be inappropriately high for the nutritional state of the individual and imply the same failure of normal regulatory processes presumably operative in the patient with a high FCR.

How tumours alter host metabolism has not been determined but has been extensively debated (Trotter, J.M. et al (1981b), Shaw, D. et al 1981, Costa, G. 1977a, Theologides, A. 1979, Blackburn, G.L. et al 1977). Some localised tumours can cause considerable cachexia, and patient 6 with a localised tumour had an increased FCR of albumin presumably tumour-induced. The data presented provides no simple way of determining whether patients with tumours of similar bulk and histological type, are hypercatabolic or not. Neither plasma albumin concentration nor anthropometric data provide a clue about the underlying metabolic rate. The renal nitrogen excretion may provide a clue since renal nitrogen excretion exceeded 8 g/24 hr in patients 1, 2 and 7 but was under 5 g/24 hr in patients 3, 4 and 5. Urinary nitrogen for patient 5 was about 5.0 g/24 hr. All patients were in negative nitrogen balance. Although nitrogen excretion tends to parallel the FCR values, caution must be exercised in reaching this conclusion. For a patient in negative nitrogen balance conservation of nitrogen is usual but is also dependent on dietary intake.

A fall in plasma albumin can be due to factors other than increased catabolic rate. Reduced albumin synthesis is usual in PEM and it may be impaired in patients with extensive liver disease (Warnold, I. et al 1978). Patient 2 had significantly impaired hepatic function due to metastatic disease, but unlike patients with cirrhosis had both an elevated FCR and FSR of albumin. In addition, in the group of patients with cirrhosis reported by Rosenoer (Rosenoer, V.M. 1977), neither albumin synthesis rates nor plasma albumin concentration predicted survival.

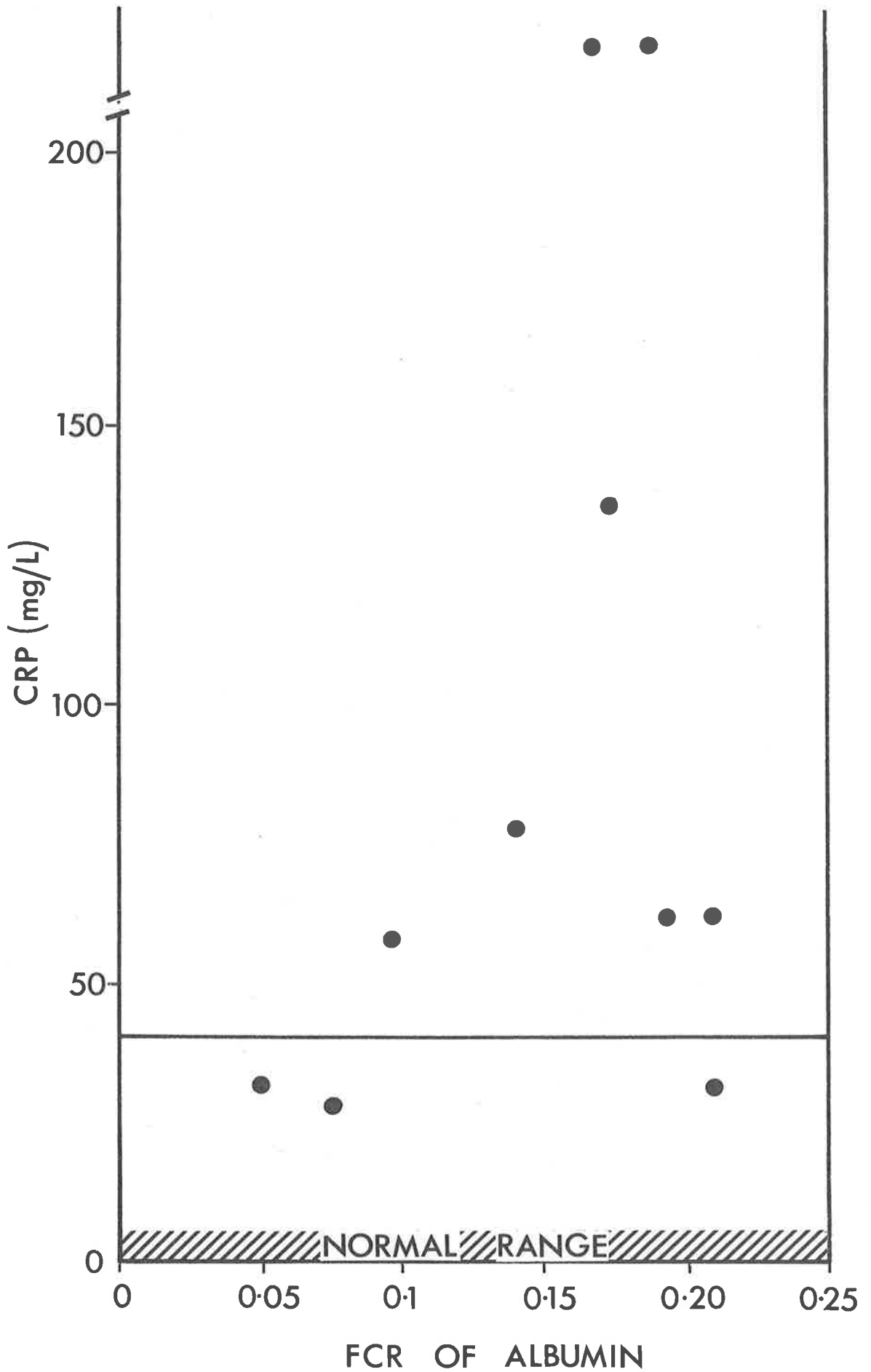
Plasma albumin concentration can also fall if there is an increase in the TCER or E/P ratio of albumin. All but one patient in this study had an elevation of TCER and Corradi, C. et al, (1966) have reported similar findings. There is some data to suggest that albumin catabolism takes place principally in the vascular endothelium (Waldmann, T.A. 1977). The increase in the passage of albumin across the capillary wall to the extravascular space (measured on TCER) may be yet another remote effect of malignant disease on the host, and may contribute to the increase in the FCR of albumin. The very low FCR in patient 3 co-exists with a low TCER. Hypertension can increase the TCER (Rossing, N. et al 1976) but no patient in this study was hypertensive. An elevated capillary permeability is usually also seen in acute inflammatory states (Ellman 1984, Anderson et al 1979) where there is an associated acute phase response. Although an acute phase response may be postulated to be responsible for the elevated TCER, the rise in TCER occurs within 3 hours of cardiac surgery unlike the 7 hours usually needed to generate an acute phase response (Fleck, A. et al 1985). All patients had an elevation of CRP and 5 (of the 9 assayed) also had an elevation of alpha-1-AT. The reason for the association of cancer with an acute phase response is unclear, but patients 2, 7, 8 and 9 with the highest

CRP values also tended to have the highest FCR values (Figure 3.17). Any direct relationship has yet to be established, and caution is needed because infection will produce a marked rise in acute phase proteins and, especially in the presence of fever, an increase in metabolic rate. Such patients may show a similar relationship between TCER and acute phase proteins. These results tend to support the association of a relationship between CRP and nitrogen balance demonstrated previously (Section 2, part 8) and suggest that CRP is more likely to be elevated if the metabolic rate is increased.

Although the E/P ratio has been reported to be elevated in cancer patients (Rossing, N. 1968), it would seem to bear no close relation to either FCR or TCER. No patient had clinical evidence of oedema or fluid collection which might have accounted for elevated E/P ratios although it is possible that patients 3 and 4 with oesophageal malignancy had some obstruction of the thoracic duct thereby slowing lymphatic return. Two patients (6 and 9) had a high TCER but a low E/P ratio. Both patients had higher haematocrits and haemoglobin concentrations at the commencement of the study than on admission and these subsequently stabilised at lower values after several days of the study. No other patients demonstrated these changes.

Gut loss of I^{131} -albumin was insignificant in those patients with available stool measurements to account for any contribution to the hypoalbuminaemia in these patients. Although some iodine lost to the gut may be reabsorbed, thus rendering evaluation of losses by faecal analysis unreliable, Waldmann et al (1963) did not demonstrate any excessive gut loss of albumin when using I^{131} -polyvinylpyrrolidone (PVP) to study albumin metabolism. PVP is a macro-molecule unaffected by intestinal enzymes.

C-REACTIVE PROTEIN PLOTTED AGAINST THE
FRACTIONAL CATABOLIC RATE OF ALBUMIN



Normal concentrations of the plasma globulins have been previously reported in cancer (Huggins, C. 1949). There was no correlation between plasma globulin concentrations and the FCR of albumin in this group of patients.

In conclusion, hypoalbuminaemia occurs in many cancer patients sometimes in association with small tumours. In this group of patients it is possible that a hypermetabolic state exists with an increase in the FCR of albumin, an increased TCER and possibly also an increased E/P ratio. It is suggested that this group of patients will respond poorly to nutritional support and will have a poor prognosis unless they respond to anti-cancer therapy.

Another group of patients responds to increased protein and energy intake with the metabolic response seen in PEM. This group of patients may benefit from nutritional support prior to anti-cancer therapy. The albumin synthesis data tends to support this view. While neither FCR nor FSR may reflect the overall net albumin metabolism, FCR seems to provide the best overall index of the metabolic response of the host to the tumour. An acute phase response often occurs in association with malignant disease and is usually related to an elevation in the TCER of albumin and also of the E/P ratio. The mechanism for these changes remains to be elucidated, but it is clear that they contribute to the hypoalbuminaemia of the cancer patient.

SUMMARY

Albumin metabolism was studied in a group of ten malnourished cancer patients with serum albumin concentration of less than 30 g/l. All patients had progressive disease but none had received cytotoxic chemotherapy within the preceding four weeks. Anorexia-induced dietary insufficiency was supplemented with fine-bore nasogastric tube feeding in

8 patients. The distribution and rate of excretion or synthesis of the appropriate radio-active products were determined following injection of ^{131}I -albumin, Na^{125}I and $\text{Na}_2^{14}\text{CO}_3$. From this data, the fractional catabolic rate (FCR), transcapillary escape rate (TCER) and extra-vascular to intravascular ratio (E/P) of albumin were determined. The fractional synthesis rate of albumin was calculated by the ^{14}C -carbonate method originated by McFarlane and others by determining the specific activity of plasma urea and the guanidine carbon of the arginine of albumin, and by correcting for losses from the intravascular compartment due to distribution, catabolism and excretion (utilising the radio-iodinated decay curve of the catabolic study). Seven of the 10 patients had an elevated FCR and most had rises in TCER and E/P. These results are contrary to those expected in uncomplicated protein-energy malnutrition. Some patients (3) demonstrated a reduced or normal FCR consistent with normal adaptation to starvation and these patients had the best objective response to nutritional support. Net albumin synthesis was a feature of patients with low albumin catabolism but not in patients with a high FCR of albumin. It is concluded that the metabolic response to cancer is variable and that patients with a tumour-induced hypercatabolic state are less likely to respond to nutritional support than patients who respond to the same protein-energy deprivation by reducing their basal metabolic rate and protein turnover.

Nutritional aspects of plasma exchange in cancer patients

J. M. Trotter, D. Shaw, E. Carlyle, J. Shephard and K. C. Calman

University of Glasgow, Glasgow (U.K.)

“False facts are highly injurious to the progress of science, for they often endure long, but false views, if supported by some evidence, do little harm, for everybody takes salutary pleasure in proving them wrong”.

Darwin
The Descent of Man

INTRODUCTION

The association of malignant disease with weight loss and progressive wasting of body tissues has been known for thousands of years. The poor prognosis of patients with progressive weight loss has been appreciated at least since the time of Hippocrates. Cancer cachexia, a syndrome characterised by anorexia with weight loss and wasting of lean body mass in the presence of increased metabolic requirements, is a leading cause of morbidity and mortality in patients with malignant disease. The metabolic consequences of cancer cachexia have been extensively investigated and a large number of metabolic abnormalities determined [1, 6, 21, 25].

Abnormalities of carbohydrate, lipid and protein metabolism can often be demonstrated in patients with cancer and these are not due solely to protein-calorie malnutrition. Whereas this latter problem can be largely overcome by providing adequate nutritional support, the cancer-induced metabolic abnormalities remain. The hypothesis on which this presentation is based is that plasma exchange can be used to alter these metabolic abnormalities in the favour of the host and at the same

time help to prove or disprove a number of existing theories on the aetiology of a variety of para-neoplastic syndromes.

The following hypotheses are therefore proposed and arguments in favour of each are presented from the literature. To the best of our knowledge hypotheses 4, 5 and 6 in this context have not been previously published and it is possible to test their validity. Methods how this can be done are suggested and some experimental data are presented.

Hypotheses

- 1) that malignant tumours or the tumour bearing host produce substances which are released into the host circulation
- 2) that these substances affect host metabolism and contribute to, or cause, the syndrome of cancer cachexia
- 3) that these substances exert an effect on distant organs by being transported either free or bound in the plasma
- 4) that plasma exchange should remove these substances and result in changes in host metabolism towards normal
- 5) that any demonstrable improvement in host metabolism following plasma exchange would lend support to hypothesis 1
- 6) that reinfusion of exchanged plasma should reproduce the metabolic abnormalities
- 7) that dialysis of exchanged plasma could be a preliminary step in establishing the nature and physical characteristics of these postulated substances.

TUMOUR AND HOST PRODUCTS

The suggestion that tumours have distant metabolic effects on the host is not a new concept. It is hard to understand how a small tumour can sometimes produce severe metabolic derangement leading to cancer cachexia without postulating the elaboration by the tumour of "toxins" or "chemical mediators". It is well documented that some tumours do produce substances that affect aspects of host metabolism. Ectopic hormone synthesis is an example of the secretion of such a mediator and it is clear that the hormone or hormone analog circulates in the plasma. In addition, a number of these "ectopic hormones" have now been measured in plasma and their structure elucidated.

The anaemia associated with malignant disease has been attributed in part to "tumour toxins" [10]. Fever is not uncommonly found in patients with advanced malignant disease and it is not always caused by infection. The best known example is the fever that develops in some patients with Hodgkin's disease and non-Hodgkin's lymphoma. Although endogenous leukocyte pyrogens [13] or aetiocholanolone may be responsible, this is not proven and it might result from the secretion of metaboli-

cally active substances by the tumour. Patients with these malignancies who have either a fever or a significant loss of weight have in addition an abnormality of collagen metabolism expressed as a pathologically increased excretion of hydroxyproline [15] and exploration of the role of plasma exchange as an investigative and therapeutic modality in this situation may prove rewarding.

In addition to the above, a number of authors have purported to have isolated specific tumour toxins that could affect host metabolism [5, 9, 10]. "Toxohormone" is probably the best known of these toxins and has been shown to depress hepatic catalase *in vivo* [14]. Cell-free extracts of tumours have been shown to have metabolic effects on the liver in mice [11]. In this model, reductions in acetyl-CoA and citrate were described. There is, therefore, increasing evidence for the existence of tumour derived (and perhaps host-derived) substances that alter host metabolism. Theologides [24] postulated, on the basis of such evidence, that tumours produce intermediary metabolites and short-chain oligopeptides which are responsible for causing the anorexia of malignant disease by their effect on the satiety centre of the brain situated in the area postrema of the fourth ventricle.

Significant abnormalities of carbohydrate, protein and fat metabolism have been described in patients with malignant disease [22, 26]. In particular, there is a high incidence of diabetic-type glucose tolerance in cancer patients and this is associated with insulin resistance. Although it is possible that the insulin resistance may be related to quantitative changes in insulin receptor status, qualitative changes are also possible [22]. These qualitative changes, it could be postulated, may be caused by tumour-derived "toxins".

Alteration of protein metabolism in malignant disease is readily appreciated in any patient with cancer cachexia where muscle wasting is a prominent feature. The hypoalbuminaemia of malignant disease may be the result of reduced synthesis plus an increased fractional catabolic rate [18]. The reason for this paradoxical finding is obscure, but the fact that peptides are often secreted in the urine of patients with malignant disease suggests that the tumour releases substances which may affect the host-protein synthesis [19, 25]. It is possible, of course, that tumours induce the host to produce peptides which then affect its own metabolic pathways.

It can be appreciated from the foregoing review that there is considerable evidence that metabolically active substances are produced by the tumour or by the host in response to the tumour, and these substances are capable of causing a considerable derangement of the host metabolism. Further, these metabolic upsets are part of the syndrome of cancer cachexia. Nutritional repletion by currently available techniques is able to reverse at least in part the protein-calorie malnutrition associated with cancer cachexia but clearly is unable to reverse many of the abnormalities in protein, fat and carbohydrate metabolism. Although it is true that curing the malignant process will also cure the metabolic abnormalities, most malignancies remain resistant to aggressive therapy at the present time. Therefore, it might be that removal of tumour-derived toxins would improve host metabolism and this could be particularly per-

tinant as improving the nutritional status of the patients appears to improve the response rates to specific treatments [4]. In addition, if it were shown that patients' metabolism improved following the removal of these substances this would support the hypothesis that circulating mediators effect host metabolism.

PLASMA EXCHANGES AND HOST METABOLISM

Clearly one of the best ways of removing substances circulating in plasma is by plasma exchange or plasmapheresis. These procedures have been used on a limited basis in patients with malignant disease on the assumption that plasma exchange can remove "blocking antibodies" that reduce host cell mediated immunity [7-9]. In addition, a number of authors have reported partial tumour responses by this method, although these have generally been short-lived [7, 8].

Brown et al. [3] reported a fall in the serum blocking effect on control T-cells after plasma exchange of 2 litres in two patients with malignant disease and this effect lasted about 4 weeks. Enhancement of T-lymphocyte activity after exchange, without washing of lymphocytes, lasted 4-7 days. These results suggest that some effects of plasma exchange may persist for up to 4 weeks, and that T-lymphocyte activity could be enhanced for up to a week with only a 2.0 litre exchange. Israel et al. [9], on the basis of the time taken for host recovery of serum protein estimations, suggested that plasma exchange for optimum results needed to be performed every 48 h. The basis for this conclusion is, however, rather tenuous. Measuring time-course changes in proteins after plasma exchange does not necessarily reflect their synthesis rates nor does it necessarily reflect the synthesis rates of the "non-specific blocking factors" which were presumed to be responsible for the immune suppression mentioned above. Not only do fractional catabolic rates vary from one protein to another, but also the extravascular and intravascular compartments change during and after plasma exchange. It is well-known that haemoglobin values immediately post-exchange are usually lower than those observed on the following day, which is presumably due to changes in the intravascular volume. It is argued, therefore, that some effects of a single plasma exchange may last in excess of 48 h and up to 1-2 weeks. Indeed, long-term remissions of several weeks or more have been reported following plasma exchange for myasthenia gravis [17] and immune thrombocytopenia purpura [2]. Although these illustrations are not necessarily representative of malignant disease, they serve to illustrate both the variability and complexity of the matter and the crudeness of the tests available to measure response.

Design of clinical studies to investigate metabolic effects of plasma exchange in cancer patients

From the discussions above, it can be appreciated that plasma exchange is potentially

a useful method of investigating the causes of some of the metabolic consequences of malignant disease and at the same time perhaps benefiting the patient. If tumours do produce substances that alter host metabolism, a reversal or improvement in these changes should be evident if the substances are removed in sufficient amounts. Because some of the metabolic effects of malignant disease are difficult to measure, it was decided that problems that were potentially reversible and evaluable should be investigated. These included the problems of taste, anorexia, protein metabolism, glucose metabolism and endocrine abnormalities.

In a pilot study, a 35-year-old white male patient with advanced metastatic renal carcinoma was treated with three plasma exchanges at weekly intervals and a fourth 10 days after the third exchange. Anorexia was monitored by measuring anthropometric data and careful dietary assessment by the oncology dietitian. Those plasma proteins that are good indices of nutritional status were measured: transferrin (TF), retinol-binding protein (RBP), pre-albumin (PA) and albumin (Alb) together with the acute phase protein, C-reactive protein (CRP). The poor nutritional status of this patient was improved with 2 weeks of nasogastric fine bore tube feeding during which time he gained 2 kg in weight. This weight gain was almost entirely the result of the tube feeds because his appetite and consequently his voluntary oral intake fell with feeding, although this is a little unusual in our experience. His oral voluntary protein ingestion was 34 g at the commencement of feeding but only 20 g at completion. His energy intake had remained constant (1500 kcal at commencement compared with 1400 kcal at completion) only because of the ingestion of high glucose drinks.

Nasogastric feeding increased albumin (Fig. 9.1), RBP (Fig. 9.2), but lowered TF (Fig. 9.3) and CRP (Fig. 9.4). There was no significant change in skin fold thickness (triceps and subscapular) or upper arm circumference. During feeding, an average of 70 g of nitrogen and 2200 kcal were supplied daily by nasogastric tube. At the completion of 14 days feeding, the first plasma exchange was performed. All exchanges were accomplished using a Haemonetics model 30 cell processor and the replacement solution was human pooled fresh frozen plasma on all occasions. Exchanges of 4.2, 3.3, 4.1 and 4.3 litres were performed at days 18, 25, 33 and 46 from the onset of nasogastric feeding which was stopped on day 16. No other therapy was given throughout this period.

Results of weekly plasma exchange

Subjectively the patient felt better after the first exchange with an improvement in appetite that was maintained until after the fourth exchange. At this time, because of evidence of enlarging intrapulmonary metastases, further plasma exchanges were cancelled. Careful dietary history on the day of the second exchange revealed a protein intake of about 41 g daily and an energy intake of 1800 kcal. Protein intake at the time of the fourth exchange was 52 g/day with an energy intake of 2500 kcal. It can be seen that despite progressive disease, energy consumption and

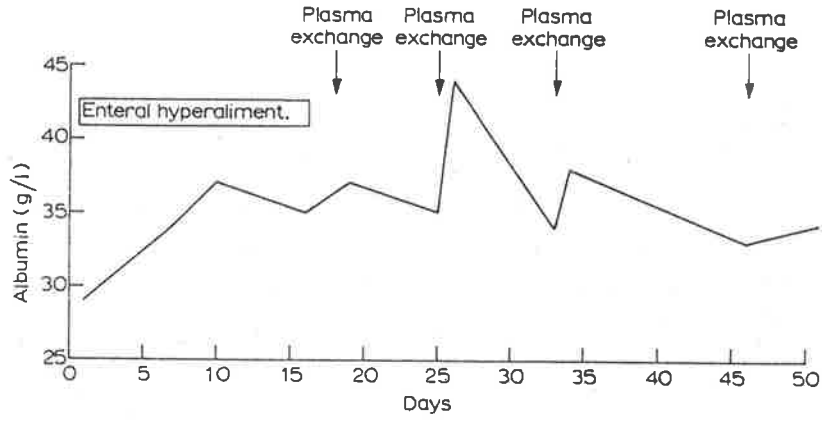


Fig. 9.1. Albumin with serial plasma exchange.

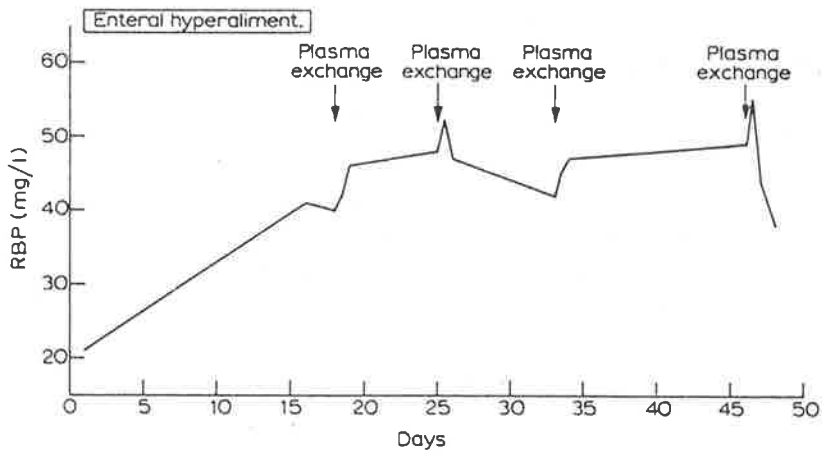


Fig. 9.2. Retinol-binding protein with serial plasma exchange.

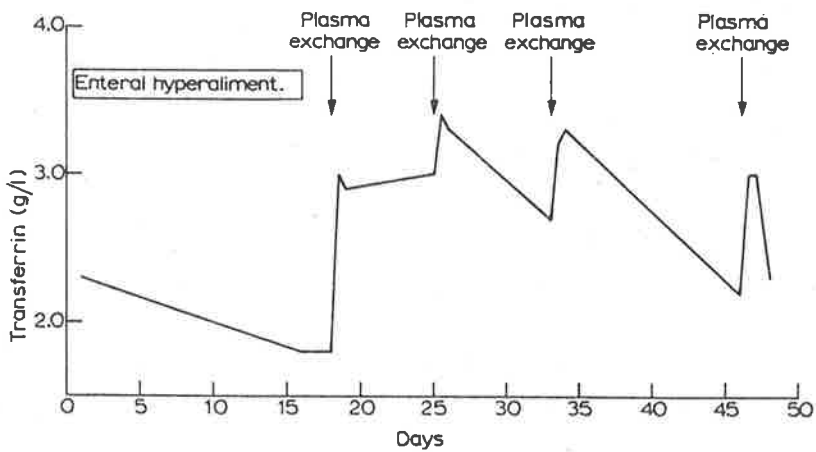


Fig. 9.3. Transferrin with serial plasma exchange.

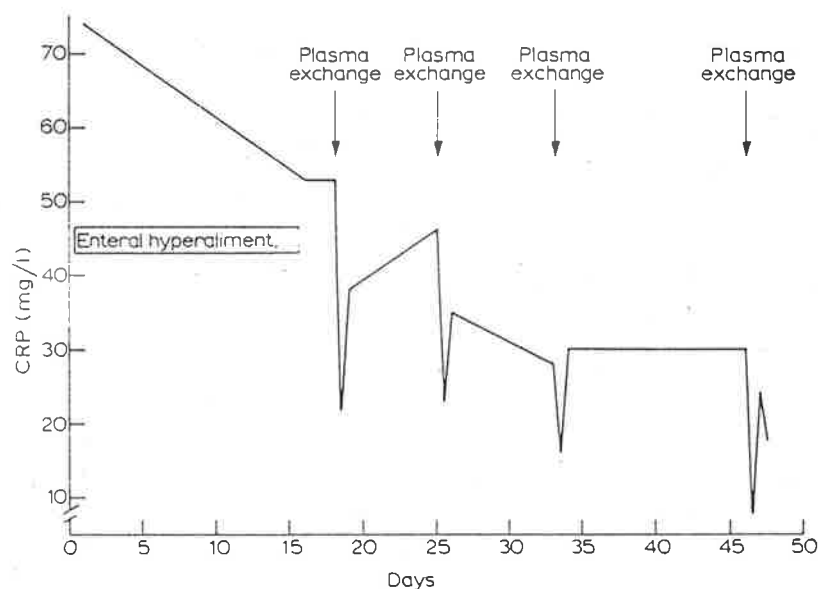


Fig. 9.4. Plasma C-reactive protein with serial plasma exchange.

protein consumption remained higher than at the commencement or completion of nasogastric feeding, with voluntary protein intake of more than double that at the completion of nasogastric feeding. Throughout the month of plasma exchange, no significant weight change was observed. Weight at commencement was 45.8 kg and at completion of the fourth exchange 45.4 kg. Retinol-binding protein demonstrated brief rises following plasma exchange, but the general pattern was one of a stable RBP level throughout the period of plasma exchange. This is particularly relevant considering that the half-life of this plasma protein is about 12 h. The transferrin levels rose with each exchange but fell steadily over the period of study. This protein has a half-life of about eight days which makes the fall during enteral hyperalimentation and following plasma exchange difficult to explain. This protein, however, has been reported as an unpredictable assessor of nutritional status because it can be influenced by a number of factors unrelated to nutrition such as iron deficiency [23]. The CRP values demonstrate an interesting and steady fall in values over the four exchanges, the smaller trough in relation to the second exchange presumably reflecting the smaller volume of exchange (Figs. 9.2-9.4).

Fig. 9.5 shows serial changes in selected plasma amino acids. It can be seen that high fasting values of the branched chain amino acids, leucine and isoleucine, fall rapidly with nutritional support, as did ornithine and histidine. Subsequently these values remained low throughout the period of plasma exchange, presumably reflecting the stable dietary intake. Slight falls in leucine and isoleucine following the second exchange were corrected with the larger third exchange, as were rises in ornithine and histidine. These changes suggest that plasma exchange per se might be influencing protein metabolism but this needs further study for confirmation.

These results reveal that repeated plasma exchange at about weekly intervals over a

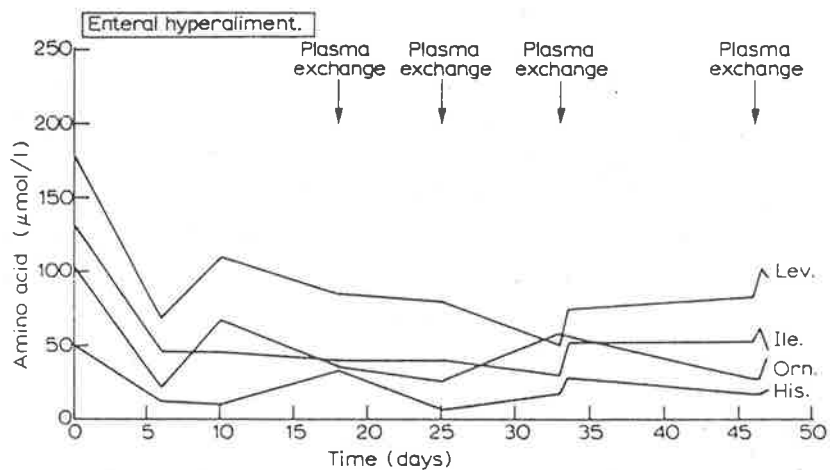


Fig. 9.5. Amino acids with serial plasma exchange.

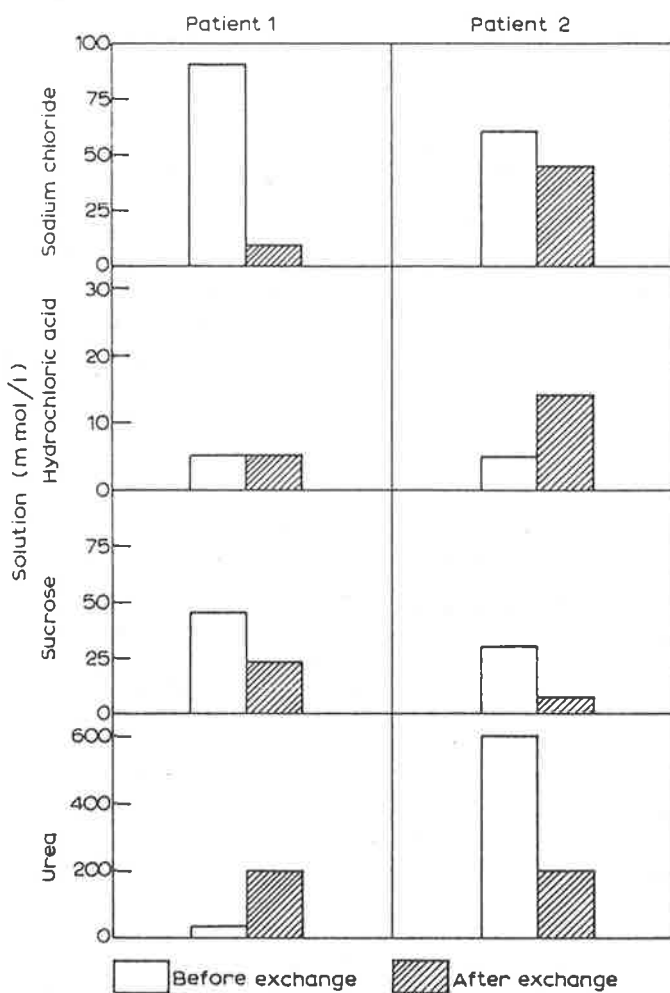


Fig. 9.6. Taste recognition thresholds.

period of four weeks was associated in this patient with ingestion of sufficient oral food to maintain weight and those plasma proteins that are sensitive indices of nutritional status. It could be postulated that the reason for this was removal of anorexigenic peptides resulting in improved appetite and/or possible removal of "toxins" influencing plasma protein metabolism. CRP is an acute-phase reactant and its fall with plasma exchange, in the absence of an infective lesion, might best fit this latter hypothesis.

So that the metabolic consequences of plasma exchange, could be monitored in closer detail, it was decided to investigate changes in glucose metabolism, protein metabolism and plasma proteins following a single exchange. All patients for this protocol had advanced metastatic malignant disease which had failed to respond to conventional therapy. Plasma exchange of 4-4.5 l was carried out using a Haemonetics cell separator as described for the previous case report. On the day prior to exchange a 3 h glucose tolerance test (GTT) was performed with 100 g glucose load and blood samples taken at 0, 30, 60, 90, 120 and 180 min for glucose, insulin, cortisol and growth hormone estimation. Simultaneously, urea synthesis was determined using the method described by Jones et al. [11]. The acute-phase reactant (CRP)

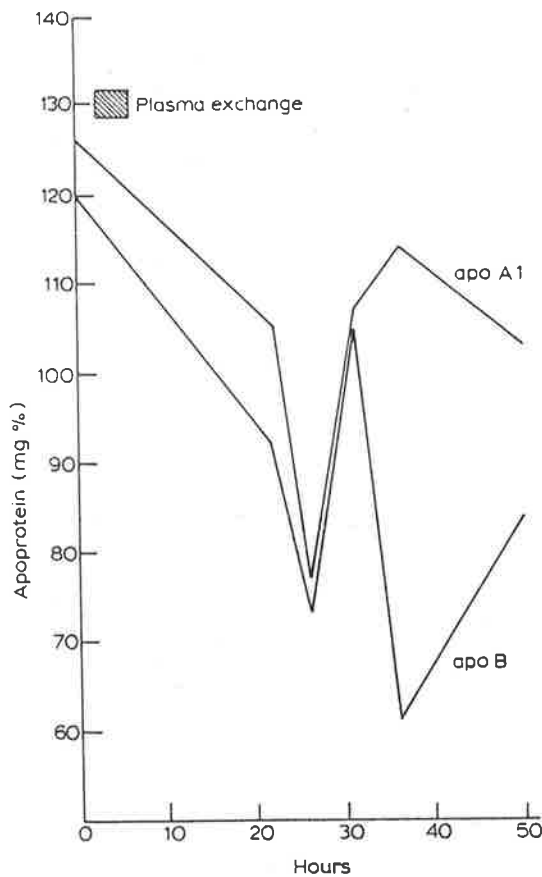


Fig. 9.7. Plasma apoproteins before and after plasma exchange.

together with the plasma proteins, RBP, PA and TF, were measured immediately pre-exchange and subsequently 6 hourly for 72 h together with lipoprotein apoprotein determination. At 48 h after commencement of the plasma exchange and about 44 h after its completion, a repeat GTT with hormone assays was performed as described above together with a repeat urea synthesis study. The clinic dietitian assessed dietary energy and protein intake before and after the exchange, assessed the patient's appetite using a linear analog scale and tested for changes in the four primary taste modalities. No drug alterations were made during the time of the protocol and no patient had had any chemotherapy within the preceding three weeks. It should be emphasised that all results were preliminary and that this study is continuing.

RESULTS

To date, two patients have been studied; however, not all the results are discussed here. Both patients are male and have disseminated metastatic malignant disease, one with malignant melanoma, the other with renal cell carcinoma. They had a weight loss of 15% and 6%, respectively, in association with anorexia. Skin-fold thicknesses were within normal limits. Plasma exchanges of 4 litres were accomplished without side-effects, except for transient pyrexia in one patient presumed to be due to a transfusion reaction. There was no change in protein or caloric intake in either patient at 2 days or 7 days post-exchange. The results of taste testing is shown in Fig. 9.6. It is of interest that taste recognition thresholds for several of the primary tastes showed a decrease after exchange. Although this might be accounted for by the experience gained by repeated testing, it does not explain the elevation in threshold of several tests.

Total serum triglyceride and cholesterol demonstrated no change at 48 h post-exchange from central levels. HDL cholesterol concentration remained constant as did (VLDL + LDL) cholesterol. Serial plasma changes in one patient of apoproteins A₁ and B are shown in Fig. 9.7 and demonstrate a nadir at 24 h post-exchange and a rise to the 20 h values by 48 h.

Acute changes in RBP, CRP and TF following plasma exchange were monitored for 48 h. There were transient falls in RBP in both patients which rose above basal levels at 36 h. CRP was not detected in the patient with a smaller weight loss. Levels in the other patient had returned to basal levels at 36 h. There were no significant changes in transferrin levels.

SUMMARY

Cancer cachexia with its attendant metabolic abnormalities is a common cause of morbidity and mortality in the patient with malignant disease. Mechanisms by which

these metabolic abnormalities occur have been discussed together with evidence from the literature in support of the hypothesis that substances derived either from the tumour or from the host affect host metabolism. It is postulated that such substances may affect protein, carbohydrate and lipid metabolism and cause anorexia and taste abnormalities. Furthermore, it has been suggested that removal of such substances by plasma exchange may alter host metabolism towards normal. Methods of examining this hypothesis are discussed and preliminary data are presented suggesting that anorexia, taste and protein metabolism may be altered by plasma exchange. In an attempt to provide definitive answers, this study will be continued.

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SECTION IV

SUMMARY AND CONCLUDING DISCUSSION.

.....causa finita est

St. Augustine

Sermons bk. 1

SECTION IV

SUMMARY AND CONCLUDING DISCUSSION

Voilà le commencement de la fin

On the announcement of Napoleon's defeat
at Borodino 1812 (Attr.)

Charles-Maurice de Talleyrand (1754-1838)

Malnutrition is a major problem for many cancer patients. A survey by a liaison health visitor of oncology outpatients attending an oncology clinic in Glasgow revealed that just over half of the patients complained of poor appetite and for more than a quarter of those no iatrogenic cause was evident. The potential for this to cause significant nutritional deficiencies was further highlighted with a survey of dietary intakes of cancer patients by the oncology dietitian. Many patients had dietary intakes well below the recommended levels for not only protein and energy, but also essential vitamins and minerals.

Attempts to provide nutritional support with the use of oral nutritional supplements hinge largely on the palatability of the product. Personal preference is, of course, the deciding factor, but the study in this thesis of a number of commercial products demonstrated that some were unacceptable for both normal control and cancer patients. Interestingly, some products were rated better by cancer patients than control groups, a finding since confirmed by others (Gallagher and Tweedle 1983). Taste abnormalities may account for these differences in palatability and taste thresholds in cancer patients were shown to be significantly higher for bitter and salt with a suggestion that this also

applied to sour and sweet. Others (De Wys and Walter 1975 and Gallagher and Tweedle 1983) have reported higher sweet and lower bitter thresholds for cancer patients but different patient populations may account for the different findings for bitter in the thesis study. It is clear, however, that cancer patients frequently have an altered taste threshold which may alter appreciation of basic foodstuffs and this fact should be considered when nutritional supplementation and dietary advice is given. The high incidence of such problems means that a trained dietitian should be available to consult each cancer patient, especially during routine outpatient visits, so that dietary modifications can be discussed when appropriate.

Malnourished cancer patients (patients with significant weight loss) often have very severe nutritional deficits. The lack of correlation between anthropometric data and plasma protein data suggests a rather more complex metabolic process than that commonly seen in simple protein-energy malnutrition (PEM).

Hair root morphology and protein content was not shown to be a useful index of malnutrition in the cancer patient although typical morphological changes characteristic of malnutrition were usually present. There appeared to be no measurable changes in hair root morphology with nutritional supplementation. In addition, enteral nutritional support in malnourished cancer patients was shown to be unsuccessful in correcting the nutritional deficits in nearly all patients. Heber et al (1986) also failed to demonstrate a benefit from nutritional support in head and neck cancer patients despite a daily mean positive nitrogen balance.

Most cancer patients studied in this thesis were significantly catabolic, many with higher negative nitrogen balance than would have been expected for simple PEM, suggesting a possible hypercatabolic state.

In addition, elevated C-reactive protein in many patients correlated moderately with nitrogen balance suggesting that in hypercatabolic states CRP is more likely to be elevated. Very recent literature (Beutler and Cerami 1987) describes cachectin as an inflammatory mediator and it is possible that may be the cause for both the elevated metabolic rate often seen in malignancy and of the elevated CRP or that it is part of the same metabolic sequence of events. This does not mean that cachectin (tumour necrosis factor, TNF) is the ultimate cause of cancer cachexia. However, cachectin is a possible candidate for the host derived substance which was hypothesised in the paper on plasma exchange.

Aderka et al (1985) have shown elevated cachectin levels in some cancer patients and interestingly those who showed the greatest rise in TNF to PHA stimulation were the most emaciated and had the shortest survival. Work in this thesis has shown a trend toward shorter survival for patients with the highest CRP levels. C-reactive protein changes may therefore mirror changes in cachectin plasma concentrations. The data on albumin distribution suggest that albumin was redistributed to the extravascular compartment in cancer patients and this therefore contributes to the hypoalbuminaemia. This redistribution was also demonstrated in patients with injury and this data has been since published (Fleck et al 1985). Cachectin is directly toxic to vascular endothelial cells (Beutler and Cerami 1987) and may be the agent responsible for these noted changes of albumin distribution particularly if the serum rises in injury or stress rise more rapidly than acute phase reactants such as CRP.

It is suggested in analysis of the enteral nutrition data, the albumin data and the amino acid data that two groups of malnourished cancer patients exist - those with a hypermetabolic response (presumably induced by host and/or tumour products) and those with a normal or

hypermetabolic response to starvation. More recently, Ristrain (1986) also makes this point but separates the two groups of patients into protein calorie malnutrition (PCM) and hyperalbuminaemic malnutrition (that due to stress or hypermetabolic malnutrition). Although the patient numbers were small, it is argued that these two types of malnutrition can be seen in the albumin metabolic study where high and low fractional catabolic rates of albumin were noted and where those patients with low fractional catabolic rates tended to fare better with nutritional support. The majority of cancer patients who more closely resemble the hypercatabolic state of stress do not respond well to nutritional support and this mirrors the situation in patients with acute trauma. The abnormalities of increased metabolic rate in cancer patients have been shown by others, in more recent years, to be definite with respect to protein metabolism (Jeevanandam et al 1984) although the hypometabolic group was not distinguished by this latter group, probably because of patient selection.

The plasma amino acid results, it is suggested, also lends support to the concept of a mixed patient population with respect to metabolic rate changes in response to malignancy. Such changes may be important with respect to the likelihood of response to nutritional support. It may also be possible, as suggested in the discussion on plasma exchange, to alter the host metabolic response to the cancer by removing the offending substances from the plasma, providing that the frequency of plasma exchange is such that it exceeds the half life of the substance in question. If CRP acts as a marker of the offending substance or substances (e.g. cachectin) it may be possible to pursue this investigational method since CRP falls were readily demonstrated following plasma exchange. This topic is worthy of further research.

Measurement of protein synthesis changes following plasma exchange

is not easy due to the length of time involved for most methods. Measurement of urea synthesis as an indication of whole body protein turnover is a possibility since the procedure is of short duration. In conjunction with the studies presented in this thesis, preliminary studies of urea synthesis using ^{14}C -carbonate were undertaken pre- and post-plasma exchange using methodology similar to that previously published (Charlwood 1965, Regoeczi et al 1965). Results calculated by Seamus Caine, using methodology since published (Caine and Fleck 1984) are shown in Appendix VI and although there is not a significant difference between pre- and post-plasma exchange fractional synthesis rate of urea, there is a trend in most patients toward a lower post-exchange synthesis rate. Further investigation of this approach would seem warranted in further exploring these hypotheses. Indeed, since this data was obtained, Matthews and Downey (1984) have published data validating the measurement of urea kinetics in humans and Kosanovic (1985) has utilised the method for monitoring nutritional care in the acutely ill patient.

How dull it is to pause, to make an end,
To rust unburnish'd, not to shine in use!
As tho' to breathe were life. Life piled on life
We're all too little, and of one to me
Little remains: but every hour is saved
From that eternal silence, something more,
A bringer of new things.

Ulysses 1.6

Alfred Lord Tennyson

(1809-1892)

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APPENDIX I

The following is a list of publications (including abstracts) and presentations of papers of scientific meetings related to material presented in this thesis.

Papers presented at scientific meetings

Nutritional aspects of plasma exchange in cancer patients at the First International Seminar on Plasmapheresis as a Method of Immune Modulation and Treatment of Cancer Patients at Neuilly, France, 26th September, 1979.

Nutritional support in cancer patients - at an International Workshop on Nutrition and Metabolism in Cancer at Freiburg Im Breisgau, West Germany, 7th and 8th December, 1979.

Albumin metabolism and distribution in cachectic cancer patients at the Twenty-first Annual General Meeting of the British Association for Cancer Research, Southampton, April, 1980.

Plasma amino acid profiles in cancer patients with weight loss at the Twenty-first Annual General Meeting of the British Association for Cancer Research, Southampton, April, 1980.

Albumin metabolism in cancer patients with weight loss at the E.O.R.T.C. Symposium on Nutrition of the Cancer Patient, Brussels, Belgium, 8th-9th January, 1981.

Enteral hyperalimentation in cancer patients with weight loss at the E.O.R.T.C. Symposium on Nutrition of the Cancer Patient, Brussels, Belgium, 8th-9th January, 1981.

Poster presentations

At the Association of Clinical Biochemists Symposium on Laboratory Support in Malignant Disease, Glasgow, 1st October, 1980.

- (i) Plasma amino acids in malignant disease.
CARLYLE, J.E., CALMAN, K.C., TROTTER, J.M.
- (ii) The nutritional status of the cancer patients with weight loss.
TROTTER, J.M., CARLYLE, J.E., McALLISTER, E.J., CALMAN, K.C.

Publications (including abstracts)

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TROTTER, J.M., CALMAN, K.C. Nutritional support in cancer patients. In Nutrition and Metabolism in Cancer. ed. Kluthe R., Lohr, G.W., Georg Thieme Verlag Stuttgart. New York 1981, 50-55.

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APPENDIX II

NUTRITIONAL ABNORMALITIES IN CANCER PATIENTS WITH WEIGHT LOSS

Patient	Tumour Group	Sex	Age	Wt.	%Wt. loss	MAMC (grade)	TSFT (grade)	Skin test	Alb	TP	TF	RBP	PA	CRP	Zn	Urea	Vit. A	Survival months	Response to Rx
M.A.	3	F	82	35	22.2	5	6	0	30	65	4.3	14	0.2	82	9.7	3.6	-	4.0	No
W.A.	3	M	62	41	38.5	4	6	-	30	58	2.2	19	-	205	11.7	9.9	1.8	0.5	No
T.B.	1	M	63	64.6	12.2	3	6	-	38	77	2.3	27	-	110	11.5	4.0	1.0	0.75	No
D.B.	2	M	70	102.7*	-	2	1	-	20	71	-	32	0.06	162	9.0	7.7	0.8	0.75	No
H.B.	2	F	64	67.6*	-	2	1	-	30	56	2.4	37	-	205	8.7	7.4	-**	0.3	No
T.C.	2	M	64	53.5	16.4	4	6	0	35	49	1.3	48	0.07	56	5.8	6.1	1.04	2.0	No
J.C.	2	M	56	49.4	21.9	5	6	-	23	60	3.1	-	-	-	-	36.3	0.55	0.1	No
J.C.	2	F	45	41.2	14.1	4	6	3	27	58	2.9	40.8	0.13	15.8	8.9	2.5	1.7	3.75	No
M.D.	1	F	60	48.5	23.7	2	3	1	34	77	3.8	21	0.13	35	8.3	3.2	1.1	3.0	No
J.D.	2	M	57	48.5	27.6	4	5	-	26	64	2.4	27	0.16	0	6.4	4.0	1.3	2.5	Yes
J.D.	3	M	39	61.5	28.5	2	6	-	22	43	1.7	30.2	-	47	9.8	5.7	-	3.0	No
J.D.	3	M	76	47.6	35.0	4	6	-	34	80	2.0	51.7	0.23	32	12.3	8.5	2.3	0.5	No
J.E.	1	M	52	69	-***	3	1	0	33	60	3.5	17	0.35	27	9.9	7.1	2.5	5.0	No
E.F.	3	F	61	50.3	7.7	2	5	-	32	58	2.1	16	-	170	11.1	1.5	-	1.5	No
P.F.	3	M	45	68	15	-	-	-	32	64	3.0	39	0.19	35	6.2	3.2	-	2.0	No
D.F.	1	M	62	52.2	25.4	3	6	0	28	66	2.8	36.9	0.17	36.2	13.2	2.2	1.2	0.5	No
D.G.	2	M	61	58	22.7	4	6	-	31	63	-	-	-	-	-	5.6	-	3.5	No
J.G.	3	M	37	47.7	16.8	3	6	-	29	55	2.3	21	-	74	9.4	4.7	0.4	5.0	No
K.G.	2	M	51	70.6	8.3	1	6	-	37	80	3.2	40.4	-	225	10.3	4.9	0.8	3.5	No
I.H.	3	F	43	49	26.4	5	5	0	36	69	1.5	84	0.04	213	5.8	7.0	1.4	1.0	No
R.H.	3	M	46	45.0	21.3	5	6	0	38	61	1.9	25.7	-	39	10.3	2.8	1.1	4.0	No
I.H.	3	M	34	48.2	27.5	-	-	-	33	80	2.2	35	0.15	52	12.5	4.0	-	1.0	No
J.H.	2	M	55	46	23.9	4	6	3	25	67	2.7	38.7	0.11	0	8.3	3.7	0.7	7	No
W.H.	1	M	55	51.4	12.3	4	6	2	37	70	2.3	22	0.18	22	15.5	5.8	1.7	2.5	No
M.J.	3	F	69	42	16.0	4	6	0	18	51	-	15.9	0.07	7	3.3	2.2	0.2	>12.0	Yes
J.K.	3	F	44	44	22.5	3	5	-	27	62	2.9	25	0.09	123	7.9	2.8	1.84	1.25	No
S.L.	3	M	54	63.9	5.8	4	5	-	28	73	1.9	-	0.17	-	9.6	6.6	6.4	2.5	No
J.L.	3	M	65	57.8	13.5	4	6	0	29	70	2.8	25.4	0.09	136	9.3	4.1	-	1.0	No
M.M.	3	M	62	42.8	20.0	5	6	-	33	61	2.2	30	-	82	9.2	7.8	1.8	0.25	No

NUTRITIONAL ABNORMALITIES IN CANCER PATIENTS WITH WEIGHT LOSS (cont.)

Patient	Tumour Group	Sex	Age	Wt.	%Wt. loss	MAMC (grade)	TSFT (grade)	Skin test	Alb	TP	TF	RBP	PA	CRP	Zn	Urea	Vit. A	Survival months	Response to Rx
R.M.	3	M	53	76	11.6	2	3	-	30	75	2.6	59	0.13	90	7.5	8.9	-	>9	Yes
P.M.	3	F	31	34.5	31.0	5	5	-	41	73	-	-	-	-	-	-	-	1.0	No
L.M.	3	M	64	54.6	19.7	-	6	-	24	54	2.7	25	0.05	145	-	6.3	-	2.0	No
G.N.	2	M	64	57	16.2	3	6	-	33	59	3.0	31	-	0	6.4	2.8	-	5.0	No
R.N.	3	M	50	59.9	17.9	2	6	-	36	78	2.6	35.8	-	31	11.7	5.9	2.02	12.25	No
J.N.	3	M	20	*	-	5	6	-	35	66	2.0	25.7	-	49	8.5	4.8	1.58	2.0	No
J.O.	1	M	69	37	31.0	4	6	0	30	64	3.1	127	0.21	0	-	7.2	1.04	1.5	No
J.O.	1	M	68	49.4	29.4	5	6	-	26	68	1.9	15.7	-	255	8.6	8.3	1.46	1.5	No
A.P.	2	M	65	45.6	32.9	3	6	-	33	61	2.1	37	-	29	9.0	8.7	-	0.5	No
D.R.	3	F	70	44.4	31.2	4	6	0	31	54	2.6	-	0.17	0	9.5	8.6	3.6	14.5	Yes
J.S.	3	M	52	43	32.4	4	6	-	36	64	-	-	-	40	12.0	7.0	1.1	1.5	No
J.S.	1	M	66	60.5	5	3	6	3	29	67	-	46	0.24	87	10.2	8.3	1.42	1.0	No
M.S.	2	F	81	34.4	35.3	5	6	-	29	64	3.1	36	0.13	36	12.3	6.7	-	5.0	No
M.S.	2	F	75	48.1	19.8	2	3	-	29	56	2.0	15.7	-	94	8.6	-	0.68	3.5	No
W.T.	1	M	50	55.4	17.6	3	6	4	33	80	3.4	81	0.06	0	12.7	4.8	2.9	>5	No
A.T.	2	M	58	43.5	38.6	4	6	-	33	76	-	40	0.13	10	11.1	5.2	1.13	6.0	No
H.W.	3	F	54	55	14.8	-	-	-	23	69	2.1	28	0.1	237	10.4	3.9	1.1	2.0	No
J.A.	2	M	61	79.2	18.9	3	3	0	18	67	1.1	15	0.05	180	10.0	4.1	0.32	2.0	No
D.H.	1	M	64	33.6	20.0	5	6	0	23	63	1.6	38	0.1	62	10.8	6.1	1.8	1.0	No
A.M.	3	F	51	37.6	24.8	6	5	-	23	58	-	17.3	0.04	171	6.7	4.6	2.1	0.5	No
J.M.	1	M	72	47.5	19.8	4	6	0	23	74	1.7	50	0.09	162	-	5.6	0.84	>6	No
J.M.	2	M	59	50.4	20.0	3	4	-	30	72	2.6	14	0.14	82	8.8	19.4	1.0	1.0	No
M.M.	2	F	63	55.6	5.3	2	4	-	33	68	3.5	65	0.22	0	9.0	4.8	1.82	11.0	No

* Data not assessable due to oedema (patient D.B.) and ascites (patients H.B., J.N.)

** Some vit.A assays not available due to interference in assay with turbidity.

*** Weight loss inaccurate due to cushingoid habitus secondary to dexamethasone.

APPENDIX III

ENTERAL NUTRITION STUDY - ANTHROPOMETRIC DATA AND CHANGES WITH NUTRITIONAL SUPPORT

*Weight changes not assessable due to oedema secondary to malnutrition. (a) Before (b) After nutrition

Number	Tumour	Sex	Age	Weight		Wt Change	% Wt.loss at start	MAMC			TSFT		
				(a)	(b)			(a)	(b)	Change	(a)	(b)	Change
1	Ca. lung	M	63	64.6	64.5	-0.1	12.2	21.3	21.4	+0.1	5.4	5.7	+0.3
2	Ca. stomach	M	64	53.5	51.5	-2.0	16.4	20.0	19.9	-0.1	3.8	3.4	-0.4
3	Ca. oesophagus	F	45	41.2	42.9	+1.7	14.1	16.4	16.9	+0.5	6.6	5.9	-0.7
4	Ca. lung	F	60	58.0	58.6	+0.6	8.8	22.4	22.1	-0.3	13.8	13.4	-0.4
5	Ca. stomach	M	57	48.5	50.0	+1.5	27.6	17.8	18.3	+0.5	8.5	9.2	+0.7
6	Lymphoma	M	45	61.5	63.8	+2.3	28.5	22.9	22.9	0.0	6.6	6.6	0.0
7	Ca. lung	M	52	69.0*			*	20.3	21.0	+0.7	23.2	24.5	+1.3
8	Ca. lung	M	62	52.2	50	-1.8	25.4	21.0	19.6	-1.4	4.8	4.8	-0.3
9	Ca. kidney	M	37	47.7	50.0	+2.3	16.8	22.7	23.4	+1.3	3.6	3.5	-0.1
10	Ca. colon	M	51	70.6	67.1	-2.5	8.3	26.2	25.2	-1.0	5.6	5.6	0
11	Ca. ovary	F	43	48.2	49.5	+1.3	26.4	15.6	15.6	+0.0	11.8	10.6	-1.2
12	Lymphoma	M	46	45.0	51.0	+6.0	21.3	17.6	18.7	+1.1	2.8	2.7	-0.1
13	Lymphoma	M	46	44.0	45.8	+1.8	23.1	16.3	16.6	+0.3	2.1	2.5	+0.4
14	Ca. colon	M	54	46.0	49.0	+3.0	23.9	20.0	19.3	-0.7	5.4	5.4	0.0
15	Ca. cricoid	F	44	43.0	44.0	+1.0	24.3	19.0	18.2	-0.8	11.0	12.2	+1.2
16	Ca. stomach	M	65	57.8	60.8	+3.0	13.5	19.9	19.5	-0.4	6.8	7.2	+0.4
17	Ca. lung	M	72	47.5	52.0	+4.5	19.8	19.6	20.5	+0.9	2.8	3.2	+0.4
18	Ca. colon	F	63	55.6	55.8	+0.2	5.0	21.7	21.3	-0.4	12.0	13.4	+1.4
19	Ca. stomach	M	64	57.0	58.7	+1.7	16.2	22.0	22.4	+0.4	6.4	6.5	+0.1
20	Ca. maxillary antrum	M	50	59.9	60.5	+0.6	17.9	22.9	22.9	0.0	6.6	6.6	0.0
21	Mesothelioma	M	68	49.4	51.5	+1.8	29.4	17.6	17.5	-0.1	3.0	3.2	+0.2
22	Lymphoma	F	70	48.2	52.6	+4.4	25.3	17.3	18.4	+1.1	10.2	11.4	+1.2
23	Ca. lung	M	66	60.5*			*	21.4	21.3	-0.1	6.7	6.8	+0.1
24	Ca. oesophagus	F	81	34.4	38.3	+3.9	35.3	16.1	16.5	+0.4	4.6	4.7	+0.1
25	Ca. lung	M	50	55.4	58.0	+2.6	17.6	21.2	22.6	+1.4	4.8	5.0	+0.2
26	Ca. oesophagus	M	58	43.4	45.6	+2.2	38.6	18.1	18.8	+0.7	4.5	4.6	+0.1
27	Ca. colon	M	61	79.2*			*	20.8	20.3	-0.5	10.8	8.6	-2.2
28	Ca. stomach	M	45	52.3	55.5	+3.2	21.7	20.0	19.6	-0.4	3.2	3.0	-0.2

ENTERAL NUTRITION STUDY - LABORATORY DATA AND CHANGES WITH NUTRITIONAL SUPPORT

a = Before b = After nutritional support. Normal ranges: Refer to table 2.16a.

Number	Alb.			T.P.			T.F.			R.B.P.			P.A.			C.R.P.			Zn.			Vit. A		
	a.	b.	a-b	a.	b.	a-b	a.	b.	a-b	a.	b.	a-b	a.	b.	a-b	a.	b.	a-b	a.	b.	a-b	a.	b.	a-b
1	38	31	-7	77	71	-6	2.3	1.9	-0.4	27	32	+5				110	89	-21	11.5	7.2	-4.3	1	1.7	+0.7
2	25	24	-1	49	53	+4	1.3	1.1	-0.2	48	17	-31	0.07	0.05	-0.02	56	111	+55	5.8	9.6	+3.8	1.04	1.34	+0.3
3	27	27	0	58	59	+1	3.0	3.2	+0.2	49	50	+1	0.13	0.14	+0.01	16	30	+14	9.7	9.9	+0.2	1.7	1.65	-0.05
4	37	32	-5	73	69	-4	3.4	3.7	+0.3	65	43	-22	0.09	0.10	+0.01	38	52	+14	8.3	10.1	+1.8	0.9	1.1	+0.2
5	26	25	-1	64	59	-5	2.4	2.7	+0.3	27	41	+14	0.16	0.18	+0.02	0	0	0	6.4	6.1	-0.3	1.3	1.9	+0.6
6	22	31	+9	63	66	+3	1.7	2.5	+0.8	30	29	-1				47	175	+128	9.8	10.4	+0.6			
7	33	33	0	60	65	+5				17	103	+86	0.35	0.47	+0.12	27	18	-19	9.9	12.9	+3.0	2.5	3.7	+1.2
8	28	28	0	66	67	+1	2.8	2.6	-0.2	37	40	+3	0.17	0.16	-0.01	36	31	-5						
9	29	35	+6	55	67	+12	2.3	1.8	-0.5	21	41	+20				74	53	-21	9.4	10.5	+0.9	0.4	2.3	+1.9
10	37	36	-1	80	82	+2	3.2	5.2	+2.0	40	70	+30				225	24	-201	10.3	11.6	+1.3	0.8	2.1	+1.3
11	36	18	-18	69	60	-9				84	28	-56	0.04	0.08	+0.04	213	183	-30	5.8	2.6	-3.2	1.4	1.2	-0.2
12	38	29	-9	61	58	-3	1.9	1.9	0	26	21	-5				39	58	+19	10.3	9.5	-0.8			
13	26	21	-5	51	47	-4	1.9	1.5	-0.4	27	26	-1	0.07	0.16	+0.09	42	25	-15	6.0	7.0	+1.0			
14	29	27	-2	74	64	-10	2.7	2.8	+0.1	39	29	-10	0.11	0.10	-0.01	0	6	+6	8.3	3.7	-4.6	0.7	0.6	-0.1
15	34	27	-7	78	62	-16	3.3	2.9	-0.4	27	25	-2	0.11	0.09	-0.02	86	123	+37	10.8	7.9	-2.9	1.5	1.1	-0.4
16	29	22	-7	70	50	-20	2.8	3.2	+0.4	25	39	+14	0.09	0.06	-0.03				9.3	11.4	+2.1			
17	23	26	+3	74	80	+6	1.7	2.0	+0.3	50	32	-18	0.09	0.11	+0.02	162	62	-100				0.84	1.32	+0.48
18	33	36	+3	68	72	+4	3.5	3.8	+0.3	65	57	-8	0.22	0.4	+0.18	0	0	0	10.3	8.2	-2.1	1.8	3.6	+1.8
19	33	34	+1	59	64	+5	3.0	3.2	+0.2	31	32	+1				0	32	+32	6.4	9.1	+2.7			
20	36	35	-1	78	70	-8	2.6	2.6	0	36	36	0				31	31	0	11.7	9.9	-1.8	2.0	1.9	-0.1
21	26	22	-4	68	69	+1	1.9	1.8	-0.1	16	21	+5				255	180	-75	8.6	8.5	-0.1	1.46	1.3	-0.2
22	31	31	0	54	53	-1				101	122	+21	0.17	0.19	+0.02	0	0	0	10.2	7.9	-2.3	2.2	8.0	+5.8
23	29	29	0	67	71	+4				47	67	+20	0.24	0.08	-0.16	87	75	-12	10.2	10.6	+0.4			
24	29	27	-2	64	72	+6	3.1	3.3	+0.2	36	49	+13	0.13	0.2	+0.07	36	17	-19						
25	33	33	0	80	71	-9	3.4	2.8	-0.6	81	49	-32	0.06	0.23	+0.17	0	132	+132	12.7	8.7	-4.0	2.9	1.1	-1.8
26	33	38	+5	76	75	-1				39	53	+14	0.19	0.2	+0.01	10	44	+34	11.1	12.7	+1.6	1.13	1.95	+0.82
27	18	21	+3	67	94	+24	1.1	1.1	0	15	26	+11	0.05	0.04	-0.01	180	142	-38	10.0	12.3	+2.3	0.3	0.4	+0.1
28	35	26	-9	68	65	-3	1.8	2.75	+1.0	26	25	-1		0.1		168	100	-68	9.2	10.1	+0.4	2.8	0.6	-1.2

APPENDIX IV

NUTRITIONAL STUDIES RESULTS (A)

NAME

No.

D.O.B.

Diagnosis

Extent of disease

Performance Status

0 1 2 3 4

Study

Dates

1	2	3	4
---	---	---	---

Anthropometric Data

Normal Wt.

Calculated Wt.

Study	Date	Height	Weight	%wt loss	Actual wt Normal wt	U.A.C	Triceps	Subscap.

Hair Root Data

Study	Date	% Anag	% Atro	AT/ Anag	Shaft Diam.	Bulb Diam.	Anag. Prot.	Atro. Prot.	Average Prot.

Skin Recall Tests

Study	Date	P.P.D.	Sk/Sd	Mumps	Candida	Trich rubrum

APPENDIX IV CONTINUED

PLASMA EXCHANGE STUDIES : RESULTS .(A)

Name

No.

D.O.B.

Diagnosis

Performance Status 0 1 2 3 4

Exchange Dates

1	2	3	4	5	6

Anthropometric Data.

N. wt.

Calc wt.

Ht.

Exchange	Date	Weight	%wt loss	Actual wt Est. N wt.	V.A.C.	Triceps	Subscap.

G.T.T.

Time (mins)	B.S.L.	Insulin	G.H.	Time (mins)	BSL	Insulin	G.H.
0				0			
30				30			
60				60			
90				90			
120				120			
180				180			

Skin Recall Tests

Date	PPD	sk/sd	Mumps	Cand.da	T. rubrum.

APPENDIX IV CONTINUED

PLASMA EXCHANGE STUDIES - RESULTS (B)

Blood

No.

Date	Time	Urea	Creat	ALP	Alb	T.P	CRP	Transf	P.A.	R.B.P	V.M	V.C	Zn	Co.

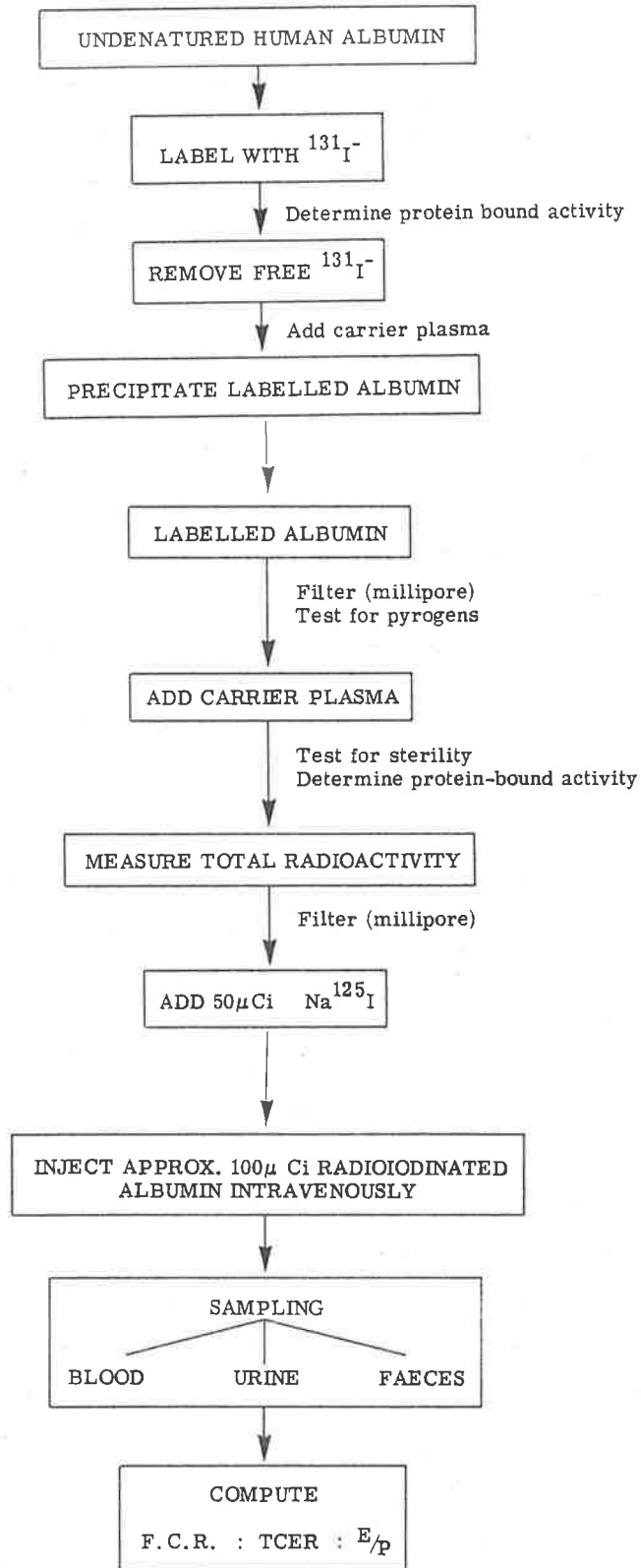
Hormones

Date	Time	Insulin	BSL	Cortisol	G.H.	And.		Urinary	Urinary	Urinary	Urinary

Albumin Metabolic Studies

APPENDIX V

PREPARATION of RADIOIODINATED HUMAN ALBUMIN



APPENDIX V CONTINUED

EQUATION for DECAY of RADIOIODINATED
ALBUMIN in PLASMA

$$P = \sum_{i=1}^{n=3} A_i e^{-b_i t}$$
$$= A_1 e^{-b_1 t} + A_2 e^{-b_2 t} + A_3 e^{-b_3 t}$$

Where A = Y intercept at time 0.

b = exponential.

EQUATION for CALCULATION of F. C. R.

$$\text{F. C. R.} = \frac{1}{\int_0^{\infty} P}$$
$$= \frac{1}{\int_0^{\infty} \sum_{i=1}^{n=3} A_i e^{-b_i t}}$$
$$= \frac{1}{\frac{A_1}{b_1} + \frac{A_2}{b_2} + \frac{A_3}{b_3}}$$

APPENDIX VI
UREA SYNTHESIS RATE DATA

¹⁴C-urea

NORMAL SUBJECTS

Number	K _{1/2} (min.)	*FSRu (d ⁻¹)	Efficiency r	Number of samples n
1	501	1.991	0.994	5
2	370	2.696	0.991	5
3	473	2.111	0.983	6
4	575	1.736	0.993	6

CANCER PATIENTS

1	1039	0.961	0.890	6
2	354	2.822	0.994	6
3	477	2.093	0.997	6
4	491	2.033	0.996	6
5	473	2.111	0.093	5

CANCER PATIENTS PRE (a) AND POST (b) PLASMA EXCHANGE

6a	329	3.02	0.002	7
6b	589	1.695	0.996	4
**6a	357	2.796	0.973	6
6b	374	2.664	0.994	6
7a	810	1.231	0.992	6
7b	337	2.970	0.958	6
***7a	544	1.836	0.995	6
7b	613	1.626	0.979	5
8a	495	2.015	0.987	7
8b	527	1.893	0.993	6
9a	700	1.427	0.981	7
9b	729	1.370	0.999	6

- * FSRu (d⁻¹) = fractional synthesis rate of urea per day.
 ** 3 months after first study.
 *** 2 months after first study.

APPENDIX VII

REPRINTS OF PUBLISHED PAPERS

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Clinical Topics

Problems of the oncology outpatient: role of the liaison health visitor

J M TROTTER, R SCOTT, F R MACBETH,
J G McVIE, K C CALMAN

Abstract

A survey by a liaison health visitor of outpatients attending an oncology department has identified and enumerated the principal problems with which she is confronted, and defined her role. The main medical symptoms of concern to the patient at home and needing attention by the liaison health visitor were anorexia, nausea, vomiting, and constipation; inadequate pain control due to poor drug compliance was also common. Other functions of the liaison health visitor include providing nursing aids and prostheses, support for bereaved relatives, and liaison with the community health care team.

Introduction

During their illness patients with malignant disease are con-

Gartnavel General Hospital, Glasgow G12 0YN

J M TROTTER, FRACP, research fellow department of clinical oncology

R SCOTT, RGN, DIPN, liaison health visitor

F R MACBETH, MRCP, registrar in clinical oncology

J G McVIE, MD, MRCP, senior lecturer in clinical oncology

K C CALMAN, MD, PHD, cancer research campaign professor of clinical oncology

fronted by various medical and social problems. The liaison health visitor has important roles not only in helping to provide social and nursing care, but also to be an important link between the hospital oncology team and the community health care team, and between the patient at home and the hospital. To accomplish these tasks the liaison health visitor, who is a trained nurse, undertakes a 12-month course that includes studies in the early detection of ill health; the surveillance of high-risk groups; and sociology, social policy, and psychology. This preparation, together with wide nursing experience, equips her to meet the mental, physical, and emotional needs of the individuals and families in the community.

This study was undertaken to document:

(1) The extent of nursing and social support provided by the liaison health visitor for outpatients attending the clinical oncology service of a large hospital.

(2) The symptoms of which patients complained to the visitor.

(3) The adequacy of pain relief and the degree of drug compliance.

These data were used to define the role of the liaison health visitor in managing outpatients attending an oncology department.

The study was undertaken in a clinical oncology unit that manages 70-80 outpatients a week. The predominant malignancies treated are cancers of the breast, ovary, gastrointestinal tract, and lung. The liaison health visitor attends these outpatient clinics, as do the dietitian, pharmacist, clinical psychologist, research nursing sister, and data manager.

Method

One of us (RS), a liaison health visitor who has been working with the oncology unit for several years, documented the reason for her assessment of outpatients and the source of referral. It was considered that outpatient assessment (especially home visits) might highlight problems different from those of patients in hospital. Although many patients were seen more often than once, especially by home visit, only data from the first assessment during the five-month study period were collected. The provision of prosthetic or nursing aids was noted, as was the number of patients requiring placement in a hospice or convalescent home, or liaison with general practitioner, district nurse, or health visitor.

Specific symptoms such as anorexia, nausea, vomiting, constipation, diarrhoea, dyspnoea, and depression were recorded. No attempt was made to use rating scales for these symptoms. Finally, patients were

questioned in detail about pain and analgesic ingestion. The adequacy of any prescribed analgesia was recorded and a check made on the compliance in taking these and other prescribed drugs.

Results

Over the five months' study period, 237 assessments were made, a mean of about 12 a week. Table I shows that 46% of assessments were carried out by the liaison health visitor either during a home visit or during a routine outpatient attendance by the patient. Relatively few patients (11% of those assessed) were referred by the medical staff. Interestingly, 10% of interviews were at the request of relatives and a further 9% entailed providing psychological support to bereaved relatives. Although 9% of the first assessments during the study period were for tracing clinic defaulters, the actual outpatient non-attendance rate is only 5% (mean yearly figure 1979).

Arranging the provision of nursing and prosthetic aids formed a considerable part of the work load of the liaison health visitor (table II). Nursing aids—for instance, "sheepskin" rugs, urinals, commodes, bed cages, and back rests—were needed by 35 patients, and wigs by 27 patients with drug-induced alopecia. Breast prostheses needed renewal on 15 occasions. Fifteen walking aids and two stomal appliances were also supplied.

Table III shows that 31% of patients assessed had clinic appointments either arranged or altered for their convenience. Arranging or

TABLE I—Reasons for assessment of 237 patients by liaison health visitor and source of referral over a five-month period

	No (%) of patients
Home visit for follow-up or psychosocial support	58 (24.5)
Seen during routine oncology outpatient attendance	51 (21.5)
Home visit after discharge from hospital	28 (11.8)
Referral by doctor of oncology team	27 (11.4)
Providing assistance at request of relatives	25 (10.5)
Providing support to bereaved relatives	22 (9.3)
Visiting patients after outpatient clinic default	22 (9.3)
Home assessment before discharge of patient	4 (1.7)

rearranging transport was needed by 12% of patients. Home help, district nurse, community health visitor and general-practitioner referrals were also arranged by the liaison health visitor where these were considered appropriate. Most general-practitioner referrals were for the control of pain. Thirty patients were placed in short-term (under one week) or long-term (over one week) care in hospice or convalescent home, and 30 patients were provided with social/or financial assistance, or both, with the help of the social worker.

Of the symptoms that patients volunteered, anorexia was by far the commonest and the one that seemed to concern patients most. Anorexia occurred in 121 patients (51% of those interviewed) and was

TABLE II—Number (%) of patients needing nursing aids and prostheses

	No (%) of patients		No (%) of patients
Nursing aids	35 (14.8)	Occupational therapy aids	6 (2.5)
Provision of wigs	27 (11.4)	Stomal appliances	2 (0.8)
Mammary prostheses	15 (6.3)	Other	2 (0.8)
Walking aids	15 (6.3)		

TABLE III—Number (%) of patients needing liaison and placement assistance

	No (%) of assessments		No (%) of assessments
Arranging clinic appointments	74 (31.2)	Arranging home help*	24 (10.1)
Arranging transport	30 (12.7)	Arranging district nurse and health visitor	20 (8.4)
Short-term care placement	18 (7.6)	Referrals to general practitioner	9 (3.8)
Long-term care placement*	12 (5.1)		
Social/financial assistance*	30 (12.7)		

*With social worker.

often associated with nausea (31%) and vomiting (18%) (table IV). In almost half these patients the major cause of the anorexia was cytotoxic chemotherapy, with radiotherapy and analgesics implicated in 16% and 7% respectively (table V). Thirty-three (27%) of the anorectic patients, however, had no obvious iatrogenic cause for their anorexia.

TABLE IV—Number (%) of patients who suffered gastrointestinal symptoms

	No (%) of patients		No (%) of patients
Anorexia	121 (51.0)	Constipation	54 (22.8)
Nausea	75 (31.6)	Diarrhoea	10 (4.2)
Vomiting	44 (18.6)		

TABLE V—Causes of anorexia in 121 patients

	No of patients	% Total assessments	% Patients with anorexia
Cytotoxic chemotherapy	59	24.9	48.8
Radiotherapy	20	8.4	16.5
Analgesics	9	3.8	7.4
No obvious therapeutic or iatrogenic cause	33	13.9	27.3

which may have been caused by the malignant disease itself or psychological factors or both. Oral nutritional supplements were supplied to 38 patients by the visitor during home visits. Constipation, probably often related to analgesics, worried 23% of patients interviewed. Diarrhoea was an infrequent problem, occurring in only 4% of patients (table IV).

Problems with analgesia were found more often than expected (table VI). Eleven patients said that they had pain but no analgesic had ever been prescribed. Fifty-nine had been prescribed inadequate analgesia as judged by the fact that they complained of pain despite taking the prescribed dose of analgesic. In addition 49 were not taking their analgesic as prescribed and, except one case, this resulted in taking less than the prescribed dose even though they were aware of the prescription directions. Seven patients who misunderstood the prescription directions took an inadequate dosage.

Ten patients failed to take oral cytotoxic drugs as prescribed, usually because of nausea and vomiting, and nine patients misunderstood prescription directions. Non-compliance with various other drugs was found in 25 patients.

Forty-three patients complained of dyspnoea and 53 of being depressed. No attempt was made to measure depression by psychometric testing, and the figure may not represent the true incidence of clinical depression. It does, however, illustrate the extent of overt psychological stress experienced by patients with cancer.

TABLE VI—Problems with analgesia in 237 patients

	No (%) of patients		No (%) of patients
Patients with no pain	67 (28.3)	Not taking analgesic as prescribed	49 (20.6)
Patients taking inadequate analgesia	44 (18.6)	Analgesic needed but not prescribed	11 (4.6)
Inadequate analgesic prescribed	59 (24.9)	Misunderstanding directions	7 (3.0)

Discussion

Of the members of the hospital oncology team, the liaison health visitor is in a unique position. She is the one person who not only sees patients both in hospital and at home but who has regular personal contact with hospital nursing and medical staff, general practitioners, community nurses, and social workers. Her role as it has evolved in this clinical oncology unit is threefold: firstly, she gathers information about patients, relatives, and their problems; secondly, she co-ordinates the provision of support services; and, thirdly, she is a counsellor.

Her usefulness depends on her efficiency in identifying those patients who need her help and on the ease with which she can contact the appropriate sources of advice and help. Table I shows that most assessments resulted from her own vigilance while attending ward rounds and outpatient clinics and talking informally to patients and relatives. That only 11% of assessments were instituted by referral from medical staff reflects this vigilance rather than the doctors' inefficiency.

Home visits are an essential part of her job. Patients and relatives are likely to be less anxious in their own surroundings and more prepared to discuss problems that they might not mention in the busy atmosphere of ward or clinic. She can also assess the home conditions herself and therefore the need for particular aids, prostheses, nursing care, or social support. Finally, she can get a better idea of the family interactions and ability to cope. Local general practitioners have been told by letter of her existence and of the possibility that she may visit selected patients at home. A home visit is often done without prior consultation with the general practitioner.

The informal rapport that develops is probably the main reason why the liaison health visitor uncovered an unsuspected high incidence of gastrointestinal symptoms, inadequate control of pain, and non-compliance with drugs. The distressing symptoms of anorexia and constipation are often overlooked in a busy chemotherapy clinic. She usefully provides simple dietary advice and through the hospital or general practitioners supplies laxatives.

Although problems of drug compliance are common to all groups of patients,^{1,2} this study shows that poor compliance with analgesics was seldom due to misunderstanding of prescription directions. Instead, it was usually due to self-imposed underdosage by patients. The liaison health visitor recorded that this was often in the belief that the regular use, or use of larger doses of the drug, would reduce the efficacy of the drugs if the severity of the pain were to increase. In only one patient was drug abuse detected, with the consumption of a narcotic

analgesic in excessive amounts. Better education of the patient when prescribing the drug may obviate these problems. The high incidence of inadequately prescribed analgesia, as interpreted by the liaison health visitor, is important. It remains to be determined whether this is because of inadequate analgesic prescription by medical staff or inadequate description of the severity of the pain to the doctor. Probably, however, some patients minimise symptoms to avoid the addictive drugs about which they are concerned.

The liaison health visitor has therefore become an essential part of the oncology team, integrating the hospital and community services and supporting patients through chronic illness and toxic treatment by assessing their problems, anticipating their needs, and mobilising maximal support.

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T-cell dependent or T-cell independent polyclonal B-cell activators, with or without the addition of purified T cells from normal allogeneic donors. T cells from the patient, however, were able to support differentiation of IgA-secreting cells when co-cultivated with allogeneic B cells in a pokeweed-mitogen driven system. Thus, a B stem-cell maturation defect appears to be the underlying defect in the patient.

Selective IgA deficiency is often associated with a relative or even total lack of IgG2.⁴ In the donor-recipient pair described here, however, normal levels of IgG subclasses were found. Specific antibodies against carbohydrate antigens are normally mainly of the IgG2 subclass,⁷ although in children substantial amounts of specific IgG1 antibodies are also formed.⁸ Despite having normal IgG2 serum levels, however, both children showed a relative lack of specific IgG2 anti-carbohydrate antibodies. We have observed the same type of aberrant subclass distinction in occasional IgA-deficient adults (unpublished), which may suggest a defect more fundamental than a mere lack of IgA.

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Correspondence should be addressed to L. H., Department of Clinical Immunology (F79), Huddinge Hospital, S-141 86 Huddinge, Sweden.

INCREASED VASCULAR PERMEABILITY: A MAJOR CAUSE OF HYPOALBUMINAEMIA IN DISEASE AND INJURY

A. FLECK* GAIL RAINES†
FELICITY HAWKER‡ J. TROTTER§
P. I. WALLACE|| I. MCA. LEDINGHAM¶
K. C. CALMAN**

Departments of Pathological Biochemistry, Anaesthetics, and Surgery and Oncology, Western Infirmary, Glasgow G11 6NT

Summary The rate of loss of albumin to the tissue spaces (measured as transcapillary escape rate) rose by more than 300% in patients with septic shock, and the average increase within 7 h of cardiac surgery was 100%. The transcapillary escape rate in cachectic cancer patients was twice that of a group of healthy individuals. The rate of loss of albumin to the tissue spaces is normally 5%/h, which is more than 10 times the rates of synthesis and catabolism, and these large rate increases indicate that increased vascular permeability is an important cause of the lowered concentration of albumin commonly seen in acute and chronic disease.

Introduction

THE concentration of albumin in plasma is commonly below normal during infection,¹ after injury (including

Present addresses: Department of Chemical Pathology,* Charing Cross and Westminster Medical School, St Dunstan's Road, London W6 8RF. Department of Chemical Pathology,† Royal Liverpool Hospital, Prescott Street, Liverpool L7 8XW. The Paramatte Hospital,‡ Westmead Centre, Westmead, New South Wales, 2145, Australia. Department of Medical Oncology,§ Royal Perth Hospital, Box X2213 GPO, Perth, Western Australia 6001. Anaesthetic Department|| and Department of Surgery,¶ Western Infirmary, Glasgow G11 6NT. Department of Clinical Oncology,** Glasgow University, 1 Horselethill Road, Glasgow G12 8QQ.

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elective surgery)² and myocardial infarction,³ in patients with malignant disease,⁴ and in critically ill patients.⁵

The factors which determine the concentration of circulating proteins include: changes in circulating fluid volume, exchange with or loss to the extravascular tissue space, lymphatic return, catabolism, synthesis, and losses.⁶

The daily loss of albumin to the extravascular spaces (5%/h in healthy individuals⁷) can be determined by measuring the transcapillary escape rate (TER) of albumin. Slight increases in the loss of albumin to the tissue spaces have been reported in hypertensives⁸ and diabetics.⁷ There have been few, if any, attempts to measure the return flow of protein in lymph to the circulating blood in disease in human beings, and reliable determination of the concentration of proteins in the extracellular fluid presents many problems.⁹

10% of the intravascular albumin is catabolised or replaced by synthesis each day in healthy subjects,^{10,11} but the rate of loss to, or exchange with, the tissue spaces is more than 10 times greater.^{6,10} In the present study we determined whether increases in TER occur in acute and chronic disorders which are commonly associated with hypoalbuminaemia.

Daily losses of albumin in the urine¹² or from the gut¹³ seem to be rarely more than about 30 g/day. Losses with haemorrhage are usually replaced within about 3 days¹⁴ and in elective surgery are rarely more than 1 litre.¹⁵ Thus, although haemorrhage or other losses may contribute to the reduction in the concentration of plasma albumin after injury, change in vascular permeability may be the most important cause of hypoalbuminaemia in many diseases.

Subjects and Methods

The "normal" range of the TER of albumin was determined in 7 laboratory staff and before operation in 3 patients admitted for minor elective surgery who had no signs of infection or active disease. TER was measured at various intervals up to 17 days after the onset of septic shock¹⁶ in patients in the intensive care unit.

TER was also measured in 16 patients within 7 h after the start of cardiopulmonary bypass for coronary-artery vein graft, mitral-valve replacement, or aortic-valve replacement and in a group of 11 cachectic cancer patients, most of whom had metastases and all of whom had a subnormal plasma albumin concentration (less than 31 g/l). None of the patients had hypertension, which increases TER;⁸ the patients with septic shock and cardiopulmonary bypass patients were slightly hypotensive. Blood loss from the wound site in the septic-shock and cardiac-surgery patients made a negligible contribution to the lowered plasma albumin concentration. Changes in fluid volume were unrelated to the low albumin concentration in the cardiopulmonary bypass patients. Loss of albumin in wound drainage was negligible in the septic-shock patients. In all patients proteinuria was absent or scarcely detectable. In those with fistulae, no albumin was found in the fistula fluid.

TER was measured by means of either autologous radioiodinated human plasma albumin or albumin prepared from an Australian-antigen-free pool.⁸ Thyroid uptake of radioactive iodine was blocked either by giving sterile sodium iodide intravenously, initially at a rate of 180 mg/24 h then 120 mg/24 h for up to 2 weeks, or by oral administration of 60 mg potassium iodide, initially 3 times daily then twice daily for 2 weeks.

After insertion of an intravenous 'Cathlon' cannula into a forearm vein to facilitate frequent blood sampling, 5–10 μ Ci sterile radioiodine-labelled albumin was rapidly injected into the opposite arm. 14.2 ml blood samples were taken at 3, 6, 9, 12, and 15 min after injection then at 5-min intervals up to 60 min. The exact time of sampling was noted.

The radioactivity of the plasma samples was measured by pipetting 0.75 ml plasma into the sample tube with an 'Oxford pipette', the accuracy of which had been carefully determined beforehand. After correction for background the counts were plotted semilogarithmically against time. The gradient of the line was calculated with the least squares method after eliminating any grossly deviant points. All TER values were obtained from lines computed from at least 5 data points. The gradient, expressed as %/h, gave the TER.

To avoid even slight denaturation, albumin was prepared by ammonium sulphate precipitation¹⁷ and labelled with McFarlane's iodine monochloride method¹⁸ to not more than 2 atoms of iodine per molecule of albumin. After iodination 2 ml of the patient's plasma, which had been kept sterile, was added, and the labelled albumin re-isolated by repeating the salt fractionation to minimise the proportion of non-albumin iodine-labelled proteins present. The final preparation was sterile filtered before use and a sample tested to exclude bacterial contamination and pyrogen.

Results

There were no significant differences either in plasma albumin concentration or TER between the 6 healthy men and 4 healthy women. The median normal range of TER of albumin in these 10 subjects was 5.0%/h with an overall range of 4.4–6.1%/h. This is within the range found by others for healthy individuals.⁸ This was not the case when a commercial source of radioiodinated albumin was used, and so we prepared, labelled, and tested human albumin for this study. The median plasma albumin concentration in the healthy subjects was 43.5 g/l (range 42–47 g/l).

In the disorders studied, or after operation, the concentration of albumin in patients' plasma was either clearly subnormal or close to the lower limit of the accepted normal range of 35–50 g/l.¹⁹

The changes in TER after septic shock are shown in fig 1. TER was initially elevated in all patients by at least 200%, but after the first 2 days the TER fell towards normal. The wider range and levels of TER observed in 5 patients between days 6–17 after the shock episode may be due to recurrence of infection. The numbers of patients in whom TER was determined from days 0 to 5 were: 6, 2, 4, 3, 3, and 3, respectively. The measurements at day 0 were made within 24 h after the

onset of shock, at which time the mean and median values were 13.4%/h and 11.1%/h, respectively. The values of TER in these patients in shock are significantly different from those for the 10 healthy subjects—eg, comparing the values on day 0 with those for the healthy subjects gives $t=4.61$, 14 df; and for day 5, $t=4.30$, 11 df.

In 4 patients with septic shock who had received steroids (methylprednisolone 30 mg/kg) TER was close to normal within 24 h of the onset of shock. This was in contrast to the larger group not given steroids. The patient, given steroids, in whom the TER was marginally raised (7%/h) had not received steroids until 2 days after the onset of shock. 3 patients who had received a single dose of steroids 3, 4, and 17 days before the measurement had raised TER, 10.1%/h, 15.5%/h and 10.8%/h, respectively, and were not classified with the group given steroids.

Comparisons of preoperative and postoperative measurements of TER and albumin concentration in plasma in the cardiopulmonary bypass groups of patients are shown in fig 2.

After operation TER had risen considerably, in some cases by 300% in 3 h. Plotting the change in TER (ie, postoperative value minus preoperative) against time did not show a clear

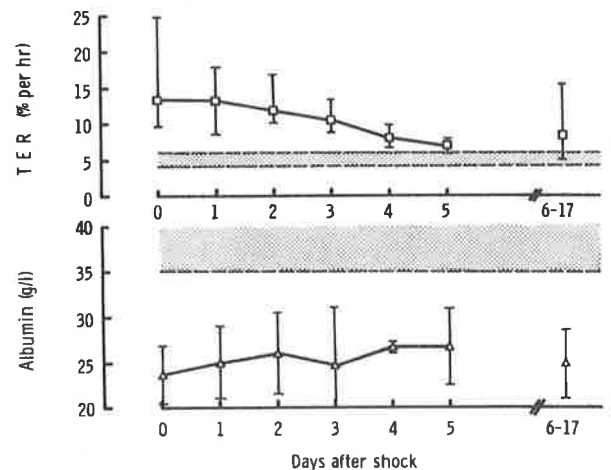


Fig 1—Transcapillary escape rate and plasma albumin concentration in septic shock.

Data are shown as mean \pm range. Shaded areas indicate normal reference ranges.

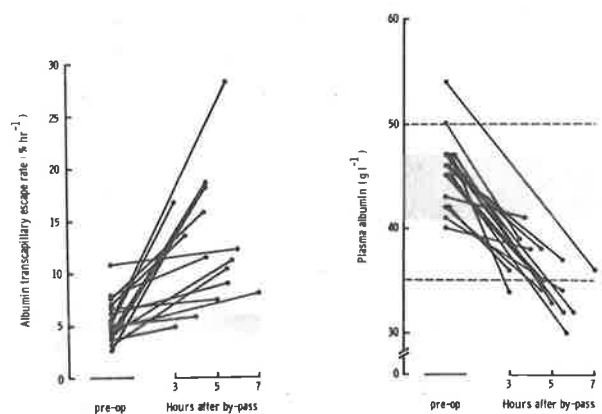


Fig 2—Transcapillary escape rate and plasma albumin concentration after surgical operation.

Individual values are shown. The shaded areas indicate the normal reference ranges.

pattern of increase in postoperative TER with elapsed time after the start of the bypass.

Analysis of variance indicated that there were no significant differences between any of the 3 cardiac-surgery operative groups in preoperative or postoperative albumin concentration, TER, or time of measuring TER after bypass had begun, which was on average 75 min after the first skin incision. We concluded that it would be acceptable to group the results from all 16 of the cardiac surgery patients together.

9 out of the 11 patients with cancer cachexia had a significantly raised TER: median 12.1%/h, range 5.6–26.4%/h. The corresponding concentrations of albumin in serum were: median 25 g/l, range 20–30 g/l. There were 2 exceptions with normal TER. These were the only patients with cancer (of the oesophagus) in this series to show a response to nasogastric tube feeding.

Discussion

To determine the normal range of TER of albumin it is essential that the labelled albumin preparation used is not denatured, otherwise slightly elevated values of TER will result.⁸ We used autologous albumin where possible, or undenatured albumin carefully prepared from Australia-antigen-free blood donors.

Cardiac surgery leads to a prompt (within 3 h) increase in TER. Thus, although some patients were in mild congestive cardiac failure before surgery, which could have contributed to the raised preoperative TER observed in 5 of the 16 patients,²⁰ TER did not fall in any patient after surgery. Since fluid replacement was only equivalent to measured losses the increase in TER was due to the response to tissue damage and not to haemodynamic changes, although a small amount of haemodilution could have contributed to the fall in the concentration of albumin.

Our results indicate that, in patients with sepsis and cancer, while processes leading to tissue damage continue TER is likely to be raised. However, in patients treated for septic shock it is likely that elevated TER falls (fig 1) in response to effective treatment. Although it appears from fig 1 that as TER falls towards normal the concentration of albumin rises, we did not find a significant correlation between these 2 variables. The infusion of large volumes of crystalloid solutions to maintain central venous pressure and cardiac output might in part account for this.

The pattern of the changes in TER shown here is in contrast with the changes of the acute-phase response. The acute-phase plasma proteins do not show an increase in concentration until 7 h after the first skin incision of elective surgery,^{21,22} whereas TER in this series was raised within 3 h of the first skin incision. Also, after minor surgery, such as herniorrhaphy, although the acute-phase response is clearly demonstrable there is no fall in the concentration of albumin.²¹ This is consistent with the failure to find a change in TER of albumin after minor surgery (Moore P., personal communication). Thus, although the increase in TER after surgery is less sensitive to the magnitude of injury than the acute-phase response, it occurs earlier.

An increased leakage of albumin into the extravascular spaces will reduce the oncotic pressure difference across the walls of small blood vessels and must alter the exchange of water between blood vessels and tissues, so that oedema is more likely. Thus, it is possible that an increase in TER is an important factor in the development and maintenance of

oedema in septic shock and, if the pulmonary capillaries are equally affected, in adult respiratory distress syndrome.²³

Although we have measured TER, the value obtained includes a contribution from catabolism, which is about 10% of the total in healthy individuals and in patients in septic shock. It may include an undetermined contribution from losses—eg, from the gut or in urine. Thus, in septic shock the raised value of the TER of albumin merely gives a combined index of pathological processes which influence the concentration of albumin, but the true rate of loss of albumin to the extravascular space is likely to make the greatest contribution to this value.

An increase in TER may be followed by an increase in lymph flow of both fluid and protein,^{24,25} but this is not enough to maintain or return to normal the ratio of extravascular to intravascular albumin, increases in which have been noted after burning injury²⁴ and surgery²⁶ and which would inevitably follow increased microvascular permeability. In addition, when the mass of extravascular protein increases the mass flow of protein in the lymph will rise,⁶ hence it is the fractional rate of return of protein from the tissue spaces which would have to increase for there to be an ameliorative effect on the concentration of protein in plasma.²⁷

Although our data do not permit a clear delineation of the duration of the changes in TER after uncomplicated surgery, we have shown that increased microvascular permeability is an important cause of hypoalbuminaemia in serious acute and chronic disease.

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RENAL FAILURE AND THE USE OF MORPHINE IN INTENSIVE CARE

MADELEINE BALL
R. A. MOORE
A. FISHER

H. J. MCQUAY
M. C. ALLEN
J. SEAR

Nuffield Departments of Clinical Biochemistry and Anaesthetics, John Radcliffe Hospital and Radcliffe Infirmary, Oxford; and Oxford Regional Pain Relief Unit, Abingdon Hospital, Abingdon, Oxon

Summary Intravenous morphine infusions were given to 20 patients in the intensive-care unit to provide sedation and analgesia. In 10 of the patients renal impairment was already present or developed during intensive care. Plasma morphine concentrations for a given dose of morphine and morphine clearance depended on renal function; dose-related plasma morphine concentrations rose as renal function deteriorated. Reduced morphine clearance leads to increased elimination half-life of the drug, and neurological impairment caused by unrecognised high concentrations of morphine could result in an incorrect diagnosis of cerebral damage in patients in intensive care.

Introduction

A NUMBER of drugs used for sedation in the intensive-care unit (ITU) have lately been withdrawn.¹ As a result there has been an increase in the use of opiates, particularly morphine.² However, many ITU patients who require sedation also have renal or hepatic impairment, which could interfere with morphine metabolism, leading to high plasma morphine concentrations and impaired recovery.

Drugs of the morphine family can cause respiratory depression of unexpected degree and duration in patients with renal impairment.^{3,4} Cancer patients with raised plasma creatinine levels need less morphine for pain relief.⁵ The implication is that morphine elimination is reduced in renal failure.

Evidence for the dependence of morphine elimination on intact renal function came from studies in renal-transplant patients, in whom no morphine elimination occurred until the donor kidney began to function.⁶ This suggested that there was little or no hepatic involvement in morphine elimination at therapeutic concentrations, and this view has been strengthened by clinical⁷ and experimental⁸ work.

ITU patients may be given high doses of drugs, over long periods; many have hepatic or renal complications, or both. Understanding the physiological background of drug elimination is important in these circumstances, because it may help the interpretation of otherwise unexpected clinical events which may have dire consequences for the patient. Morphine is a particularly important example because of its widespread use in intensive care and because of controversy about the mechanism of its elimination in man.⁹ This study investigated plasma morphine concentrations during intravenous morphine infusions in intensive-care patients with or without renal or hepatic dysfunction.

Patients and Methods

20 patients were investigated while receiving intravenous morphine infusions in the intensive-care unit of the John Radcliffe Hospital, the study having been approved by the local ethics committee. Patients were considered to have abnormal renal function if the plasma creatinine was above 140 $\mu\text{mol/l}$. 8 patients had abnormal renal function on admission, renal failure developed in 2 on the unit, and the other 10 had normal renal function throughout their stay. Patients were considered to have normal liver function if plasma concentrations of bilirubin, aspartate transaminase, γ -glutamyl transaminase, and alkaline phosphatase were within the normal range for the laboratory; elevation of unconjugated bilirubin and aspartate transaminase following blood transfusion or surgery were not regarded as indicating liver disease.

Arterial blood samples were taken from an indwelling arterial catheter at the same time as routine biochemistry and haematology; this was usually at 8 AM and 4 PM. Haemodialysis, when required, was done against 'Renalyte', using a hollow-fibre dialyser for 3 h; additional blood samples were collected before and after dialysis.

Creatinine was measured on an American Monitor Parallel analyser using the kinetic Jaffe reaction. Plasma morphine was measured with specific radioimmunoassay¹⁰ using a method shown not to cross-react with the main morphine metabolite, morphine-3-glucuronide. Morphine clearance (in ml/min/kg) was calculated by dividing 1000 times the morphine infusion rate over the previous 4 h (in nmol/min) by the product of morphine plasma concentration (nmol/l) and the patient's weight (in kg).

Results

Details of the patients are given in the table. 13 of the 20 patients required sedation for ventilation after surgery, 4 had respiratory disorders, 2 had multiple trauma, and 1 had pancreatitis.

10 patients had no renal or hepatic complications, and these were studied for 1 to 8 days. The median 4-hourly morphine

DETAILS OF PATIENTS

Patient no	Sex	Age (yr)	Weight (kg)	Condition
<i>Normal renal function:</i>				
1	F	62	68	Pneumonia
2	M	62	76	Oesophagogastrrectomy
3	F	70	68	Total hip replacement
4	M	58	70	Bowel resection (Crohn's)
5	M	35	69	Gastrectomy (Crohn's)
6	M	79	79	Aortic aneurysm repair
7	M	74	85	Aortic valve replacement
8	F	73	70	Mitral valve replacement
9	M	20	67	Road traffic accident
10	M	75	50	Aortic valve replacement
<i>Renal dysfunction:</i>				
11	F	73	71	Road traffic accident
12	M	59	67	Pneumonia
13	M	63	75	Aortic aneurysm repair
14	M	52	81	Respiratory/renal failure
15	M	77	73	Aortic valve replacement
16	F	72	60	Pancreatitis
17	M	64	76	Aortic aneurysm repair
18	M	60	97	Aortic valve replacement
19	F	69	54	Aortic valve replacement
20	M	51	70	Pneumonia

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suggest that ibuprofen has minor effects on the cardiovascular system, but our experience points to the contrary.

Care should be exercised in prescribing ibuprofen to people who are liable to take overdoses.

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¹ Adams SS, Bough RG, Cliffe EE, *et al.* Absorption and distribution and toxicity of ibuprofen. *Toxicol Appl Pharmacol* 1969;15:310-30.

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Department of Medicine, Hope Hospital, Salford M6 8HD

DIANA P HUNT, MB, CHB, senior house officer
RICHARD J LEIGH, MB, MRCP, tutor in medicine

Plasma exchange to control sweats and pruritus in malignant disease

Pruritus and sweating attacks in malignant diseases such as the lymphomas are well recognised and disappear with successful treatment of the malignancy. Cimetidine, a potent histamine H₂-receptor antagonist, controls these symptoms in Hodgkin's disease,¹ but their pathogenesis is not explained. If pruritus and sweating were caused by metabolically active substances released into the plasma by the tumour such substances might be removed by plasma exchange.² We have tested this idea and report our preliminary findings.

Case reports

Case 1—A 54-year-old woman had non-Hodgkin's lymphoma (diffuse poorly differentiated lymphocytic) diagnosed in October 1977. She had left supraclavicular and epigastric masses and complained of general ill health and severe generalised itch. She initially responded well to cyclical administration of mustine hydrochloride, vinblastine, procarbazine, and prednisolone, with disappearance of the itch; but this and subsequent responses to chlorambucil, vinblastine, procarbazine, and prednisolone and then doxorubicin, bleomycin, vincristine, and dacarbazine were not maintained. In autumn 1979 she received palliative radiotherapy to an abdominal mass. General ill health, wasting, and intractable itch continued, the itch being unrelieved by cimetidine 800 mg daily. A therapeutic trial of plasma exchange was conducted with a Hemonetics model 30 cell processor, with human pooled fresh-frozen plasma as replacement solution. On the first occasion 4.9 l plasma was removed, and eight days later 4.3 l. Itching disappeared after the first exchange and remained virtually absent for several weeks. No other treatment was given. She died two months after the plasma exchange.

Case 2—A 53-year-old man had a left nephrectomy for renal carcinoma in April 1979. Radiography showed numerous small discrete lung metastases and he was treated for four months with iphosphamide at three-week intervals, with no evidence of progression. Lung metastases then enlarged and tamoxifen was substituted but discontinued after only two months because of progressive disease. There was a painless mass in the nephrectomy scar 5 × 4.5 cm. His only notable symptom was severe night sweats. Plasma exchange performed as in case 1 (3.4 l plasma removed initially) resulted in an immediate and sustained reduction in the number and severity of night sweats, with only light sweating occurring not more than twice weekly. Four further plasma exchanges (3.3, 4.6, 4.0, and 3.6 l) were conducted over the next nine weeks. The mass in the nephrectomy scar regressed to 4 × 3 cm, but the lung metastases continued to enlarge. No other treatment was given. Medroxyprogesterone acetate 100 mg thrice daily was prescribed two weeks after the fifth plasma exchange, though the light sweating at night had not increased beyond twice a week.

Comment

From these observations plasma exchange may control severe itching or sweating in advanced malignancy when drugs have failed to do so. This apparently confirms the suggestion that itching and sweating are caused by circulating factors produced by the tumour or as a host response, though it does not exclude the possible effect of an active blocking factor added by the fresh-frozen plasma. The results justify further investigation of plasma exchange to elucidate the

mechanisms producing the symptoms. It may be possible to isolate circulating factors in extracorporeal blood with in-series selective affinity columns³ and use dialysis of exchanged plasma to establish their nature and physical characteristics.

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University Department of Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY

D SHAW, MD, MRCP, lecturer in therapeutics

University Department of Clinical Oncology, Gartnavel General Hospital, Glasgow G12 9LY

J M TROTTER, MB, FRACP, research fellow

K C CALMAN, MD, PHD, professor of clinical oncology, Cancer Research Campaign

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