ENERGY EXPENDITURE AND SUBSTRATE METABOLISM IN PATIENTS WITH CANCER AND WEIGHT LOSS

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Dedicated to

my wife and parents.

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LIST OF ABBREVIATIONS

The following abbreviations are used in this thesis:

REE	Resting energy expenditure
RQ	Respiratory quotient
LBM	Lean body mass
$\dot{V}O_2$	Oxygen consumption
$\dot{V}CO_2$	Carbon dioxide production
A-P	Abdomino-perineal
CI	Confidence interval
s.e.m.	standard error of the mean
HB	Harris-Benedict
KL	Kleiber
RR	Robertson-Reid
FL	Fleisch
MAMC	Mid-arm muscle circumference
MAC	Mid-arm circumference
TST	Triceps skinfold thickness
TPN	Total parenteral nutrition
DS	Dextrose-saline
AA	Amino acid
GAF	Glucose-amino acid-fat

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DECLARATION OF WORK PUBLISHED AND PRESENTED

Some of the work contained in this thesis is currently under consideration by scientific journals. Listed below are the publications, published abstracts and presentations to societies to date.

Publications

(1) Hansell DT, Davies JWL, Burns HJG.
The relationship between resting energy expenditure and weight loss in benign and malignant disease.
Annals of Surgery 1986; 203: 240-5.

(2) Hansell DT, Davies JWL, Burns HJG.
The effects of hepatic metastases on resting energy expenditure in patients with colorectal cancer.
British Journal of Surgery (in press).

(3) Hansell DT, Davies JWL, Burns HJG.
The effects on resting energy expenditure of different tumour types.
Cancer (in press).

(4) Hansell DT, Davies JWL, Shenkin A, Burns HJG.
The oxidation of body fuel stores in cancer patients.
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The following papers have been presented and published in abstract form where indicated.

(1) Hansell DT.
Energy balance in cancer patients.
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(2) Hansell DT, Davies JWL.
Inaccuracy of Harris-Benedict formula in weight-losing patients.
MRC Critical Care Meeting, Manchester - September 1984.
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Surgical Metabolic Group, Glasgow - November 1985.

(14) Hansell DT, Davies JWL, Shenkin A, Garden OJ, Burns HJG.
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(15) Hansell DT, Davies JWL, Shenkin A, Garden OJ, Burns HJG.
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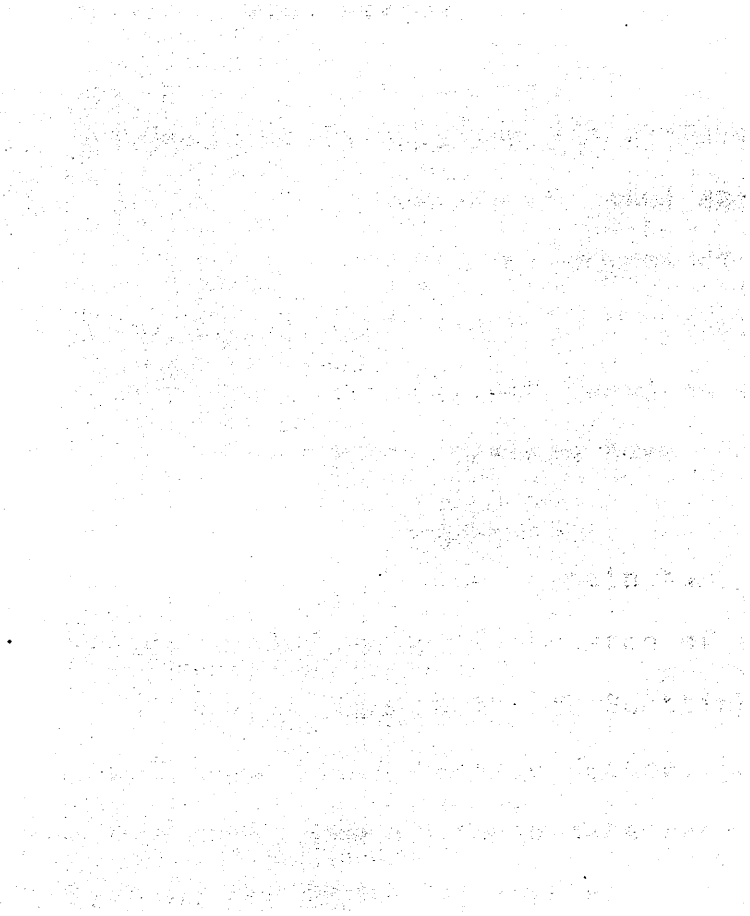

STATEMENT OF COLLABORATION

All study designs were constructed by myself with advice from Professor D.C. Carter, Mr. H.J.G. Burns and Dr. J.W.L. Davies. The study design involving the investigation of peripherally-administered intravenous nutrition was constructed with the assistance of Mr. O.J. Garden.

All calorimetry measurements were performed by myself and Dr. J.W.L. Davies.

All blood and urine sampling was performed by myself. The initial processing of these samples was performed by myself, with the assistance of the laboratory technical staff later in the project. Biochemical measurements were performed in the Department of Biochemistry, Glasgow Royal Infirmary.

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All the references cited in the text have been read by myself.

The entire contents of this thesis, including tables and figures, have been typed by myself using the Apple II Word Processing Programme, the PFS Graph Programme and a plotting programme designed in the University Department of Surgery.

SUMMARY

Cachexia is commonly seen in patients with cancer, and there is evidence to suggest that these debilitated cancer patients are at an increased risk of morbidity and mortality following surgical procedures.

This thesis is concerned with two main avenues of investigation. In the first part, various mechanisms implicated in the development of cancer cachexia have been investigated in weight stable and weight losing patients with cancer and nonmalignant illness. The second part is concerned with ways of influencing the metabolic response in cancer patients undergoing moderate and major surgical procedures.

Energy and substrate metabolism have been investigated in weight stable and weight losing patients with recently diagnosed cancer and nonmalignant illness. Colorectal, gastric and non-small cell bronchial cancer were the commonest types of tumour present in the patients with malignant disease. Cholelithiasis, peptic ulceration and benign colorectal polyps were the commonest benign diseases.

These studies involve the measurement of resting energy expenditure (REE) using an accurate indirect calorimeter designed and built in the Department of Surgery in 1979. Measurements of oxygen consumption, carbon dioxide production and urinary nitrogen

excretion provided the rates of fat and carbohydrate oxidation. Protein turnover was measured using a primed, continuous 24 hour infusion of ^{15}N-glycine.

The studies have shown that patients with cancer do not have significant elevations of REE compared with patients with nonmalignant illness. Abnormalities of REE appear to be more closely related to weight loss than to the presence of cancer, suggesting that the host's response to illness is a more important determinant of REE than the presence of cancer.

Patients with different types of tumour appear to show differing relationships between REE and body size, highlighting the possible disadvantages of using heterogeneous groups of cancer patients in studies of REE. The longitudinal study of patients before and after surgery for colorectal cancer, which showed no significant differences in REE either following a curative resection or progression of hepatic metastatic disease, provides further evidence that REE is not affected by cancer or increasing tumour burden.

The inability of commonly used predictive formulae to provide an accurate estimate of REE in many patients has been demonstrated. It is concluded that subtle differences in body composition of ill patients compared with healthy individuals from which these

formulae were derived is responsible for these inaccuracies. An alternative method of estimating REE, namely, the anthropometric measurement of mid-arm muscle circumference, has been investigated. This measurement has been found to correlate closely with REE, but prospective evaluation of the derived equations is required.

The inaccuracies associated with expressing REE in terms of body weight have been discussed. It is stressed that REE should be expressed in terms of the metabolically active portion of body weight. However, the possible errors associated with using either total body water or total body potassium measurements to estimate the mass of metabolically active tissue have been discussed.

Abnormalities in the metabolism of endogenous carbohydrate, fat and protein have been demonstrated in cancer patients. Decreased carbohydrate oxidation and increased fat oxidation occurs in patients with cancer, and are more pronounced in those patients with hepatic metastases. The increased fat oxidation rates may contribute significantly to the development of cancer cachexia, and may be related to the production by the tumour-bearing host of cachectin, which has been shown to interfere with fat metabolism. Patients with colorectal and bronchial cancer have increased rates of whole body protein turnover (WBPT) compared

with patients who have gastric cancer or nonmalignant illness. However, this increased rate of WBPT is not related to weight loss and has no detectable effect on REE.

The possibility that an acute phase protein response is responsible for some of these metabolic abnormalities has been discussed. This phenomenon would be consistent with the finding that abnormalities of REE appeared to be related more closely to weight loss than to the presence of cancer. It would also be consistent with the abnormalities seen in fat metabolism, possibly mediated through cachectin production.

In the second part of the thesis, the effects on the metabolic response to surgery of peripherally-administered intravenous nutrition and pharmacological manipulation have been investigated in patients undergoing surgery for colorectal or gastric cancer.

The postoperative administration of a peripheral intravenous nutritional regimen containing glucose, amino acids and fat to patients with colorectal cancer results in a positive nitrogen balance with minimal phlebitic complications. Although the administration of amino acids alone results in body fat mobilisation, it has only a transient effect on postoperative

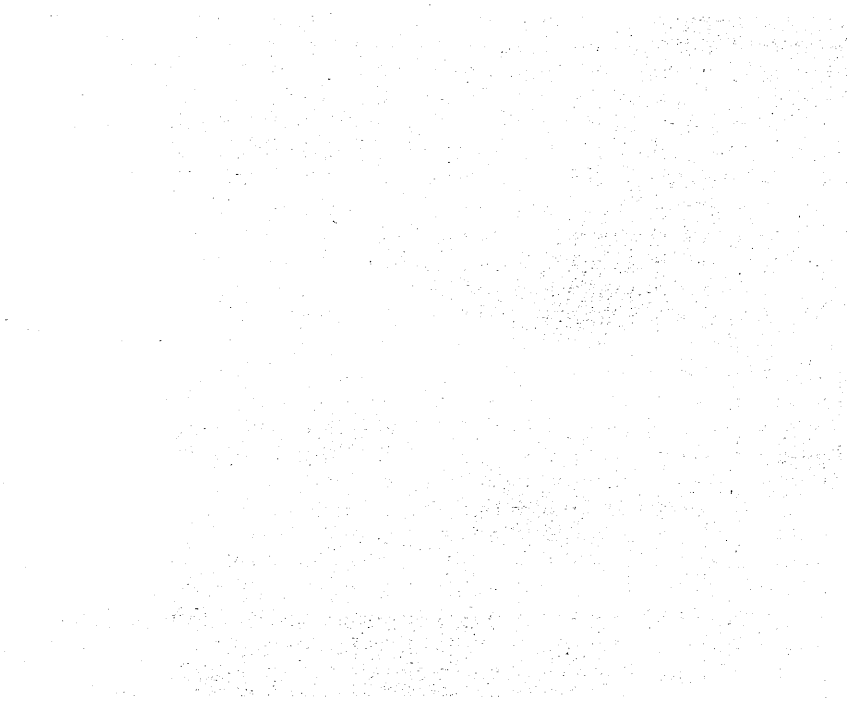
nitrogen balance, and has little to offer compared with a standard dextrose-saline regimen. It is concluded that where the provision of postoperative peripherally-administered intravenous nutrition is desired, the use of a nutritional mixture containing glucose, amino acids and fat should be used.

The use of the anabolic steroid stanozolol appears to improve postoperative nitrogen balance in patients receiving amino acid solutions following colorectal surgery. There is also a trend towards improved postoperative nitrogen balance in patients receiving a combination of glucose, amino acids and fat.

In patients receiving a dextrose-saline regimen following gastric surgery, stanozolol appears to result in a late improvement in postoperative nitrogen balance. While naftidrofuryl had no demonstrable effect on postoperative nitrogen balance, both this agent and stanozolol may have some infuence on endogenous fat metabolism. It is possible that alteration of the dose or timing of administration of stanozolol and naftidrofuryl may enhance their effects on the metabolic response to surgery and it is recommended that further investigation of these agents is warranted.

In conclusion, various abnormalities in the

metabolism of patients with cancer have been identified, some of which may contribute to the development of cancer cachexia. It has been shown that postoperative nitrogen losses can be reduced in cancer patients using peripherally-administered intravenous nutritional support. There is also some evidence to suggest that pharmacological manipulation of the metabolic response to surgery using stanozolol and naftidrofuryl may improve postoperative nitrogen balance and influence substrate metabolism in these patients.



CHAPTER 1

INTRODUCTION AND AIMS OF THE THESIS

INTRODUCTION

Cachexia is commonly seen in patients with cancer (1,2), and various contributing factors have been implicated in its development. Anorexia is often present and inevitably contributes significantly to the wasting process (3,4), but there are some cancer patients who exhibit severe weight loss despite a reasonable dietary intake (5). Abnormalities of energy and substrate metabolism may play an important role in the development of the cachectic state (6-9), although there are many poorly controlled studies and conflicting reports in the literature (10-12).

There is some evidence to suggest that debilitated cancer patients undergoing surgery are at increased risk of morbidity and mortality (13-14), and consequently many studies have investigated ways of improving the nutritional status or minimising the deleterious effects of the catabolic response to surgery in these patients. Intravenous nutrition has been shown to improve nutritional status preoperatively and postoperatively, but no consistent benefit to clinical outcome has been demonstrated (15-17). An alternative approach involves the pharmacological manipulation of the metabolic response to trauma, in an effort to minimise postoperative nitrogen and protein losses. Anabolic steroids (18,19), growth hormone (20), and naftidrofuryl (21)

have been shown in some studies to improve postoperative nitrogen balance but, as with nutritional support, there is little evidence to suggest that this confers significant benefit to the patient in terms of clinical outcome.

The aims of this thesis, therefore, are:

a) To assess the effects of cancer, weight loss, tumour type and tumour burden on the resting energy expenditure of patients with malignant disease.

b) To assess the accuracy of predictive formulae and anthropometric measurements in the assessment of REE.

c) To assess the effects of cancer and weight loss on the metabolism of endogenous protein, carbohydrate and fat in patients with malignant disease.

d) To assess the effects of different peripherally-administered intravenous nutritional regimens in patients following surgery for colorectal cancer.

e) To assess the effects of pharmacological manipulation of the metabolic response to trauma in patients undergoing surgery for colorectal and gastric cancer.

CHAPTER 2

HISTORICAL REVIEW OF THE LITERATURE

CANCER CACHEXIA

Cachexia, characterised by marked asthenia with loss of both body fat and protein, is a common finding in cancer patients (1,2). Indeed, in a study of 500 autopsies on cancer patients, Warren (22) reported that cachexia was the commonest single cause of death. It accounted for more than 22% of the deaths, particularly in patients with breast, colon and gastric cancer. Several causes have been implicated. For example, anorexia and mechanical obstruction of the gastrointestinal tract result in a decreased food intake which leads to weight loss (3,4,23). However, many cancer patients maintain a reasonable intake but continue to lose weight (5).

Several causes for this weight loss have been suggested. Alterations in energy metabolism of the tumour-bearing host have been implicated, with many reports (6-8) suggesting that cancer patients have a raised resting energy expenditure (REE). Abnormalities of protein, carbohydrate and fat metabolism have been noted in tumour-bearing patients (2,9). It has also been postulated that tumours may produce metabolites which may interfere with normal enzyme function (2). These abnormalities of substrate metabolism may lead directly to weight loss, or they may affect REE by involving the host in wasteful metabolic pathways which deplete the energy resources of the

tumour-bearing host.

Energy metabolism

The basal metabolic rate (BMR) is defined as the energy output of an individual who is bodily and mentally at rest, more than 12 hours after a meal and in a neutral thermal environment (24). Since these conditions are difficult to achieve, particularly in hospitalised patients, resting metabolic rate (RMR) or resting energy expenditure (REE) is more commonly measured. REE is determined in an individual lying at rest, two to four hours after a light breakfast (25). This measurement represents energy which is produced by the combustion of body fuels for the metabolic processes involved in the maintenence of body cell function and the integrity of the host.

A raised REE has been implicated repeatedly as a factor in the development of cancer cachexia (6-8). However, many of these reports, particularly the earlier ones, were anecdotal, and some more recent studies of REE in cancer have omitted the use of control groups (8,26). In many instances where controls have been studied, they have been young, healthy individuals not strictly comparable with the older hospitalised cancer patients (27). Furthermore, the methods of measuring REE have changed considerably

over the years and even today some of the techniques employed have considerable disadvantages (see Chapter 3).

One of the earliest studies of REE in cancer patients was published in 1914 by Wallersteiner (28), who measured the exchange of oxygen and carbon dioxide in 33 patients, most of whom had gastric cancer. Fifteen patients had REE values greater than his chosen reference value (30kcal/kg body weight/day), 16 patients had values between 26-30kcal/kg body weight/day, and two patients had low REE values. REE fell in one patient following surgical removal of the tumour, but increased when the tumour recurred.

Many of the early reports suggesting that cancer was associated with a raised REE involved patients with leukaemia (29-31). Shortly thereafter, other malignancies were reported to have similar effects on REE (32,33). However, there were few controlled studies until recently. In 1978 Warnold and colleagues (34) compared ten heterogeneous cancer patients with nine hospitalised patients with nonmalignant illness who were of a comparable age. REE was calculated from measurement of heart rate and was related to separate measurements of oxygen uptake at different levels of heart rate. They reported a mean REE in the cancer patients of 1630 kcal/day compared with 1170 kcal/day in the control patients. When a

further study was performed at the same centre using a more sophisticated indirect calorimeter (35), a small (148 kcal/day) but significant increase in REE was found in cancer patients, particularly in those who had lost weight.

Macfie and colleagues (27) also reported a small increase in REE but only patients with metastatic disease had an REE significantly greater (289 kcal/day) than that of their younger control group. Other workers have also reported an association between increased REE and metastatic disease or tumour load. For example, in 1921 Gunderson (36) found that the elevation in REE correlated with the proportion of immature cells in the circulation of patients with leukaemia. Arbeit and colleagues (11) compared 11 healthy controls with nine patients who had localised malignancies and four patients who had metastases. They found that all the cancer patients had a raised REE, especially those with metastatic disease. Furthermore, they claimed that REE fell following surgical excision of the tumour in four patients. A fall in REE following tumour removal or regression, and a rise following tumour recurrence, have been reported previously (6,28,37).

Some authors (26,38,39) have compared REE in cancer patients, not with control groups, but with a value predicted by the Harris-Benedict formula, which

was derived from the metabolic investigation of young healthy volunteers (40). Shike and colleagues (26), in a study of 31 patients with small cell bronchial cancer, found the mean REE to be significantly higher than predicted values, especially in those patients with metastases. Those patients who responded to chemotherapy showed a fall in REE. Dempsey and colleagues (39), in a study of 173 patients with gastrointestinal malignancies, made similar comparisons with the Harris-Benedict formula and found a wide range of values, with some patients apparently markedly "hypometabolic" and others "hypermetabolic". They concluded that tumour type was a major determinant of REE, with pancreatic and hepatic cancer patients tending to have low values and gastric cancer patients tending to have raised values. However, the accuracy of predictive formulae in estimating REE has been questioned. Roza and Shizgal (41) found the Harris-Benedict formula to be inaccurate in predicting REE in malnourished patients while Mullen and colleagues (42) found a wide error in prediction using the Harris-Benedict and Kleiber (43) predictive formulae.

Very few authors have reported an unchanged REE in cancer-bearing patients. Burke and colleagues (44) found no difference in REE between 42 patients with gastrointestinal cancer and 24 with benign gastrointestinal disease. They were also unable to

find any differences in dietary intake between the two groups. This relationship between dietary intake and REE has been studied extensively. There appear to be fundamental differences in the responses of REE to simple starvation compared with the anorexia associated with neoplastic disease. The usual response to a reduction in food intake in a patient with a nonmalignant illness is a reduction in oxygen consumption and hence REE (45). This occurs through a decreased requirement for ATP, the formation of triglycerides, fatty acids and glycogen which normally follow a transient excess of food intake being diminished. There is some evidence to suggest that there is loss of this starvation adaption in cancer patients who decrease their food intake and consequently lose weight (7,46,47). These patients therefore will have a relative increase in REE, since they have a decreased mass of body tissue.

It has also been suggested that in patients with cancer the REE actually increases in the presence of a decreased food intake (35,48). Indeed, Waterhouse (47) reported that glycolysis and oxidative metabolism persisted at increased rates in the postabsorptive state in cancer patients. It was suggested, however, that this relative or real increase in REE probably failed to account for all the observed calorie deficit. An increase in the amount of energy required to metabolize ingested nutrients and an increase in

the energy cost of performing routine daily activities have been proposed as possible factors which contribute to the increased REE in cancer patients (46). Furthermore, Fenninger and Mider (7) suggested that the normal REE and absence of weight loss seen in some patients with cancer may indicate that at certain stages of tumour growth REE was not increased, or that dietary intake could keep pace with an increased REE for some time during tumour growth.

Animal studies have provided evidence in support of some of the above hypotheses. For example, an increase in host REE following tumour transplantation in rats has been demonstrated (49). Furthermore, this increase can occur almost immediately following tumour transplantation and therefore before any significant tumour growth has occurred (50).

Resting energy expenditure is obviously related to the metabolism of protein, carbohydrate and fat (2), and various abnormalities in their metabolism have been identified in cancer patients. It has been suggested that these disorders could be responsible for at least a proportion of the supposed increase in REE seen in some patients with cancer (51).

Protein metabolism

The important relationship between protein metabolism and REE has been stressed repeatedly (28,51,52). The early studies of protein metabolism involved mainly measurements of nitrogen balance and the nitrogen content of tumours and other organs. For example, Mider and colleagues (53,54) and White (55) showed that the carcasses of rats in which Walker 256 carcinoma had been growing contained less nitrogen than matched controls. Furthermore, they showed that the total nitrogen content of the tumour was greater than the amount of ingested nitrogen, leading to the conclusion that some of the nitrogen in the tumour must have come from the tissues of the host. This theory was supported by Sherman and colleagues (56) who demonstrated a loss of nitrogen from most tissues during the growth of Walker 256 carcinoma in rats. The liver and spleen appeared to be exceptions to this phenomenon, initially gaining nitrogen.

Patient studies tended to agree with the conclusions drawn from the animal work. As early as 1914, Wallersteiner (28) reported nitrogen balances in 12 patients with advanced cancer which suggested that nitrogen retention occurred as tumour growth continued. Thirty four years later, Mider and colleagues (53) postulated that tumours acted as "nitrogen traps", whereby the incorporation of amino

acids into the tumour was a one-way mechanism, unlike the dynamic interchange between the amino acid pool and other host tissues. Various studies shortly thereafter supported this theory (6,57-59). Other workers suggested, however, that during tumour regression the nitrogen stored in the tumour could be used by the host (60). The limitations of nitrogen balance studies have been emphasised by the observation that some tumour-bearing patients could be in positive nitrogen balance but in negative energy balance, suggesting that tumours could perhaps store nitrogen even in the presence of a total energy deficit (6). Furthermore, even when nitrogen balance was positive, this did not necessarily imply that nitrogen was being stored uniformly in the host tissues (37).

Nitrogen balance studies, therefore, are a very crude way of determining the various aspects of protein metabolism. In contrast, the stable isotopes of nitrogen in leucine and glycine have provided estimates of protein metabolism in terms of protein turnover, synthesis and breakdown, not only for the body as a whole, but also for individual organs such as the liver and skeletal muscle (52,61-63). Young (51) emphasised the important association between protein metabolism and REE, estimating that protein turnover could account for as much as 50% of the host's REE. The response of protein turnover to a

reduced energy intake is similar to the response of REE, namely, it falls as energy intake falls (64). It has been suggested that this adaptive mechanism may be impaired in patients with malignant disease (1,65). Indeed, it has been reported that in some cancer patients the rate of whole body protein turnover is elevated (52,61,62,66,67). However, not all studies have shown this increase in patients with cancer (68,69).

The presence of a tumour affects protein metabolism differently in different organs. For example, decreased protein synthesis and increased protein breakdown have been demonstrated in skeletal muscle biopsies of patients with cancer (63,70), while an increase in liver protein synthesis was observed (63). Similarly, protein turnover studies in the liver and skeletal muscles of rats showed a decreased synthesis in skeletal muscle (71-71) and an increased synthesis in the liver (74). These results may explain the increased liver weight seen in tumour-bearing rats (75) and also the finding that the liver appeared not to lose nitrogen as readily as the other organs of rats with Walker 256 carcinoma (55). However, not all the increased protein synthesis in the liver is due to the synthesis of hepatic tissue protein. Scherstén and colleagues (76) suggested that a considerable proportion of the increased hepatic protein synthesis was due to the synthesis of acute phase reactants and

other proteins.

The nitrogen-retaining properties of tumours, referred to earlier in this section, have been confirmed by protein turnover studies, which showed that protein synthesis in rat tumours was greater than that of any other tissue studied (77), accounting for 25% of the total body protein synthesis. This increased protein synthesis in the tumour may be at the expense of protein synthesis in skeletal muscle, which accounts for over 50% of the whole body protein synthesis (74). Scherstén and colleagues (76) estimated that the increased protein synthesis in the liver and tumour of sarcoma-bearing mice accounted for approximately 20% of the energy deficit seen in these animals, and concluded that other metabolic abnormalities must contribute significantly to the development of cancer cachexia.

Carbohydrate metabolism

It has been recognised for many years that neoplastic cells have high rates of glucose utilisation associated with increased production of lactic acid (78,79). Waterhouse and colleagues (6) suggested that this disordered glucose metabolism may cause wasteful energy expenditure and contribute to the increased REE which she observed in patients with

leukaemia and Hodgkin's disease. Some years later Waterhouse (47) measured exogenous glucose utilisation following the administration of trace amounts of glucose, and showed enhanced production of glucose in cancer patients compared with controls. When exogenous glucose was administered over a prolonged period, the normally accelerated rate of disappearance of blood glucose (80) was slower in patients with cancer, due either to a slower rate of entry of glucose into cells or else a persistent increase in Cori cycle activity (81), which would be expected to decrease following glucose loading in normal subjects. It was concluded from these studies that cancer patients had a fixed rate of glucose utilisation which was unaffected by the ingestion of nutrients (47).

The lactic acid produced by glycolysis can either be utilised by host tissues or else resynthesised to glucose in the liver. This cyclical metabolism of glucose is known as the Cori cycle (81). If the glucose is utilised by host tissues, maximal energy production is achieved, whereas its resynthesis to glucose in the liver is an energy-consuming pathway (7,82). Increased Cori cycle activity has been reported frequently in cancer patients (47, 82-84) and some authors have claimed that this futile cycling significantly increases the REE of the tumour-bearing patient (7,83,85). Holroyde and colleagues (82), using radiolabelled glucose, studied glucose

metabolism in 14 patients with metastatic cancer, six of whom had lost no weight and eight of whom had progressive weight loss. The six weight stable patients had normal glucose metabolism, whereas those with progressive weight loss had increased glucose turnover, increased glucose oxidation and increased Cori cycle activity. These findings agree with other studies of glucose metabolism (47,82-84, 86). REE was greatest in three of the four patients with high Cori cycle activity, and they concluded that the energy loss associated with this increased futile cycling contributed to the development of cachexia. However, Young (51), reviewing Holroyde's data (82), calculated that Cori cycle activity accounted for less than 10% of daily REE.

Abnormalities of glucose metabolism other than disordered Cori cycle activity have been reported in tumour-bearing patients and animals. Increased glucose turnover has been demonstrated in patients (83,87) and rats (88) with cancer. Kokal and colleagues (89), in a study of 11 patients with colorectal cancer, concluded that glucose turnover was increased in Dukes C and D tumours compared with Dukes B tumours, but found no difference between the groups with respect to Cori cycle activity. Lundholm and colleagues (83) claimed that 80% of the increased glucose turnover was due to increased Cori cycle activity, the remainder being due to increased glucose oxidation, ketone formation and

lipid synthesis. They estimated that the increased glucose turnover accounted for 30-40% of the increased oxygen consumption seen in weight losing cancer patients compared with weight stable patients without cancer. Increased rates of gluconeogenesis from alanine (90) and glycerol (91) as well as lactate (92) have been reported in cancer patients. Of these three precursors lactate appears to be used most commonly for gluconeogenesis.

Impaired glucose tolerance (93-96) and abnormal insulin responses (93,95,97,98) have been reported in tumour-bearing patients and rats. Kisner (99) attributed the abnormal glucose tolerance to abnormal insulin production and insulin resistance, rather than to a reduction in peripheral insulin receptors. Low insulin production has been reported in tumour-bearing rats (100) and patients with metastatic breast cancer (101). In a study of substrate flux across the forearms of six patients with localised oesophageal cancer and weight loss, Burt and colleagues (102) found increased glucose utilisation compared with six healthy controls, despite significantly lower serum insulin levels. They suggested that the increased glucose utilisation may be due to the presence of non-suppressible insulin-like activity (NSILA) (103), a substance possibly produced by the tumour itself (104). They supported the hypothesis of the "tumour trap" mechanism (87,90,105) characterised by increased

glucose utilisation both in the tumour and in peripheral tissues. This results in a fall in plasma glucose which stimulates glucose production by gluconeogenesis, Cori cycle activity and glycogenolysis. This in turn could lead to a depletion of protein in the peripheral tissues and hence could contribute to the development of cachexia.

Fat metabolism

The cachectic cancer patient exhibits a profound loss of body fat. Adipose tissue is a readily available energy source (46), and there is evidence that mobilisation of free fatty acids from host adipose tissue can occur less than 12 hours after tumour transplantation in rats (106). Free fatty acid mobilisation can also occur when a tumour is very small, and at this stage increased plasma lipid concentrations, as well as changes in plasma lipoprotein composition and plasma lipase activity are found in tumour-bearing animals (107,108). In 1949 Mider and colleagues (109) showed that rats bearing Walker 256 carcinoma had a significantly greater loss of body fat than did well matched controls. They also reported that this progressive loss of body fat commenced only when anorexia developed (110). Furthermore, Haven and colleagues (111) stated that the total lipid in tumour-bearing rat carcasses was

inversely proportional to the size of the tumour.

Lipaemia is a common finding during tumour growth in rats (111,112), but a fall in plasma lipid levels has been reported as tumours increase in size (113). Fenninger and Mider (7) interpreted this as an initial increase in fat mobilisation in order to meet the increased energy demands of the host, followed by a fall in plasma lipids as the fat stores were exhausted. This finding would be consistent with the fall in lipid content of various tumours which occurs as the tumours grow (53), indicating a lack of available lipid for storage within the tumour. An alternative theory for the development of lipaemia is that clearance mechanisms may be defective (114). This has been confirmed in rats (115), where a decrease in the amount and rate of fat absorption was also found.

In contrast to the lipaemia seen in tumour-bearing animals, serum lipids are usually normal in patients with cancer (46). Increased fasting free fatty acid levels have been reported (116) and were said to be proportional to the rate of tumour growth. However, previous dietary intake can influence fasting free fatty acid levels in man (117). It should be noted that in normal individuals who have had a high carbohydrate intake, fasting triglyceride levels will be high (118). However, the reverse is true in patients with cancer (46). Furthermore, following an

intravenous infusion of fat, cancer patients show an increased rate of disappearance of the infused fat whereas tumour-bearing animals show the opposite response (119). This finding may explain the difference between lipid levels in animals and man, with the latter unable to develop a significant lipaemia.

Cancer patients respond differently from controls in response to a glucose load. Waterhouse and Kemperman (10) showed diminished suppression of free fatty acid oxidation following a glucose load in five patients with metastatic cancer compared with controls. Other workers (7,9,11,46,106) have reported increased lipolysis in cancer patients. The increased mobilisation of free fatty acids from the adipose tissue of tumour-bearing hosts has various possible mechanisms: increased sympathetic tone (20), abnormal enzyme activation, deranged insulin/glucagon activity or a direct effect of tumour products have all been postulated (9). The isolation from tumours of "lipid-mobilising factors" has been reported (121), but the exact nature of these substances remains obscure. Arbeit and colleagues (11) reported increased fat oxidation rates in patients with metastatic cancer compared with controls, but found no significant difference between patients with localised cancer and controls. They also found no significant difference between patients with metastatic and localised cancer.

Weight losing cancer patients also have a significantly increased glycerol turnover compared with controls (12). The authors concluded that this probably indicated an increase in whole body lipolysis, perhaps related to decreased circulating insulin levels and increased adrenergic activity.

Recently, a protein produced by the macrophages of tumour-bearing hosts has been discovered (122,123). This protein, known as tumour necrosis factor or cachectin, has been shown to interfere with the control of fat metabolism in patients with cancer. It is possible that this endogenous mechanism, which seems to occur as a defense against the tumour-bearing state, may in fact contribute to the development of cancer cachexia by interfering with fat metabolism in the host.

Anorexia

Anorexia is a common symptom in the cancer patient, and inevitably leads to an inadequate dietary intake (9,124,125). It therefore plays a significant role in the development of cancer cachexia. Mechanical obstruction of the gastrointestinal tract will lead to an inadequate food intake, while altered taste sensation and the effects of chemotherapy and radiotherapy can contribute to the development of

anorexia (4,9,125). However, many patients with cancer exhibit profound anorexia in the presence of very small tumours which are distant from the gastrointestinal tract and causing no other obvious secondary effects on the host (9).

Retrospective assessment of dietary intake is inaccurate (126) and is influenced by such factors as the intelligence of the patient (127) and the mode of questioning of the interviewer (128). Wesdorp and colleagues (9) demonstrated the inaccuracies of retrospective dietary assessment by asking cachectic cancer patients to complete a dietary questionaire, showing that many of these patients were unaware of their anorexia.

The mechanisms controlling food intake are complex (124), yet normal individuals maintain a reasonably steady body weight over prolonged time intervals. It has been postulated that this normal physiological regulatory mechanism may be upset in the presence of cancer, either by a direct effect of the tumour or secondary to a host response to the tumour (129). Wurtman and colleagues (130) noticed that the dietary content of precursors of central neurotransmitters could affect behavioural patterns. Studies in rats had suggested that the neurotransmitter serotonin was involved in the regulation of food intake, whereby increased serotonin turnover was associated with a

decreased food intake (131,132) and vice versa (133,134). Tryptophan, the only amino acid precursor of serotonin is an essential amino acid and therefore is dependent on dietary intake for adequate levels in the host. Furthermore, the ingestion of carbohydrate, protein and fat increases plasma tryptophan levels (9). These findings support the theory that serotonin may be involved in the regulation of dietary intake.

Krause and colleagues conducted studies to assess serotonin status in tumour-bearing (Walker 256 carcinoma) anorexic rats (135,136) and found that brain levels of tryptophan and serotonin were increased in these rats compared with control animals. They found similar results when rats with a chronic tumour (methylcholanthrene-induced sarcoma) resulting in prolonged anorexia were studied (137). They concluded that the observed biochemical disorders were not tumour specific, and suggested that the increased levels of serotonin were caused by an increase in plasma free and brain tryptophan secondary to a reduced number of binding sites due to the decreased albumin and increased free fatty acid levels seen in patients with cancer.

There is some evidence that serotonin is involved in feeding behaviour, circadian rhythms, mood and pain sensation (9). The low food intake and vegetative depression seen in many cachectic cancer patients is

therefore in keeping with a possible serotonin effect. In a pilot study of over 20 patients with anorexia and cancer, the administration of the serotonin antagonist BC 105 resulted in improved food intake, weight gain and a decrease in depressive symptoms (9), further supporting the contention that serotonin may be involved in the anorexia of cancer.

Enzyme abnormalities

The growth of a tumour is associated with changes in the activity of many enzymes in host tissues distant from the site of the tumour (2), for example, in the activity of liver enzymes in tumour-bearing animals (138). There are also alterations in the activity of enzymes involved in gluconeogenesis (139), amino acid catabolism (140), and an increased activity of certain muscle peptide hydrolases (141). Many of these biochemical abnormalities were present when the tumour was very small and had not caused any obvious secondary effects in the host (142). The type of tumour present and the stage of tumour growth appeared to influence the observed biochemical changes.

Alterations in enzyme activity of tumour-bearing patients have also been reported. There is increased activity of hydrolysing enzymes in the liver of patients with renal tumours (143), and significantly

decreased activities of various skeletal muscle glycolytic and mitochondrial enzymes (95).

It is difficult to determine the association between these disordered enzyme activities and the development of cancer cachexia, many of which may be secondary to the cachexia, rather than the causative factor. However, these disordered enzyme activities are in keeping with the hypothesis offered by Theologides in 1972 (49), who suggested that tumours produced low molecular weight polypeptides which could interfere with the function of many host enzymes, thereby resulting in chaotic metabolic pathways in the tumour-bearing patient. This could result in a wastage of energy and thus render the patient hypermetabolic. This hypothesis could explain the metabolic abnormalities which have been reported in patients who have very small tumours which have not metastasised or resulted in secondary effects within the host.

INTRAVENOUS NUTRITIONAL SUPPORT IN THE PERIOPERATIVE PERIOD.

The metabolic response to trauma is characterised by an increase in urinary nitrogen excretion and loss of body protein (144,145). These changes are tolerated well in adequately nourished patients undergoing surgical procedures, who regain weight and positive nitrogen balance in the anabolic phase. However, debilitated patients who have lost weight prior to surgery may tolerate the catabolic phase less well, and may be at risk of increased morbidity and mortality (13,14).

In an attempt to reduce postoperative complications in these patients, various forms of nutritional support have been administered either prior to or following surgery. Where the gastrointestinal tract is functioning normally, dietary supplements or nasogastric feeding can overcome the problems of inadequate food intake or anorexia. However, in many patients the gastrointestinal tract cannot be utilised adequately either due to pathology therein or the need to fast patients for various preoperative investigations. The administration of total parenteral nutrition (TPN) in the preoperative period has resulted in a reduction in postoperative complications and mortality in some studies. For example, Dudrick and colleagues (146,147)

reported a reduction in postoperative complications and mortality in cancer patients who received 7-14 days of TPN preoperatively. Müller and colleagues (16) reported a reduction in mortality and major postoperative complications such as intra-abdominal abscess, peritonitis and anastomotic leakage in patients with gastrointestinal cancer receiving ten days of TPN preoperatively compared with similar patients receiving normal hospital diet. Other studies of preoperative TPN have yielded less convincing results (15,17) and some clinicians would argue that its use merely delays operative intervention. The case for preoperative TPN therefore remains unproven.

The use of postoperative nutritional support has also been studied extensively in patients with gastrointestinal disease. In the early postoperative period the gastrointestinal tract is frequently unable to tolerate intra-luminal nutrition and consequently the emphasis has been on intravenous nutritional support. As with preoperative TPN, the use of TPN in the postoperative period has yielded conflicting results. Hill (148) and Blackburn (149) have reported a reduction in postoperative complications and catabolism in patients receiving postoperative TPN, and although other studies have demonstrated improvements in postoperative nitrogen balance (65,150), the evidence showing that this in turn reduces postoperative morbidity and mortality is less

convincing (17,152,153).

Furthermore, the administration of TPN is not without significant hazard. The venotoxicity of hyperosmolar TPN solutions necessitates the use of the central veins for their delivery. Cannulation of the subclavian vein is associated with significant complications including pneumothorax, haemothorax, subclavian artery puncture and brachial plexus injury (154,155). Consequently, an experienced clinician is required for the safe insertion of these catheters (156). Once catheterisation is established, the main complication of TPN administration is catheter-related sepsis (154,157). Reported catheter sepsis rates vary from 0-41% (158,159). It is now well established that catheter sepsis rates can be minimised if the adminstration of TPN is supervised by clinicians and nurses who have a specific interest in nutritional support (160,161).

The lack of convincing evidence proving the benefit of TPN administration, together with the associated hazards and expense, have led many workers to investigate the role of peripheral intravenous nutrition in surgical patients. The advantages of peripheral intravenous nutrition are that little expertise is required in the placement of the peripheral venous cannula and the problem of catheter-related sepsis is considerably less. The main

disadvantage, however, is that it is not usually possible to administer as much nitrogen and energy due to the phlebitis which occurs due to the hypertonicity of TPN solutions (162).

Although isotonic dextrose solutions have been shown previously to spare nitrogen (163,164), Blackburn and colleagues (165) have challenged the rationale behind the use of these solutions in postoperative patients. They hypothesised that infused glucose stimulated insulin secretion and hence inhibited lipolysis, thus depriving the body of endogenously produced energy substrates such as free fatty acids, glycerol and ketones. They also suggested that the administration of isotonic amino acids, in the absence of infused glucose, conserved body protein stores by encouraging the mobilisation and utilisation of body fat stores, and claimed that the low insulin levels which occurred in the absence of infused glucose enhanced lipolysis, and hence prevented the breakdown of body protein for gluconeogenesis. However, various workers (166-168), comparing amino acid infusions alone with a combination of amino acids plus dextrose, have shown that the protein sparing effects of peripherally-administered amino acids are due to the infused amino acids alone, and are independent of plasma insulin levels and ketosis. Indeed, Elwyn and colleagues (169) reported that the addition of glucose

to peripheral amino acid infusions actually reduced nitrogen excretion.

More recently, Garden and coworkers (170) reported a significant improvement in nitrogen balance on only the first postoperative day in patients receiving amino acid infusions providing 10g nitrogen per day compared with patients receiving dextrose-saline infusions. Other studies have shown a more prolonged improvement in nitrogen balance in patients receiving amino acid solutions containing 10-14g nitrogen per day (169,171). The type of amino acid used, and the balance of essential to non-essential amino acids, may be partly responsible for these differences in nitrogen balance. Indeed, Tweedle and colleagues (172) have shown that solutions low in glycine and alanine produce better nitrogen balance than solutions with high non-essential amino acid concentrations in patients receiving TPN.

The high osmolarity of nutrient solutions containing large amounts of nitrogen and calories has prevented the administration of these solutions through a peripheral vein. However, Burnham and colleagues (173) have administered a combination of amino acids, fat and carbohydrate providing approximately 14g nitrogen and 3000 non-protein calories per day via the peripheral veins of patients with gastrointestinal disease and reported positive

nitrogen balance and only a few episodes of mild phlebitis. Silberman and colleagues (174) also reported a low incidence of phlebitis in patients receiving a hyperosmolar solution of amino acids, dextrose, vitamins, heparin and fat. Anecdotal evidence has suggested that the addition of fat emulsions to peripheral nutrition solutions in some way protects the vein and decreases the incidence of phlebitis. However, recently Daly and colleagues (175) found no difference in the incidence of phlebitis whether a dextrose/amino acid solution was administered alone or with fat emulsion.

There is thus no consistent evidence to show that the use of preoperative or postoperative nutritional support, whether administered via a central or peripheral vein, significantly improves postoperative morbidity or mortality. Furthermore, it is difficult to define the "at risk" patients who may benefit from some form of nutritional support, despite the various prognostic indices which have been identified (13). Until the precise indications for the use of intravenous nutritional support in the perioperative period are established, its administration should be confined to clinical trials designed to assess the possible biochemical and clinical benefits of this therapy.

MANIPULATION OF THE METABOLIC RESPONSE TO SURGERY

The loss of body protein which occurs following surgical trauma (144,176,177) may have deleterious effects on debilitated patients (13,14). The early hopes that total parenteral nutrition (TPN) would reduce postoperative complications in many of these patients have been dampened by conflicting evidence from many studies (15-17,153). These findings, together with the hazards and expense (154,157,178) associated with the administration of TPN, have led to the investigation of alternative ways of influencing the metabolic response to surgery.

Raising the environmental temperature has been shown to modify heat production and protein catabolism following burn injury (179) and long bone fracture (180,181). Davies and Liljedahl (179) demonstrated a 30% reduction in metabolism in patients with extensive burn injuries when the environmental temperature was raised from 22 degrees centigrade to 32 degrees centigrade, but observed that this effect became less as the severity of the burn decreased. Sir David Cuthbertson and colleagues (180,181) demonstrated a reduction in the metabolic response to trauma when patients with long bone fractures were transferred to a warm environment, whereas patients undergoing major or moderately severe elective surgery appeared to derive no significant metabolic benefit from a similar

rise in environmental temperature (182). The mechanism of the reduction in metabolism seen when burned patients are nursed in a high environmental temperature appears to be related to the evaporation of water from burned tissues. When the environmental temperature is high, the energy required to evaporate this water can be derived from the environment rather than the energy-rich nutritional stores of the host. Noradrenaline concentrations are persistently raised in these patients (183) and the temperature control centre in the hypothalamus appears to be reset to a supranormal level (184). These features are not seen in fracture patients or those undergoing elective surgery, where any metabolic benefit of a raised environmental temperature is probably related only to the maintenence of core temperature thereby reducing the utilisation of endogenous fuels for this purpose.

Manipulating the metabolic response to surgery by neurogenic blockade has also been investigated. Brandt and colleagues (185) demonstrated a significant improvement in postoperative nitrogen balance when epidural analgesia was administered to patients undergoing abdominal hysterectomy. Although Traynor and colleagues (186) reproduced the abolition of the glycaemic response to surgery when thoracic epidural analgesia and vagal blockade were combined during upper abdominal surgery, they failed to show any effect on the plasma cortisol levels. It is also known

that paraplegic patients undergoing surgery for the repair of lower limb fractures show the same increased catabolism of plasma albumin as found in non-paraplegic patients undergoing the same surgical procedures (187). Thus, the role of local analgesic techniques in influencing the metabolic response to surgery remains in doubt.

Pharmacological manipulation of the metabolic response to surgery has also been investigated. The reduced insulin secretion which occurs following trauma has led some workers to investigate the effects of insulin administration following surgery. It appears to reduce nitrogen losses in severely burned patients (188,189), but has little effect on nitrogen balance in the absence of an increased catabolic rate (189). Growth hormone has also been shown to improve nitrogen balance (20), but neither insulin nor growth hormone appear to diminish the release of catabolic hormones postoperatively. Injury may modify reactions which control the entry of fat and carbohydrate into the tricarboxylic acid cycle, thereby promoting oxidation of endogenous amino acids and thus increasing nitrogen excretion. Burns and colleagues (21) demonstrated improved nitrogen balance after surgery when naftidrofuryl was administered by slow bolus intravenous injection and suggested that this may be due to improved efficiency of endogenous carbohydrate and fat metabolism in the tricarboxylic

acid cycle. However, other workers (190,191) have found no significant improvement in nitrogen balance, whether naftidrofuryl was administered as a continuous infusion (190) or by slow bolus (191).

Anabolic steroids have been shown to reduce post-traumatic protein catabolism but their virilising effects have limited their use, especially in females (18). Their mode of action in influencing the metabolic response to injury is uncertain, although changes in nitrogen excretion are evident in both anabolic and catabolic phases of the response (192) and follow both minor and major trauma (193). Methandienone does not affect the rise in plasma cortisol or the excretion of urinary steroids following injury suggesting that anabolism may result from a direct effect on the tricarboxylic acid cycle (18). Norethandrolone and methandienone have been shown to reduce nitrogen excretion and weight loss in some postoperative patients (18,19) but not in others (194,195). Blamey and colleagues (196) showed that a single preoperative intramuscular 50mg dose of the anabolic steroid stanozolol reduced postoperative nitrogen balance in patients receiving a simple dextrose-saline regimen, and Michelsen and colleagues (193) reported a reduction in nitrogen excretion following total hip replacement in patients receiving nandrolone decanoate and isotonic amino acids.

There has been conflicting evidence regarding the effects of anabolic steroids on nitrogen excretion in postoperative patients receiving TPN. For example, Tweedle and coworkers (192) showed that a combination of nandrolone decanoate and TPN improved nitrogen balance moreso than nandrolone decanoate alone, whereas Yule and colleagues (197) showed anabolic steroids to have no significant effect on nitrogen balance in patients receiving postoperative TPN.

To date there have been few studies involving the use of anabolic steroids in groups of cancer patients. Most studies have involved either groups of patients with benign disease only (18,192,194,195,198,199) or where the majority of patients had benign disease (196,200-203).

CHAPTER 3

METHODS

PATIENTS

The patients studied in this thesis presented to the University Department of Surgery between October 1983 and December 1985. Informed consent was obtained from each patient prior to inclusion in the studies. In some instances patients have been included in more than one of the studies reported. All patients had been admitted for elective surgery or investigation. Patients who had clinical or bacteriological evidence of infection or obvious oedema or ascites, and those who had undergone surgery, radiotherapy or cytotoxic chemotherapy in the preceding year were not included. None of the patients studied had received nutritional support previously.

Patients were weighed wearing light night attire on beam balance standing scales (Weylux 424, U.K.). Patients were classified as weight stable or weight losing depending on the degree of weight loss reported. The patient's usual body weight (prior to the onset of their presenting illness) was compared with the value recorded at the time of study. Each patient was questioned carefully about their usual weight and weight loss. This method relied on each patient's subjective impression of their usual body weight, and while a degree of error is inevitable using this method, it was deemed to be more relevant than a comparison with desirable weight. Those

patients who had lost 10% or more of their usual body weight were classified as weight losing.

MEASUREMENT OF RESTING ENERGY EXPENDITURE

Studies of heat loss and heat production associated with the metabolism of man and animals have been performed for over two centuries (204). Energy expenditure can be derived either by measurement of heat loss (direct calorimetry) or estimation of heat production (indirect calorimetry). In direct calorimetry, the subject is completely enclosed within a chamber, which is either surrounded by water (205, 206) or ventilated by a controlled air flow (207). Energy expenditure is then calculated from the rise in temperature of the water or air. This method is impractical in the hospital situation, as patients would be denied medical and nursing care during the study period.

Indirect calorimetry provides a more suitable method of estimating energy expenditure. The maintenance of body cell function involves the constant combustion of body fuels or exogenous nutrients. This combustion consumes oxygen and produces carbon dioxide. Measurement of gaseous exchange through the lungs therefore provides an indirect estimation of the amount of energy which is being expended by the host. The ratio of carbon dioxide produced to oxygen consumed, that is, the respiratory quotient (RQ), is a useful indicator of the type of fuel being utilised. The physiological

range (0.7 - 1.2) is narrow, with an RQ of 0.7 representing net fat utilisation, an RQ of 1.0 indicating carbohydrate utilisation and RQ values greater than 1.0 indicating carbohydrate synthesis and storage.

The accurate measurement of gaseous exchange requires the measured delivery of inspired gases and the collection of expired gases, avoiding mixing with atmospheric air. This can be achieved to a variable extent in several ways. The subject can breath directly into a mouthpiece (while wearing a noseclip) or facemask. However, this technique is uncomfortable and can be tolerated for only a short duration. Furthermore, the discomfort can result in hyperventilation, especially in ill subjects (208). The development of the rigid transparent head canopy has enabled gaseous exchange to be measured for long periods, even in critically ill patients (209,210). In this closed system, the canopy is placed around the subject's head and sealed around the neck using a flexible collar. An indirect calorimeter based on this design was used throughout the present studies. The calorimeter was built and developed in the Department of Surgery in the late 1970s (see Appendix) and has been used for clinical studies since that time.

Room air of a known oxygen and carbon dioxide concentration is delivered at a controlled rate to the

canopy. A mixture of this air and the subject's expired gases is extracted from the canopy at a controlled rate. Following dehumidification the mixed air is delivered to a wall mounted dual cell paramagnetic oxygen analyser (Servomex Ltd, Crowborough, Sussex, U.K.) and a single channel infra-red carbon dioxide analyser (Sieger Ltd, Poole, Dorset, U.K.). The concentration of oxygen and carbon dioxide in the mixed air, corrected for temperature and barometric pressure, is measured, and by comparison with the oxygen and carbon dioxide concentrations of the room air, which have been measured in the same way, the oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) of the subject can be derived. The analysers were calibrated regularly using oxygen-free nitrogen, 0.80% carbon dioxide and air of a known barometric presssure. The sensitivity and accuracy of the calorimeter was checked regularly by burning butane gas in the canopy (see appendix). The whole system provides measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ which have an overall error of less than $\pm$5%. Estimates of $\dot{V}O_2$ and $\dot{V}CO_2$ were made every 30 seconds during each patient study which lasted for 40 minutes. Recording of data did not commence until a steady rate of oxygen consumption and carbon dioxide production was obtained, usually after 5-10 minutes. The 80 estimates of $\dot{V}O_2$ and $\dot{V}CO_2$ collected were processed on line by a microprocessor (PET 2001, C.B.M. Ltd.) and converted to mean energy production

(Watts) and RQ using the abbreviated formula of Weir (211):

$$\text{REE (kcal/day)} = (3.9\dot{V}O_2 + 1.1\dot{V}CO_2)1440$$

where kcal/day = Watts x 20.65

$\dot{V}O_2$ = oxygen consumption (l/min)

$\dot{V}CO_2$ = carbon dioxide production (l/min)

$$RQ = \frac{\dot{V}CO_2}{\dot{V}O_2}$$

The measurement period of 40 minutes was preceded by 30 minutes acclimatisation in the calorimeter canopy. No acclimatisation period was used in postoperative studies, as these patients were already familiar with the procedure. Each study began at approximately 09.00 hours, the patients having remained in bed since wakening. Physiotherapy, bed-baths and other nursing procedures were not permitted prior to a calorimetry run. Patients undergoing postoperative calorimetry received intravenous fluids as described in the relevant studies. For all other calorimetry runs patients received nil by mouth for 12 hours prior to the calorimetry run but received an intravenous infusion of 5% dextrose solution providing 80 ml of fluid (16kcal) per hour to maintain hydration.

CALCULATION OF SUBSTRATE OXIDATION RATES

From the measurements of oxygen consumption and carbon dioxide production obtained by indirect calorimetry, together with measurements of 24 hour urinary nitrogen excretion, the oxidation rates of fat and carbohydrate were calculated using the formulae of Frayn (212):

Carbohydrate oxidation (g/d) =

$$(4.55\dot{V}CO_2 - 3.21\dot{V}O_2 - 2.87n)\ 1440$$

Fat oxidation (g/d) =

$$(1.67\dot{V}O_2 - 1.67\dot{V}CO_2 - 1.92n)\ 1440$$

where $\dot{V}O_2$ = oxygen consumption (l/min)

$\dot{V}CO_2$ = carbon dioxide production (l/min)

n = urinary nitrogen (g/min)

These formulae are similar to others which have been used in studies of substrate oxidation (25,213).

It is important to realize that in most cases the above formulae give net rates of "utilisation" rather than true oxidation rates. Frayn points out that small errors in the calculation of fat and carbohydrate oxidation rates will occur in the presence of metabolic processes which result in the accumulation or excretion of intermediary or end products other than carbon dioxide and water. Such examples include the processes of lipogenesis and

gluconeogenesis. Lipogenesis can occur during the infusion of high concentrations of dextrose and results in RQ values greater than 1.00. No RQ values in excess of 1.00 occurred in the studies reported in this thesis. Gluconeogenesis will upset slightly the calculation of oxidation rates only if the glucose formed is not subsequently oxidised. It should be noted that Cori cycle activity, which tends to be increased in cancer patients (47,82-84), does not affect these calculations since the conversion of glucose to lactate and reconversion to glucose does not involve gaseous exchange. Frayn concludes that the net rates of oxidation calculated by these formulae may in fact be more useful than true rates in clinical practice, and emphasises that the errors involved are small.

CALCULATION OF LEAN BODY MASS

Lean body mass (LBM) was derived from measurements of total body water using the isotope dilution technique (214). Tritiated water (Amersham International plc, Buckinghamshire, U.K.) was diluted with 6ml of isotonic saline for intravenous injection. On the day of calorimetry, the tritiated saline (4MBq) was injected intravenously and serum samples obtained three and four hours after injection. Aliquots of 4ml were stored at -40 degrees centigrade and processed in batches. Immediately prior to injection patients voided urine, which was discarded. For the four hours following the injection, all urine passed was collected in sterile containers to measure the loss of tritium in the urine. The volume of urine was determined and a 20ml aliquot was stored at -40 degrees centigrade for subsequent analysis.

The serum and urine samples were allowed to thaw, and a 1ml aliquot was diluted with 10ml of liquid scintillation phosphor solution, made in the Department of Surgery. An aliquot of the solution injected, which also had been stored, was diluted 1:10,000 with normal saline. The radioactivity (counts per minute - cpm) of these specimens was measured in an Auto-gamma 500C liquid scintillation counter (Packard, Berkshire, U.K.). The patient samples were analysed in duplicate and the injection samples were

analysed in quadruplicate. A mean value of the three and four hour samples was calculated.

Total body water was calculated by comparison of the radioactivity in the injection and serum samples:

$$\frac{\text{injection sample (cpm)}}{\text{serum sample - urine sample (cpm)}} = \text{total body water (litres)}$$

$$\text{Total body water} \times \frac{100}{73.2} = \text{LBM (kg)}$$

This calculation assumes that lean tissue contains approximately 73% water. Where total body water measurements were repeated on the fourth postoperative day, a serum sample was obtained prior to the tritium injection to measure the amount of residual tritium in the serum. This "background" count was subtracted from the plasma samples during calculation of the postoperative total body water. Repeated measurements of total body water using this technique have shown a coefficient of variation of $\pm$2.3% (214).

The assumption that lean tissue contains 73% water may not be justified in all cases. Shizgal (215) observed that malnourished patients have an expanded extracellular fluid volume which will result in an overestimation of LBM using the isotope dilution technique. Correction of this overestimation would result in a small increase in the value of caloric expenditure, where REE has been expressed in terms of

kilograms of LBM.

An alternative method for deriving LBM is the measurement of total body potassium. However, Burkinshaw and colleagues (216) have reported that weight loss can result in a reduction in the intracellular potassium content, which in turn would lead to an error in the estimation of LBM in weight losing patients.

The most accurate method of deriving LBM would be by neutron activation analysis. This facility, however, was not available in this centre, and the use of this technique would have been unacceptable in many of the patients studied.

DIETARY HISTORIES AND ANTHROPOMETRIC MEASUREMENTS

One research dietician, unaware of each patient's diagnosis, was responsible for all dietary histories and anthropometric measurements. The dietician obtained a diet history by asking each patient about changes in appetite and food intake which had occurred immediately prior to admission to hospital. The amount and type of food and fluid ingested in a typical day was noted. This was converted into a daily caloric and protein intake using standard tables (217).

Mid-arm circumference (MAC) was measured by marking the midpoint between the acromion and olecranon processes in the dependent non-dominant arm with the elbow joint flexed to 90 degrees. A skinfold 1 centimetre above this point overlying the triceps muscle was pinched between finger and thumb and three readings of the triceps skinfold thickness (TST) were obtained using skin calipers. The mean of the three readings was taken as the TST measurement. Mid-arm muscle circumference (MAMC) was calculated using the formula:

$$MAMC = MAC - (0.314 \times TST)$$

where MAMC is in centimetres
MAC is in centimetres
TST is in millimetres

MAMC and TST were expressed as percentages of expected

standard values (218) where:

MAMC - male = 25.3 cm

- female = 23.2 cm

TST - male = 12.5 mm

- female = 16.5 mm

BIOCHEMICAL MEASUREMENTS

Urine was collected over a 24 hour period in storage cans containing thymol/isopropanol as preservative. The volume of urine was determined and 20ml aliquots were stored at -20 degrees centigrade and processed in batches. Total urinary nitrogen was measured with an automated micro-Kjeldahl method which uses the Berthelot reaction for quantitation, as described by Fleck (219).

Plasma glucose was measured enzymatically on a Beckman Glucose II analyser. Plasma insulin samples were stored at -20 degrees centigrade and analysed in batches using an antibody radioimmunoassay technique, using as standard MRC 66/304 insulin. Albumin was measured using the bromo-cresol green dye binding method. Serum transferrin samples were stored at -20 degrees centigrade and measured by immunoturbidity on a Centrifichem centrifugal analyser (Baker Instruments, U.K.).

MEASUREMENT OF WHOLE BODY PROTEIN TURNOVER

Whole body protein turnover (WBPT) was measured by the method based on that described by Waterlow and colleagues (220) and Sim and colleagues (221). On the day prior to measurement patients ate a standard hospital diet. After an overnight fast, patients remained in bed from the time of wakening. The baseline enrichment of ^{15}N in ammonia and urea was obtained from a urine sample taken at 08.00 hours. At 09.00 hours, a primed, constant 24 hour infusion of ^{15}N-glycine was commenced. During the 24 hour infusion patients were allowed free access to water, but not to food. The mean priming dose of ^{15}N-glycine was 0.3 mg ^{15}N/kg (99 atom% ^{15}N - Amersham International plc, U.K.) and this was followed by a continuous 24 hour infusion at a mean rate of 0.28mg ^{15}N/kg/24 hours, delivered using a peristaltic infusion pump (Ivac, Harrow, U.K.). The ^{15}N-glycine was dissolved in NaCl (150mM) and sterilised by microfiltration. During the infusion, urine was collected over two consecutive 12 hour periods into storage cans containing 20ml HCl (6mmol/l) and 8mg chlorhexidine gluconate (ICI Ltd., Macclesfield, Cheshire, U.K.).

The urine samples were prepared for mass spectroscopy using a sodium/potassium cationic ion-exchange resin (222). The resin-ammonia complex was treated with alkaline hypobromite to liberate

molecular nitrogen, and ^{15}N abundance was measured using a double collector mass spectrometer (V.G. Micromass 602B, Cheshire, U.K.) with a precision of 0.0008 atom % excess. These measurements were made by Dr. T. Preston at the Scottish Universities Research and Reactor Centre, East Kilbride.

The isotopic enrichment of urinary ammonia and urea was measured in urine collected during the 12-24 hour period of the infusion. This timed collection has previously been shown to concur with plateau isotopic enrichment of urinary ammonia and urea (223).

Rates of WBPT were calculated using the stochastic model of Picou and Taylor-Roberts (224). The basic assumption of this model is that in the steady state, and at isotopic equilibrium, the proportion of isotope excreted in the chosen end-product of nitrogen metabolism (ammonia or urea) is the same as the proportion of the nitrogen turnover excreted in that same end-product. Nitrogen turnover was calculated using the formula:

$$Q = \frac{d}{E}$$

where Q = nitrogen turnover,

d = the quantity of isotope infused,

E = the isotopic enrichment of the chosen urinary end-product.

The assumptions of the stochastic model mean that in the steady state Q is equal to the rate of protein synthesis (S) plus the rate of nitrogen excretion (E). This also equals the rate of protein breakdown (B) plus the rate of nitrogen intake (I). Thus:

$$Q = I + B = S + E$$

Since this study was performed with patients in the fasting state, the rate of protein turnover should be equal to the rate of protein breakdown. Rates of whole body protein synthesis were calculated by subtracting 24 hour urinary nitrogen excretion from Q.

STATISTICS

All statistics were performed on an Apple II computer using a statistical tests package developed and tested in the Department of Surgery. Where several groups of data were compared, an analysis of variance was used initially to test whether there were any significant differences between groups. However, the nonparametric Mann-Whitney U test and Wilcoxon Rank Sign test were used for pairwise comparisons in order to minimise the risk of detecting spurious differences in data which were not normally distributed. For descriptive purposes, data have been expressed as mean ± s.e.m. to facilitate comparison with other published results. Linear regression analysis was performed using the method of least squares and correlation coefficients (r) determined. Linear regression equations are in the form:

$$y = a + bx$$

where a is the intercept on the y axis

and b is the gradient of the line

The slopes of the linear regression lines were compared using Student's t test. All confidence intervals (CI) quoted are 95% CIs. Other statistical tests were used as indicated in the text.

Differences were considered significant when the probability of their arising by random sampling error

was less than 1 in 20 ($P<0.05$). Differences were considered highly significant when this probability was less than 1 in 100 ($P<0.01$).

CHAPTER 4

THE RELATIONSHIP BETWEEN RESTING ENERGY EXPENDITURE AND WEIGHT LOSS IN BENIGN AND MALIGNANT DISEASE

INTRODUCTION

During the past 70 years, many authors (6-8,26-28,30,33-35,82,225) have suggested that an increased resting energy expenditure (REE) may be a contributing factor in the development of cancer cachexia. The early reports were anecdotal (28,30,33), while many of the recent studies have been poorly controlled. For example, Macfie and colleagues (27) compared cancer patients with younger weight stable controls, while others (8,26) have studied patients with cancer but have offered no control data.

The aim of this study was to determine whether REE was increased in cancer patients who were losing weight. These patients were compared with three other groups: cancer patients without weight loss and groups of weight losing and weight stable patients with nonmalignant illness. The relationship between REE and various expressions of body size has been investigated, and the effects of cancer and weight loss on these relationships have been determined.

PATIENTS & METHODS

One hundred and thirty six recently diagnosed patients were included in the study. Cancer was proven histologically in 98 patients, and a control group of 38 had nonmalignant disease (Table 1). Of the 98 cancer patients, 56 were weight stable and 42 were weight losing. The controls were similarly divided into 22 weight stable and 16 weight losing patients. The mean weight loss expressed as a percentage of the mean pre-illness weight and the mean weight loss per month during the period of illness are shown in Table 2.

In the cancer patients, the presence of hepatic metastases was assessed by ultrasound and computerised tomography in all patients and confirmed histologically in those who underwent laparotomy. Eleven of the weight stable patients and eight of the weight losing patients had hepatic metastases.

The methods used are as described in Chapter 3.

TABLE 1 PATHOLOGICAL DIAGNOSES IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

Diagnosis	Cancer	
	Weight stable (n = 56)	Weight losing (n = 42)
Colorectal cancer	36	19
Gastric cancer	12	12
Bronchial cancer	5	7
Oesophageal cancer	3	2
Pancreatic cancer	-	2

	Control	
	Weight stable (n = 22)	Weight losing (n = 16)
Gastric ulceration	1	1
Duodenal ulceration	2	4
Pyloric stenosis	-	3
Cholelithiasis	14	3
Diverticular disease	3	1
Benign colorectal polyp	-	2
Ulcerative colitis	1	-
Crohn's disease	-	2
Hiatus hernia	1	-

RESULTS

Clinical and nutritional details are shown in Tables 2 and 3 respectively. There was no significant difference in mean age between the groups. There were more males in the weight stable cancer group and more females in the weight stable control group. The weight losing cancer patients had a significantly lower mean body weight and LBM than their weight stable counterparts. The weight losing controls had a significantly lower mean body weight and LBM compared with their weight stable counterparts. The weight losing controls had a significantly lower mean body weight but no difference in LBM compared with the weight stable controls. In both the weight losing groups, the mean weight loss was in excess of 15% of pre-illness weight. The rate of weight loss in these groups was 2.7 kg per month. Mean measurements of MAMC and TST were significantly lower in both weight losing groups compared with their weight stable counterparts. No significant differences could be detected in mean total energy intake between the groups, although the weight losing controls had a significantly lower mean protein intake compared with the weight stable controls. When compared with their weight stable counterparts, both the weight losing groups had significantly reduced mean serum albumin and transferrin levels. In addition, weight stable cancer patients had lower mean serum transferrin levels than

TABLE 2 CLINICAL DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
n	56	42	22	16
Male : Female	40 : 16	23 : 19	6 : 16	8 : 8
Age (years)	66 ± 1.4	65 ± 1.7	62 ± 3.0	63 ± 3.9
Body weight (kg)	64.7 ± 1.6[b]	52.6 ± 1.9[a]	65.2 ± 3.2[b]	56.3 ± 3.3
Lean body mass (kg)	51.2 ± 1.6	44.8 ± 1.6[d]	48.2 ± 2.6	46.7 ± 2.3
Weight loss (%)	3 ± 0.4	18 ± 1.0[a]	1 ± 0.6[c]	16 ± 1.3[a]
Weight loss/month (kg)	0.8 ± 0.2	2.7 ± 0.3[a]	0.3 ± 0.2	2.7 ± 0.4[a]

mean ± s.e.m.

a = $P<0.01$ versus weight stable cancer patients and weight stable controls

b = $P<0.05$ versus weight losing controls

c = $P<0.05$ versus weight stable cancer patients

d = $P<0.01$ versus weight stable cancer patients

TABLE 3 NUTRITIONAL DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
Energy intake (kcal/day)	1779 ± 79.6	1676 ± 134	2013 ± 172	1564 ± 286
Protein intake (kcal/day)	68.8 ± 3.3	68.2 ± 5.6	76.8 ± 6.0[b]	60.5 ± 6.5
MAMC (% expected)	96.7 ± 1.4	86.6 ± 1.9[a]	98.0 ± 2.1[b]	89.1 ± 2.9
TST (% expected)	102.0 ± 6.2[d]	67.1 ± 5.2[a]	112.7 ± 8.4[d]	74.5 ± 7.6
Serum albumin (g/l)	37.9 ± 0.7	33.1 ± 0.9[a]	39.8 ± 0.8[d]	35.7 ± 1.3
Serum transferrin (g/l)	2.41 ± 0.1	2.07 ± 0.1[e]	2.90 ± 0.1[cd]	2.33 ± 0.2

mean ± s.e.m.

a = P<0.01 versus weight stable cancer patients and weight stable controls

b = P<0.05 versus weight losing controls

c = P<0.01 versus weight stable cancer patients

d = P<0.01 versus weight losing controls

e = P<0.05 versus weight stable cancer patients and weight stable controls

weight stable controls.

Measurements of REE are shown in Table 4. When REE is expressed in kcal/kg body weight/day, the weight losing cancer patients have a significantly increased REE compared with both the weight stable groups. There is no significant difference between the groups when REE is expressed in terms of LBM. When REE is expressed in terms of $kg^{0.75}$, referred to by Kleiber (43) as metabolic body size, weight stable control patients have a significantly reduced REE compared with the other three groups. Significant correlations between REE and body weight, metabolic body size and lean body mass are shown in Figures 1-3. For reasons of clarity, the scatter of points around each line has been omitted. The strongest correlation was found between REE and LBM. The gradient of the cancer weight losing (CWL) regression line is significantly steeper than both the weight stable groups when REE is plotted against body weight and LBM. When plotted against metabolic body size, the CWL regression line differs signficantly only from the weight stable cancer group (CWS).

There were no significant differences in RQ between the groups (Table 4). No significant differences in REE were found when patients with hepatic metastases were compared to those without, irrespective of weight loss (Table 5). There were no

TABLE 4 RESTING ENERGY EXPENDITURE (REE) AND RESPIRATORY QUOTIENT (RQ) IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
Expression of REE or RQ	Weight stable	Weight losing	Weight stable	Weight losing
kcal/kg/day	22.5 ± 0.4	24.4 ± 0.4[a]	20.6 ± 0.7	23.5 ± 0.8
kcal/$kg^{0.75}$/day	63.6 ± 1.0	65.5 ± 1.0	57.8 ± 1.4[b]	63.8 ± 1.9
kcal/kg LBM/day	29.3 ± 0.8	28.9 ± 0.6	28.1 ± 0.8	28.7 ± 0.8
RQ	0.814 ± 0.117	0.801 ± 0.117	0.816 ± 0.171	0.830 ± 0.183

mean ± s.e.m.

a = P<0.01 versus weight stable cancer patients and weight stable controls

b = P<0.01 versus other three groups

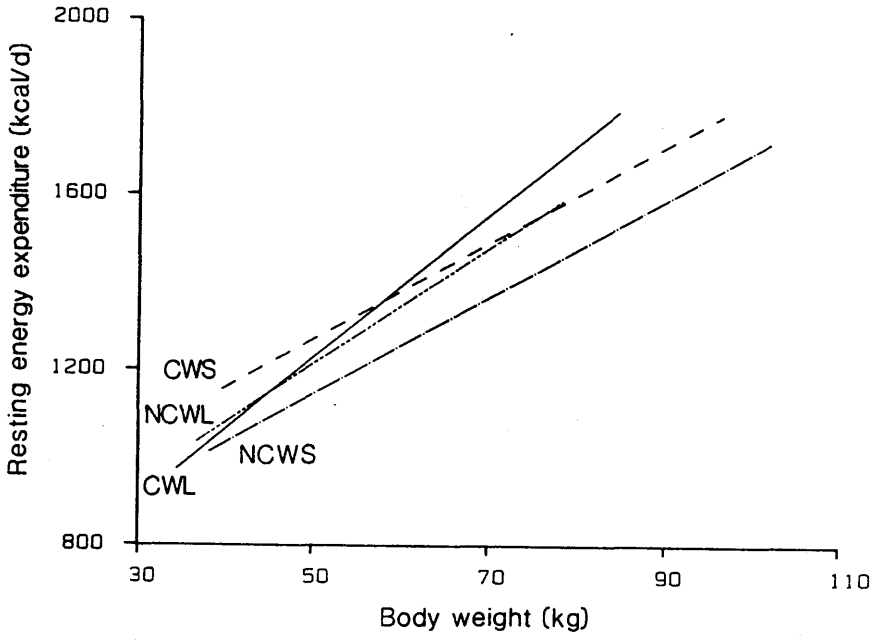


Figure 1

The relationship between resting energy expenditure and body weight in each of the groups

CWL (cancer weight losing)	y = 406 + 16.4x
n = 42; r = 0.790; P<0.01	95% CI (12.4,20.4)
CWS (cancer weight stable)	y = 712 + 11.2x
n = 56; r = 0.648; P<0.01	95% CI (7.7,14.7)
NCWL (control weight losing)	y = 543 + 13.4x
n = 16; r = 0.749; P<0.01	95% CI (7.0,19.8)
NCWS (control weight stable)	y = 587 + 11.2x
n = 22; r = 0.768; P<0.01	95% CI (7.0,15.4)

The CWL slope is significantly different from the CWS (P<0.05) and NCWS (P<0.05) slopes.

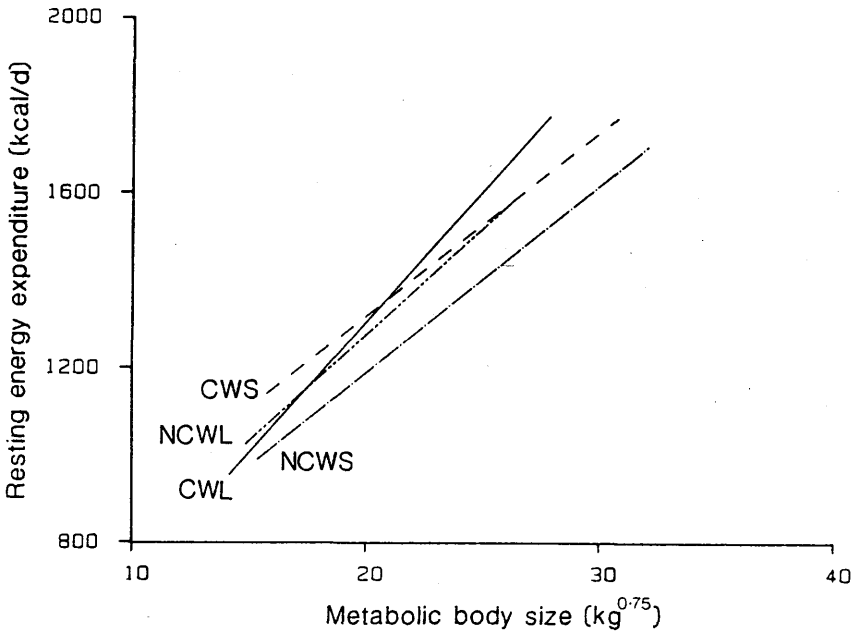


Figure 2

The relationship between resting energy expenditure and metabolic body size in each of the groups

CWL (cancer weight losing)	y = 104 + 60.0x
n = 42, r = 0.795; P<0.01	95% CI (45.5,74.5)
CWS (cancer weight stable)	y = 477 + 42.1x
n = 56; r = 0.645; P<0.01	95% CI (28.5,55.7)
NCWL (control weight losing)	y = 296 + 49.0x
n = 16; r = 0.754; P<0.01	95% CI (26.2,71.8)
NCWS (control weight stable)	y = 330 + 43.0x
n = 22; r = 0.769; P<0.01	95% CI (27.1,58.9)

The CWL slope is significantly different from the CWS slope (P<0.05).

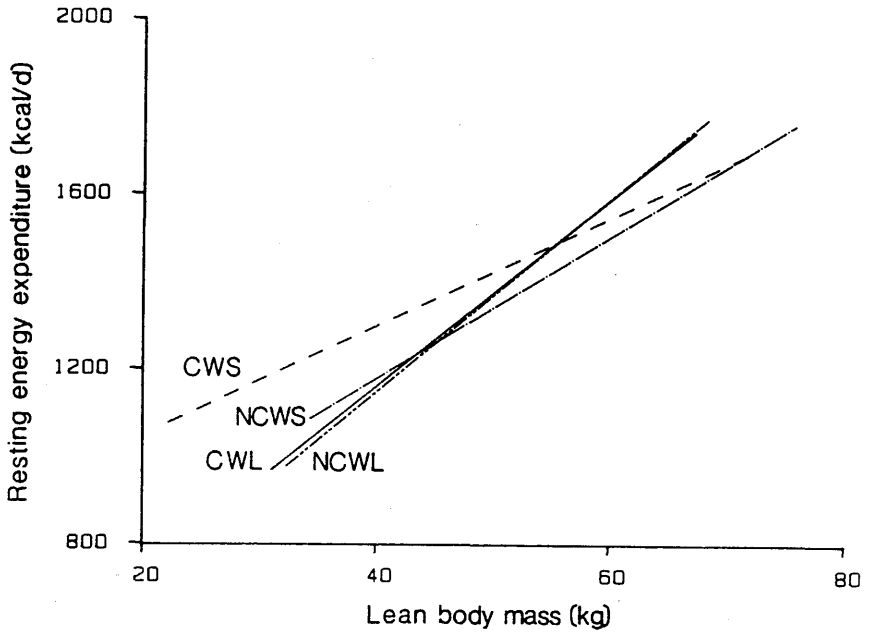


Figure 3

The relationship between resting energy expenditure and lean body mass in each of the groups

CWL (cancer weight losing)	y = 299 + 21.5x
n = 42; r = 0.835; P<0.01	95% CI (16.8,26.2)
CWS (cancer weight stable)	y = 799 + 12.5x
n = 56; r = 0.662; P<0.01	95% CI (7.2,17.8)
NCWL (control weight losing)	y = 255 + 22.3x
n = 16; r = 0.873; P<0.01	95% CI (15.7,28.9)
NCWS (control weight stable)	y = 524 + 16.4x
n = 22; r = 0.896; P<0.01	95% CI (12.8,20.0)

The CWL slope is significantly different from the CWS ($P<0.05$) and NCWS ($P<0.05$) slopes.

TABLE 5 RESTING ENERGY EXPENDITURE (REE) IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS WITH AND WITHOUT HEPATIC METASTASES

	Weight stable		Weight losing	
	No metastases	Metastases	No metastases	Metastases
REE	(n = 45)	(n = 11)	(n = 34)	(n = 8)
kcal/kg LBM/day	29.5 ± 1.0	27.7 ± 0.8	28.5 ± 0.6	28.5 ± 1.2

mean ± s.e.m.

No statistically significant differences between the groups

significant differences in REE when differing tumour types were compared (Table 6).

When REE is related to LBM and all cancer patients are compared with all control patients, there is no significant difference between the slopes of the regression lines (Figure 4). However, when weight losing patients are compared with weight stable patients irrespective of the primary diagnosis, the slopes of the regression lines are significantly different (Figure 5).

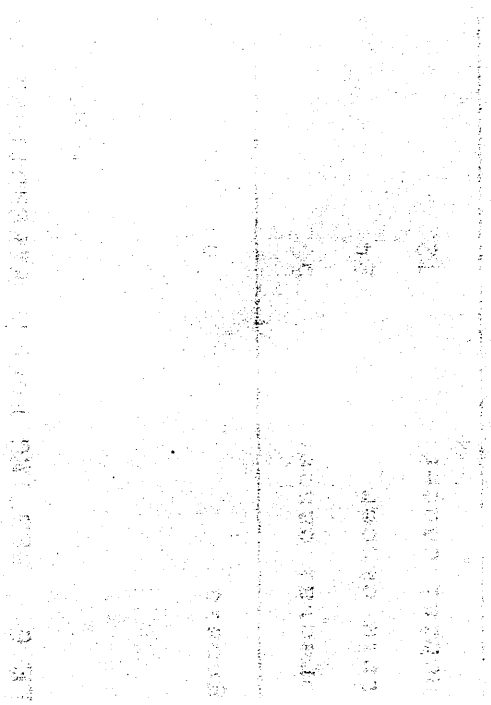


TABLE 6 RESTING ENERGY EXPENDITURE (REE) IN PATIENTS WITH DIFFERENT TUMOUR TYPES

Diagnosis	n	REE (kcal/kg LBM/day)
Colorectal cancer	55	29.1 ± 0.7
Gastric cancer	24	27.7 ± 0.8
Bronchial cancer	12	29.9 ± 0.9

mean ± s.e.m.

No statistically significant differences between the groups

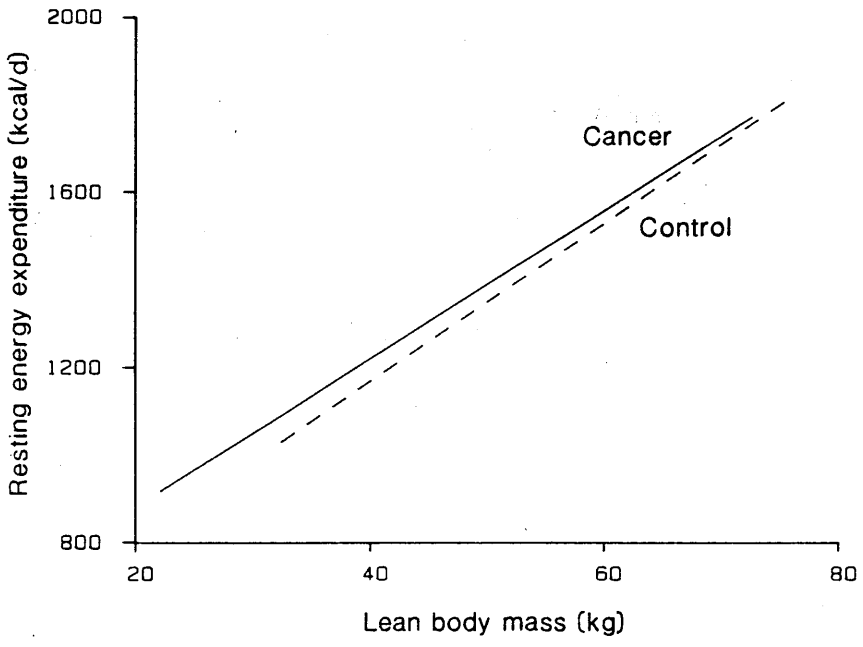


Figure 4

The relationship between resting energy expenditure and lean body mass for all cancer patients and all controls

Cancer	y = 542 + 17.0x
n = 98; r = 0.759; P<0.01	95% CI (13.9,20.1)
Control	y = 446 + 18.1x
n = 38; r = 0.876; P<0.01	95% CI (14.8,21.4)

No significant differences between the slopes.

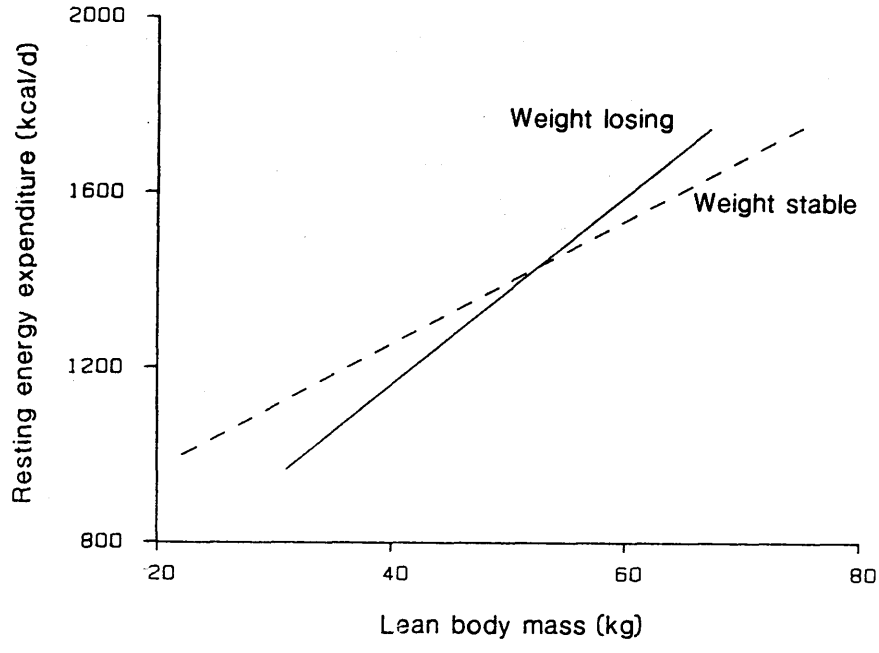


Figure 5

The relationship between resting energy expenditure and lean body mass for all weight stable patients and all weight losing patients

Weight stable	y = 685 + 14.3x
n = 78; r = 0.739; P<0.01	95% CI (11.2,17.4)
Weight losing	y = 292 + 21.7x
n = 58; r = 0.837; P<0.01	95% CI (17.8,25.6)

The weight stable slope is significantly different from the weight losing slope (P<0.01).

DISCUSSION

There have been many studies of energy expenditure in cancer patients, and most have reported an increase in REE associated with the tumour bearing state (6-8,26-28,30,33-35,82,225). It has been suggested that this increased energy expenditure could contribute to the weight loss commonly seen in these patients (6,8,27,34,35,225). Other studies, however, have failed to show any alteration in REE when comparing cancer patients to controls (44). Indeed, Mullen and colleagues have suggested that some cancer patients may in fact have a reduced energy expenditure (39).

However, measurement of REE must take into account patient size, and it is apparent from this present study that an error can be made when energy expenditure is expressed as kcal/day, kcal/kg body weight/day or kcal/$kg^{0.75}$/day. The weight losing patients in this study appear to have lost predominantly fat. Therefore, the proportion of total body weight that is represented by lean body mass increases. Since lean body mass contributes more to REE than does fat mass, any attempt to predict REE related to body weight will tend to underestimate energy expenditure in weight losing patients. This source of error has been ignored in earlier publications in this field. In this present study,

when energy expenditure is expressed as kcal/kg body weight/day, weight losing cancer patients have a significantly higher energy expenditure than weight stable cancer patients or controls. When REE is related to lean body mass this difference disappears.

It follows, in addition, that when formulae are used to predict expected energy expenditure in patients with altered body composition, they will underestimate REE if total body weight is part of the formula. Such formulae are the Harris-Benedict (40) and Kleiber (43) formulae, both of which have been used in the past to predict energy expenditure in weight losing cancer patients. Since these formulae do not take into account changing body composition, it is not surprising that they have erroneously suggested elevated energy expenditure when weight losing cancer patients are compared with control groups. In an attempt to minimise this error, lean body mass has been measured using the isotope dilution technique. As discussed in Chapter 3, this method will tend to overestimate lean body mass. However, correction of this error is unlikely to alter greatly the conclusions of the present study.

The conclusion that the weight losing cancer patients in this study have no detectable alteration in REE when compared with weight stable cancer patients or patients with nonmalignant illness is

similar to that reached by Lindmark and his colleagues (35), who compared 28 cancer patients with 43 controls. They found that weight losing cancer patients have an increase in REE of 148 kcal/day compared with weight losing controls. If it is accepted that complete oxidation of 1g of fat gives 9.1 kcal, 1g of carbohydrate gives 4.1 kcal, 1g of protein gives 4.1 kcal, and that body tissues contain 20% protein, Lindmark and his colleagues (35), using the RQ values obtained from calorimetry, estimated that this increase in energy expenditure could account for the loss of between 1 and 2 kg of body weight per month. Macfie and colleagues (27) found an increase in REE of 289 kcal/day when patients with metastatic cancer were compared with healthy controls. They suggested that this increase could account for a weight loss of 1 kg of fat per month. In the present study, neither of the weight losing groups had any detectable increase in REE when compared with their weight stable counterparts. Both goups, however, had a reported weight loss of almost 3 kg per month before coming into hospital. It is concluded, therefore, that an elevation in REE seems to contribute little to the weight loss seen in these cancer patients. Furthermore, unlike Macfie and colleagues (27), this study reveals no evidence to suggest that the presence of hepatic metastases significantly alters REE. Previous studies have suggested that advanced malignant disease was associated with an increased

REE. This observation has not been confirmed in the present study.

When regression lines relating REE to body size are drawn for the four groups (Figures 1-3) the fact that the lines seem to converge supports the argument proposed by Lindmark and colleagues (35) that cancer patients can ultimately adapt their energy expenditure to the weight losing state. The patients with the lowest lean body masses appear best able to adapt to the weight losing state. However, when all cancer patients are compared with all control patients (Figure 4), there is no significant difference in the slope of the resulting regression lines. The most interesting comparison is seen when weight losing patients are compared with weight stable patients, irrespective of the presence of cancer (Figure 5). The fact that the slopes of the regression lines are significantly different suggests that the weight losing state is more closely associated with metabolic abnormalities in patients than is the presence or absence of cancer. It seems that some cancer patients and some patients who develop nonmalignant illness respond to their illness by producing an associated metabolic abnormality which leads to the weight losing state.

To claim that the presence of a solid tumour will necessarily result in elevated energy expenditure is

probably an oversimplification. Some cancer patients respond to their illness by losing weight, as do some patients who develop a nonmalignant illness. It is not the primary pathology, but the patient's endogenous responses to it which determine whether weight loss will result. However, speaking of cancer as a uniform entity is also an oversimplification. It has been suggested that the primary site of a tumour may be important in determining the magnitude of the REE (39). In the present study, REE has been measured in patients with colorectal, gastric, and non-small cell bronchial cancer and no significant difference among the groups has been found. Bronchial cancers, however, did show a trend toward a slightly higher energy expenditure. Although this has not been shown to be statistically significant, it may be that a small subset of bronchial cancer patients do, in fact, have a higher than anticipated energy expenditure.

A possible explanation for the extent of the observed weight loss in the patients in the present study could be anorexia. Standard dietary histories have been used to assess energy and protein intakes of the patients studied. Both weight losing groups had a lower energy intake than the weight stable groups, but this difference was not statistically significant. Protein intakes were similar between the groups apart from the weight losing controls, who had a significantly decreased intake compared with their

weight stable counterparts. Standard dietary assessment techniques are inaccurate and have wide variability, and a small difference in intake may be obscured (126-128). The findings of Wesdorp and colleagues (9), who reported that most cachectic cancer patients were unaware of their anorexia, emphasises the limitations of this technique. While anorexia is likely to account for a significant proportion of the observed weight loss, another possible mechanism may be that weight losing patients have altered utilisation of endogenous substrates or of ingested nutrients. For example, the thermogenic response to food may be altered in cancer patients, leading to a reduction in the efficiency with which ingested substrate is stored.

The present study has yielded no evidence to support the hypothesis that patients who lose weight, whether they have cancer or not, have an increase in energy expenditure. There is also no evidence that tumour type or tumour stage is important in determining REE in cancer patients, although further investigation in this area is warranted. It is possible that substrate handling in weight losing cancer patients may be altered. However, the evidence points to an altered response to illness as being the major determinant of increases in REE, rather than any factor associated with the tumour itself.

CHAPTER 5

THE ACCURACY OF PREDICTIVE FORMULAE IN ESTIMATING RESTING ENERGY EXPENDITURE

INTRODUCTION

Predictive formulae are used widely to estimate the resting energy expenditure (REE) of patients in both clinical and research situations. Such predictors include the Harris-Benedict (40), Kleiber (43) and Robertson-Reid (226) formulae and the Fleisch tables (227). These predictors have been derived from calorimetric measurements in mainly young healthy subjects with presumed normal body composition, in whom the anthropometric indices of height and weight reflect accurately the metabolically active proportion of body weight. As alluded to in the previous chapter, body composition may be altered in various disease states (215), and this in turn may lead to an inaccurate estimation of REE when such formulae and tables are used. Indeed, recent studies (41,42) have shown the Harris-Benedict (40) and Kleiber (43) formulae to be inaccurate in predicting REE in a significant proportion of patients.

The aim of this study, therefore, was to assess the accuracy with which the Harris-Benedict (HB), Kleiber (KL) and Robertson-Reid (RR) formulae as well as the Fleisch (FL) tables could predict REE. The effects of sex, weight status and disease status on predictive accuracy were assessed by comparing the predicted REE values with those measured by indirect calorimetry.

PATIENTS & METHODS

The study sample consisted of 168 recently diagnosed patients, of whom 87 were male and 81 were female. These two groupings were subdivided according to whether a patient had benign (control group) or malignant (cancer group) disease. Patients were subdivided further into weight stable and weight losing groups. These subdivisions according to sex, disease status and weight status are shown in Table 7. The types of benign or malignant disease present are shown in Table 8.

The methods used are as described in Chapter 3 and below.

Predictive formulae

REE was predicted in four ways:

(1) Harris-Benedict formula (kcal/day)

Males: $66.473 + 13.752(W) + 5.003(H) - 6.755(A)$

Females: $655.096 + 9.563(W) + 1.850(H) - 4.676(A)$

(2) Robertson-Reid formula (kcal/m^2/hour)

Males: $37.405365 - 0.06944(A)$

Females: $35.15375 - 0.06149(A)$

(3) Kleiber formula (kcal/day)

Males: $71.2W^{0.75}(1+0.004(30-A)+0.010((H/W^{0.33})-43.4)$

Females: $65.8W^{0.75}(1+0.004(30-A)+0.018((H/W^{0.33})-42.1)$

TABLE 7 DISTRIBUTION OF PATIENTS ACCORDING TO SEX, DISEASE STATUS AND WEIGHT STATUS

	Cancer		Control	
Sex	Weight stable	Weight losing	Weight stable	Weight losing
Male	45	25	9	8
Female	18	26	27	10

TABLE 8 PATHOLOGICAL DIAGNOSES IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

Diagnosis	Cancer			
	Weight stable		Weight losing	
	Male	Female	Male	Female
Colorectal cancer	27	14	9	14
Gastric cancer	11	4	9	8
Bronchial cancer	5	-	5	2
Oesophageal cancer	2	-	2	1
Pancreatic cancer	-	-	-	1

	Control			
	Weight stable		Weight losing	
	Male	Female	Male	Female
Gastric ulceration	-	2	-	2
Duodenal ulceration	4	4	3	2
Pyloric stenosis	-	-	1	3
Cholelithiasis	4	14	-	2
Diverticular disease	-	1	-	1
Benign colorectal polyp	1	5	2	-
Ulcerative colitis	-	1	-	-
Crohn's disease	-	-	2	-

(4) Fleisch tables (kcal/m^2/hour)

where A = age in years, W = body weight in kilograms, H = height in centimetres.

For (2) and (4) surface area was calculated from height and weight using standard tables. The calculated REE was then multiplied by 24 to give kcal/day.

The REE derived from indirect calorimetry was then expressed as a percentage of the predicted REE:

$$\frac{\text{Measured REE}}{\text{Predicted REE}} \times 100$$

Statistics

Male and female data were analysed separately throughout the study since each formula had both male and female versions. Thus, all analyses were made with patients grouped according to weight status and sex, and also according to disease status and sex. These groupings are justified as there is no interaction between weight status and disease status. No analyses were performed with patients subdivided according to all three indices, namely, weight status, disease status and sex, as this would have resulted in certain groups having too few patients for statistical analysis. One sample t tests and 95% confidence

intervals were used to establish for which groups of patients the predictive formulae were over- or underestimating. An analysis of variance was used to identify any significant differences between the four formulae with regard to predictive ability. The use of Bonferroni's multiple comparison procedure enabled the formulae to be grouped in order of predictive accuracy for each of the patient groups.

RESULTS

Clinical and anthropometric details are shown in Tables 9 and 10 respectively. Both weight stable and weight losing female cancer patients were significantly older than their corresponding controls. The mean body weight of each of the weight losing groups was significantly lower, and the mean percentage weight loss significantly higher, than that of their weight stable counterparts. Weight losing male patients had significantly lower mean LBM values compared with weight stable male patients, irrespective of disease status. When LBM was expressed as a percentage of body weight, weight losing female patients were found to have a significantly greater percentage than their weight stable counterparts, irrespective of disease status. Mean MAMC and TST measurements for each of the weight losing groups were significantly lower than those of their weight stable counterparts.

Values for measured REE, expressed as a percentage of predicted REE, with 95% confidence intervals are shown in Tables 11a and 11b. In nearly every case, the mean percentage predicted value is greater than 100%, indicating a general underestimation of REE by the formulae. Where the confidence intervals include 100, there is no significant over- or underestimation of REE. When patients are grouped according to weight

TABLE 9 CLINICAL DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

		Cancer		Control	
		Weight stable	Weight losing	Weight stable	Weight losing
Age (years):	male	63.9 ± 1.5	62.8 ± 2.4	54.2 ± 4.2	61.5 ± 5.7
	female	67.6 ± 1.7	69.1 ± 1.6	55.1 ± 3.4	60.7 ± 4.9
Body weight (kg):	male	66.1 ± 1.7	55.6 ± 2.0[a]	68.0 ± 3.2	59.9 ± 3.1[a]
	female	60.2 ± 3.2	49.8 ± 2.4[a]	64.7 ± 2.9	52.4 ± 4.7[a]
LBM (kg):	male	54.8 ± 1.5	49.4 ± 2.0[a]	59.2 ± 2.9	52.3 ± 2.7[c]
	female	43.3 ± 2.6	39.6 ± 1.5	45.3 ± 1.6	41.3 ± 2.3
LBM/body weight (%):	male	83.3 ± 1.4	89.5 ± 1.6	87.1 ± 1.3	87.6 ± 2.5
	female	74.3 ± 3.1	80.8 ± 1.9	71.4 ± 1.7	81.5 ± 4.1[b]
Weight loss (%):	male	3 ± 0.3	19 ± 1.1[a]	2 ± 0.8	14 ± 1.3[a]
	female	4 ± 0.4	18 ± 1.1[a]	0 ± 0.7	19 ± 1.4[a]

mean ± s.e.m.

a = $P<0.01$ versus weight stable cancer patients and weight stable controls

b = $P<0.01$ versus weight stable controls

c = $P<0.05$ versus weight stable controls

TABLE 10 ANTHROPOMETRIC DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

		Cancer		Control	
		Weight stable	Weight losing	Weight stable	Weight losing
MAMC (% expected):	male	96.0 ± 1.5	87.4 ± 2.1[a]	96.0 ± 2.9	91.4 ± 3.0[a]
	female	97.2 ± 2.5	87.1 ± 2.3[a]	100.0 ± 2.4	87.0 ± 4.2[a]
TST (% expected):	male	85.9 ± 4.6	56.7 ± 5.4[a]	87.6 ± 7.9	61.8 ± 8.7[a]
	female	138.0 ± 15.2	77.7 ± 6.3[a]	136.0 ± 9.5	87.4 ± 9.6[a]

mean ± s.e.m.

a = $P<0.01$ versus weight stable cancer patients and weight stable controls

TABLE 11a MEASURED RESTING ENERGY EXPENDITURE (REE) EXPRESSED AS A PERCENTAGE OF PREDICTED REE, WITH PATIENTS GROUPED ACCORDING TO WEIGHT STATUS

	Weight stable		Weight losing	
Formula	Male	Female	Male	Female
%HB	108.0 (105.2, 110.8)	102.0 (99.0, 105.0)	111.4 (106.8, 116.0)	105.0 (102.0, 108.0)
%KL	106.5 (103.9, 109.1)	105.8 (102.2, 109.4)	109.0 (104.6, 113.4)	109.7 (106.3, 113.1)
%RR	108.7 (106.1, 111.3)	105.6 (102.8, 108.4)	107.4 (103.0, 111.8)	107.4 (104.4, 110.4)
%FL	104.2 (101.6, 106.8)	101.7 (98.9, 104.5)	103.1 (98.9, 107.3)	104.0 (101.0, 107.0)

mean
(95% confidence interval)

TABLE 11b MEASURED RESTING ENERGY EXPENDITURE (REE) EXPRESSED AS A PERCENTAGE OF PREDICTED REE, WITH PATIENTS GROUPED ACCORDING TO DISEASE STATUS

	Cancer		Control	
Formula	Male	Female	Male	Female
%HB	110.3 (107.5, 113.1)	107.3 (104.5, 110.1)	105.4 (100.8, 110.0)	98.7 (96.3, 101.1)
%KL	108.3 (105.7, 110.9)	111.9 (108.5, 115.3)	103.9 (99.5, 108.3)	101.9 (98.9, 104.9)
%RR	108.7 (105.9, 111.5)	109.5 (106.7, 112.3)	106.6 (102.4, 110.8)	103.0 (100.6, 105.4)
%FL	104.2 (101.6, 106.8)	106.2 (103.4, 109.0)	102.1 (98.1, 106.1)	99.0 (96.6, 101.4)

mean
(95% confidence interval)

status and sex, only the Fleisch formula used on weight losing males and weight stable females and the Harris-Benedict formula used on weight stable females are not significantly over- or underestimating REE. In every other case the mean percentage predictive values are significantly greater than 100% ($P<0.01$), indicating an underestimation of REE by these formulae.

When patients are grouped according to disease status and sex, all cancer patients have mean percentage predictive values which are significantly greater than 100% ($P < 0.05$). Thus, in these cases, the formulae are significantly underestimating REE. There is no significant over- or underestimation of REE in female patients with benign disease, apart from the Robertson-Reid formula, nor in male patients with benign disease when the Kleiber and Fleisch formulae are used.

Another aspect of the way in which these formulae are over- or underestimating REE is shown in Tables 12a and 12b. The percentage of patients in each group whose predicted REE differed from their measured REE by greater than $\pm$10% ranges from 14% for females with benign disease where the Harris-Benedict formula is used to 62% for weight stable males where the Robertson-Reid formula is used.

TABLE 12a PERCENTAGE OF PATIENTS IN WHOM RESTING ENERGY EXPENDITURE (REE) WAS OVER- OR UNDERESTIMATED, WITH PATIENTS GROUPED ACCORDING TO WEIGHT STATUS

	Weight stable				Weight losing			
	Male		Female		Male		Female	
Formula	over	under	over	under	over	under	over	under
HB	4	43	9	14	6	42	6	36
KL	7	30	9	30	6	39	3	56
RR	2	60	3	31	6	41	3	44
KL	4	21	10	18	9	28	6	25

where over = % patients overestimated by >10%

under = % patients underestimated by >10%

TABLE 12b PERCENTAGE OF PATIENTS IN WHOM RESTING ENERGY EXPENDITURE (REE) WAS OVER- OR UNDERESTIMATED, WITH PATIENTS GROUPED ACCORDING TO DISEASE STATUS

	Cancer				Control			
	Male		Female		Male		Female	
Formula	over	under	over	under	over	under	over	under
HB	1	49	7	39	12	23	8	6
KL	3	43	2	57	12	23	11	22
RR	3	41	2	47	6	41	3	25
FL	6	26	5	35	6	12	11	6

where over = % patients overestimated by >10%

under = % patients underestimated by >10%

A summary of the data shown in Tables 11 and 12 shows that:

(1) Sex affects the predictive ability of the Harris-Benedict formula only, predicting REE better in females with benign disease and females who are weight stable, compared with their male counterparts.

(2) Disease status affects the predictive ability of all four formulae, predicting REE better in females with benign disease compared with females with cancer.

(3) Weight status does not appear to affect the predictive ability of any of the formulae.

Whether patients are grouped according to weight status and sex or disease status and sex, an analysis of variance shows that significant differences exist between the formulae regarding their predictive ability. A more detailed comparison, using Bonferroni's multiple comparison procedure, enables the formulae to be grouped in order of predictive accuracy for each of the patient groups (Tables 13a and 13b). Those formulae which do not differ significantly using the Bonferroni method are indicated "=". The Fleisch formula is the best or equal best for all the groups studied. The Harris-Benedict formula is worst or equal worst for all male patients, irrespective of weight status or disease status. In contrast, the Harris-Benedict

formula is equal best for all female patients with benign disease, irrespective of weight status.

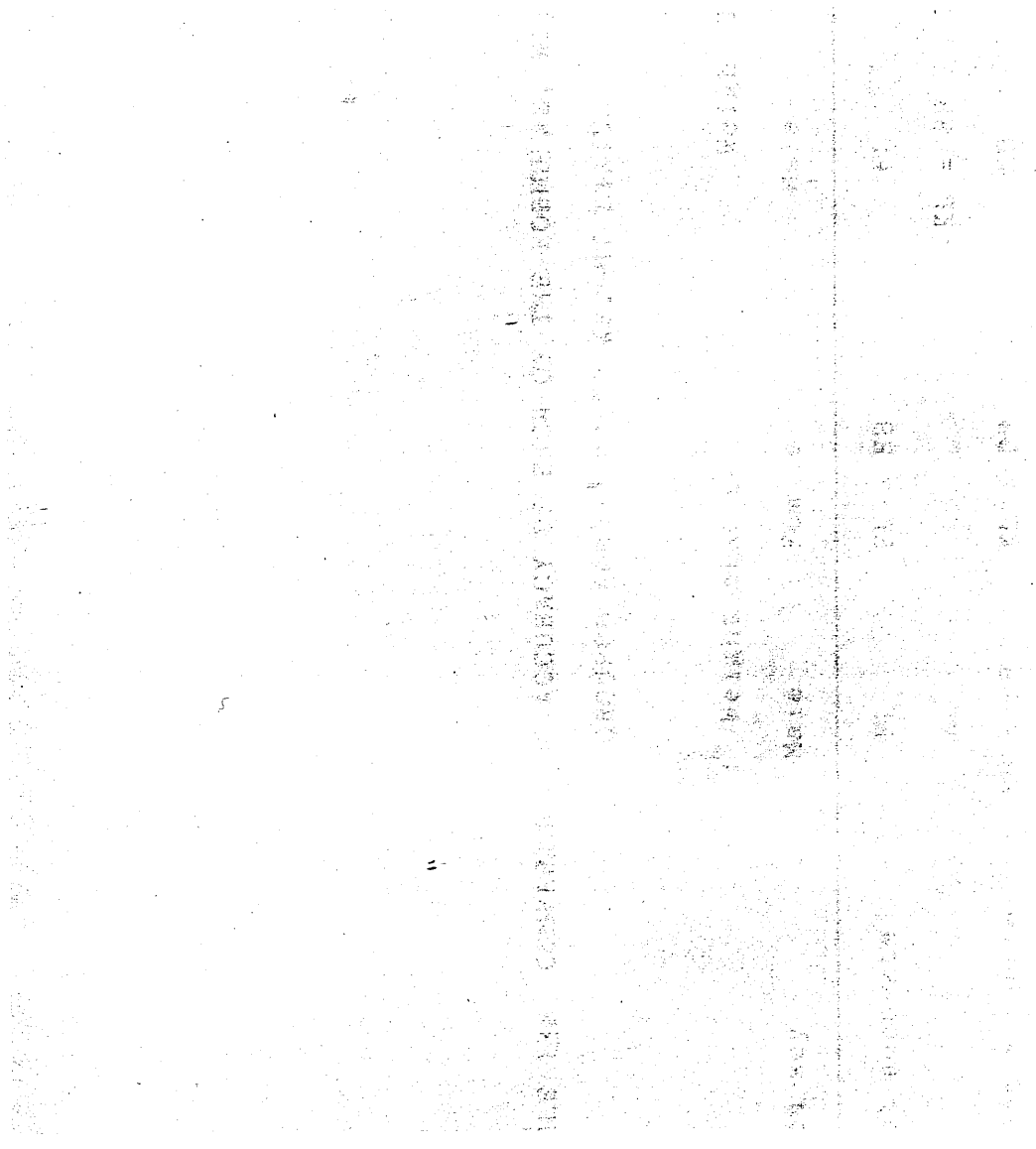


TABLE 13a COMPARISON OF ACCURACY OF EACH OF THE FORMULAE, WITH PATIENTS GROUPED ACCORDING TO WEIGHT STATUS

	Weight stable		Weight losing	
Accuracy	Male	Female	Male	Female
Most accurate	FL	FL = HB	FL	FL = HB
	KL		KL = RR	KL
Least accurate	HB = RR	KL = RR	HB	RR

TABLE 13b COMPARISON OF ACCURACY OF EACH OF THE FORMULAE, WITH PATIENTS GROUPED ACCORDING TO DISEASE STATUS

	Cancer		Control	
Accuracy	Male	Female	Male	Female
Most accurate	FL	FL	FL = KL	FL = HB
	KL	HB		
		RR		
Least accurate	HB = RR	KL	HB = RR	KL = RR

DISCUSSION

This study demonstrates significant errors in the ability of predictive formulae to estimate REE accurately in hospitalised patients. The presence of cancer in female patients decreased the predictive ability of all four formulae, whereas the presence of weight loss did not appear to affect the predictive ability of any of the formulae.

The Harris-Benedict (40) and Robertson-Reid (226) formulae were derived from indirect calorimetry measurements of REE in 239 and 2,310 healthy individuals respectively. The Kleiber formula (43) was derived from the original Harris-Benedict data, and the Fleisch tables (227) were generated from a review of 24 studies involving REE measurements. All these predictors of REE are based on the assumption that the height and weight of an individual will reflect accurately the size of the metabolically active portion of the body, which in turn will reflect the energy expenditure of this tissue. This, however, will be the case only if body composition is normal. The presence of disease states or weight loss may lead to alterations in body composition (215,228), and so the use of these predictive formulae and tables in individual patients may lead to an inaccurate prediction of REE.

Historically, Harris and Benedict showed 12% of normal individuals to have a predicted REE outwith ±10% of measured REE (40) while Boothby found only 8% of normal individuals to fall outwith this range (32,229). In contrast, in the present study 14-62% of patients were outwith this range, depending on the predictor used. In virtually all cases these predictors tended to underestimate rather than overestimate REE. This underestimation of REE has been reported by other workers (230,231), but it contrasts with the recent findings of Daly and colleagues (232) who reported a general overestimation of REE by the Harris-Benedict formula in a study of 201 healthy men and women. Other workers have also reported an overestimation of REE using predictive formulae. For example, Feurer and colleagues (42) reported that REE predicted by the Harris-Benedict and Kleiber formulae was greater than that measured by indirect calorimetry in both patients and healthy controls. It should be noted that in Feurer's study the percentage of healthy controls whose predicted REE was outwith ±10% of measured REE was 20% for the Harris-Benedict formula and 33% for the Kleiber formula. These percentages are considerably greater than the 12% and 8% reported by Harris-Benedict (40) and Boothby (32,229) respectively. One factor which could account for these differing results is the different indirect calorimetry techniques employed. For example, Robertson and Reid used the Benedict-Roth apparatus

(226), Feurer and colleagues used a portable indirect calorimeter with mouthpiece and noseclip (42), while in the present study a fixed indirect calorimeter employing a rigid sealed canopy was used.

Irrespective of any differences in actual values of REE which may result due to different techniques, comparison of the results of the various formulae in the present study, where the same indirect calorimetry technique was used throughout, demonstrate significant differences in the predictive ability of these formulae. There were no significant differences in the predictive ability of the male and female forms of each of the predictors with the exception of the Harris-Benedict formula, where the female version was more accurate than the male version in predicting REE in those females who had not lost weight and who had benign disease. The presence of cancer had a significant effect on the predictive ability of each of the formulae when applied to females, but no such difference was evident when applied to males. In contrast, the presence of significant weight loss did not appear to affect the predictive ability of any of the formulae. This finding differs from that of Roza and Shizgal (41) who, comparing 33 normally nourished patients with 41 malnourished patients, found the Harris-Benedict formula to be unreliable in predicting REE in malnourished patients. Using a multiple isotope dilution technique, they demonstrated an increased

extracellular mass and a decreased body cell mass in the malnourished patients, and concluded that the inaccuracy of the Harris-Benedict formula in these malnourished patients was due to altered body composition.

In the present study, body composition was assessed by the measurement of LBM, as well as the anthropometric indices of MAMC and TST. As discussed in Chapter 3, the derivation of LBM from total body water measurements in weight losing patients is subject to a degree of error due to the expansion of the extracellular fluid volume which occurs in the presence of malnutrition (215). This results in an overestimation of LBM using this technique. It is seen from Table 9, however, that if an allowance is made for this overestimation in weight losing patients, the LBM/body weight percentages will fall, resulting in values closer to those of the weight stable patients. Thus, using the LBM/body weight percentage as an index of body composition, there appears to be no major difference in body composition between the groups.

The anthropometric indices of MAMC and TST, however, were significantly lower in the weight losing male and female patients compared with their weight stable counterparts. Reference to Table 10 shows that the difference between weight stable and weight losing patients is more pronounced for TST measurements than

for MAMC measurements, irrespective of disease status. This suggests that the weight losing patients are losing relatively more fat than lean tissue, which would lead to altered body composition.

The LBM and anthropometric measurements do not fully explain why prediction of REE was less accurate in female cancer patients yet unaffected by weight loss. An alternative explanation for the inaccurate prediction of REE in certain groups of patients could be that these patients have abnormalities of REE as a consequence of their disease. However, in the previous chapter it was shown that any alterations in REE due to disease were very small, with the subtle difference in the relationship of REE and lean body mass appearing to be related to weight loss rather than the type of disease present. Thus, the observation that the accuracy of the predictive formulae was affected by cancer but not by weight loss is unexpected. It may be that the presence of cancer affects body composition differently than does simple weight loss. It is also possible that the rate of loss of fat stores and lean tissue is different in cancer patients compared with patients who have nonmalignant illness. This view is supported by the results of a study of body composition in 23 cachectic patients (233), in which ten patients with malignant cachexia were compared with 13 patients with cachexia due to nonmalignant inflammatory causes. The authors

concluded that lean tissue was conserved to a greater extent in the cancer patients, and noted that although both groups were overhydrated, the distribution of fluid between the intracellular and extracellular compartments was normal. Thus, it is possible that changes in body composition, not detected by the methodology used in the present study, are interfering with the predictive ability of the various formulae.

The evidence of this and other studies (41,42) concerning the inaccuracy of predictive formulae in estimating REE has a significant bearing on the use of these formulae in both clinical and research practice. In the clinical situation the use of these formulae in assessing caloric requirements for nutritional support may lead to the provision of an inappropriate amount of calories, which has been shown to have adverse clinical consequences including hepatic dysfunction (234,235) and respiratory complications (236-238). In the research situation conclusions regarding the effects of cancer on REE have been made based on a comparison of measured REE with that predicted from the Harris-Benedict formula. For example, Jeejeebhoy and colleagues (26) claimed that patients with metastases from small cell bronchial cancer had a raised REE compared with patients with localised disease, while Mullen's group (38) suggested that patients with cancer could have a low, normal or high REE, claiming that abnormalities

of REE may be related to the duration of the disease. In a further study from the same centre, Mullen and colleagues (39) suggested that different gastrointestinal cancers were associated with different REE values, with gastric cancer patients tending to have an increased REE while colorectal cancer patients had a more normal distribution of REE. In subsequent chapters evidence will be presented which will highlight the misleading results which can be obtained when the Harris-Benedict formula is used in this context.

In conclusion, this study demonstrates that the use of predictive formulae or tables in predicting the REE of individual patients or even groups of patients can produce inaccurate or misleading results. Thus, if an accurate measurement of REE is required, or if the metabolic characteristics of cancer patients are to be investigated, the use of indirect calorimetry to obtain this measurement is recommended.

CHAPTER 6

ESTIMATION OF RESTING ENERGY EXPENDITURE BY ANTHROPOMETRY

INTRODUCTION

In addition to the inaccuracies of the predictive formulae highlighted in the previous chapter, there is the further disadvantage that estimates of REE require knowledge of the patient's body weight. Since the weighing of seriously ill or ventilated patients is difficult, even if expensive weighing devices are available, a simpler method of estimating REE would be of value, particularly to the clinician prescribing nutritional support.

Simple anthropometric measurements of triceps skinfold thickness (TST), mid-arm circumference (MAC) and calculated mid-arm muscle circumference (MAMC) have been used extensively to assess nutritional status (218). These measurements are easily performed irrespective of the clinical state of most patients and require no sophisticated equipment.

In order to assess the effectiveness of anthropometric measurements in estimating REE, they have been related to REE measured by indirect calorimetry in weight stable and weight losing patients with benign or malignant disease.

PATIENTS & METHODS

One hundred and forty two recently diagnosed patients were included in the study. Cancer was proven histologically in 98 patients, and a control group of 44 patients had non-malignant disease. Of the 98 cancer patients, 54 were weight stable and 44 were weight losing. The controls were similarly divided into 27 weight stable and 17 weight losing patients. Pathological diagnoses are shown in Table 14.

The methods used are as described in Chapter 3.

TABLE 14 PATHOLOGICAL DIAGNOSES IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

Diagnosis	Cancer	
	Weight stable (n = 54)	Weight losing (n = 44)
Colorectal cancer	36	20
Gastric cancer	14	15
Bronchial cancer	2	5
Oesophageal cancer	2	2
Pancreatic cancer	-	2

	Control	
	Weight stable (n = 27)	Weight losing (n = 17)
Gastric ulceration	1	1
Duodenal ulceration	3	5
Pyloric stenosis	-	2
Cholelithiasis	15	3
Diverticular disease	3	2
Benign colorectal polyp	3	2
Ulcerative colitis	1	-
Crohn's disease	-	1
Hiatus hernia	1	1

RESULTS

Males predominated in the weight stable cancer group and females predominated in the weight stable control group (Table 15). There were no significant differences in mean age and mean height between the groups. The weight losing cancer patients had a significantly lower mean body weight, body weight$^{0.75}$, and LBM compared with their weight stable counterparts. The weight losing control patients had a significantly lower mean body weight and body weight$^{0.75}$ but no significant difference in LBM compared with their weight stable counterparts. Both weight losing groups had lost in excess of 15% of their pre-illness weight.

Anthropometric and calorimetric data are shown in Table 16. Both weight losing groups had significantly lower TST, MAC and MAMC measurements compared with their weight stable counterparts. The weight losing cancer patients had a significantly lower REE and $\dot{V}O_2$ (uncorrected for body size) than their weight stable counterparts, whereas no significant difference in REE and $\dot{V}O_2$ were found between the two control groups.

There was a significant correlation between MAMC and REE for each of the groups (Figure 6). The slope of the cancer weight stable regression line was significantly different from that of the cancer weight

TABLE 15 CLINICAL DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
n	54	44	27	17
Male : Female	38 : 16	20 : 24	7 : 20	8 : 9
Age (years)	66 ± 1.5	66 ± 1.6	62 ± 2.7	64 ± 3.8
Height (cm)	164 ± 1.3	161 ± 1.3	159 ± 1.6	162 ± 2.6
Body weight (kg)	64.2 ± 1.6[b]	52.2 ± 1.8[a]	66.0 ± 2.9[b]	55.4 ± 3.2
Body weight$^{0.75}$ (kg)	22.6 ± 0.4[d]	19.3 ± 0.5[a]	23.2 ± 0.7[d]	20.2 ± 0.9
Lean body mass (kg)	49.8 ± 1.7	43.6 ± 1.6[a]	48.9 ± 2.2	45.9 ± 2.3
Weight loss (%)	4 ± 0.5	18 ± 1.1[a]	1 ± 0.5[c]	16 ± 1.2[a]

mean ± s.e.m.

a = P<0.01 versus weight stable cancer patients and weight stable controls

b = P<0.05 versus weight losing controls

c = P<0.05 versus weight stable cancer patients

d = P<0.01 versus weight losing controls

TABLE 16 ANTHROPOMETRIC AND CALORIMETRIC MEASUREMENTS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
TST (cm)	13.9 ± 0.9	10.1 ± 0.7[b]	19.3 ± 1.7[b]	11.1 ± 1.2[c]
MAC (cm)	28.2 ± 0.5	24.2 ± 0.5[a]	29.9 ± 0.9	24.9 ± 0.9[a]
MAMC (cm)	23.8 ± 0.4	21.1 ± 0.4[a]	23.8 ± 0.5	21.4 ± 0.8[d]
REE (kcal/day)	1426 ± 25.6	1278 ± 37.8[b]	1340 ± 42.5	1279 ± 58.0[b]
$\dot{V}O_2$ (ml/min)	206.7 ± 3.53	187.3 ± 5.27[b]	193.9 ± 5.68[b]	184.1 ± 8.09[b]

mean ± s.e.m.

a = P<0.01 versus weight stable cancer patients and weight stable controls

b = P<0.01 versus weight stable cancer patients

c = P<0.01 versus weight stable controls

d = P<0.05 versus weight stable cancer patients and weight stable controls

losing regression line. The significant correlation between MAMC and REE persisted when all cancer patients were compared with all control patients, with the slopes of the regression lines being almost identical (Figure 7). When all weight stable patients were compared with all weight losing patients (Figure 8), the correlation between MAMC and REE remained significant, but on this occasion there was a significant difference between the slopes of the regression lines.

MAC also correlated significantly with REE (Figure 9), but less so than did MAMC. The slopes of the regression lines followed a similar pattern to those relating MAMC to REE. The slope of the cancer weight losing regression line was significantly different from the cancer weight stable line. When all weight stable patients were compared with all weight losing patients, there was a significant difference between the slopes of the regression lines.

There was also a significant correlation between MAMC and $\dot{V}O_2$, but this correlation was not as close as that between MAMC and REE. The correlations between MAMC and $\dot{V}O_2$ were:

Cancer weight stable: $r = 0.437$, 95% CI (1.6,6.0)
$P<0.01$

Cancer weight losing: $r = 0.684$, 95% CI (6.0,11.8)
$P<0.01$

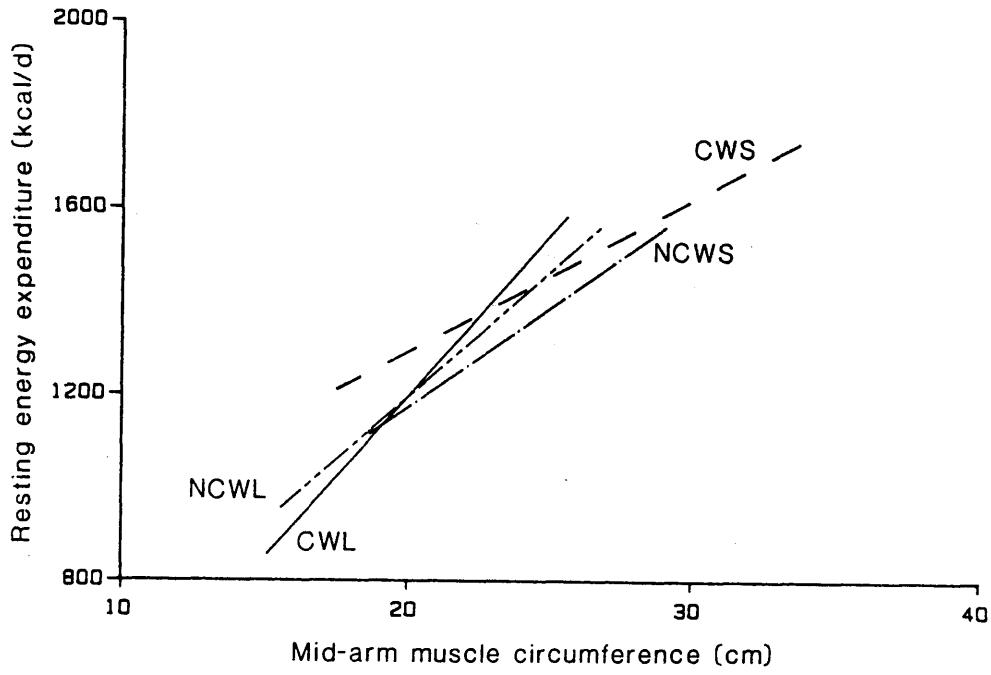


Figure 6

The relationship between resting energy expenditure and mid-arm muscle circumference in each of the groups

CWL (cancer weight losing)	y = -213 + 70.5x
n = 44; r = 0.751; P<0.01	95% CI (51.4,89.6)
CWS (cancer weight stable)	y = 628 + 33.3x
n = 54; r = 0.511; P<0.01	95% CI (17.8,48.8)
NCWL (control weight losing)	y = 89 + 55.6x
n = 17; r = 0.728; P<0.01	95% CI (28.6,82.6)
NCWS (control weight stable)	y = 304 + 43.5x
n = 27; r = 0.539; P<0.01	95% CI (16.4,70.6)

The CWL slope is significantly different from the CWS slope (P<0.01).

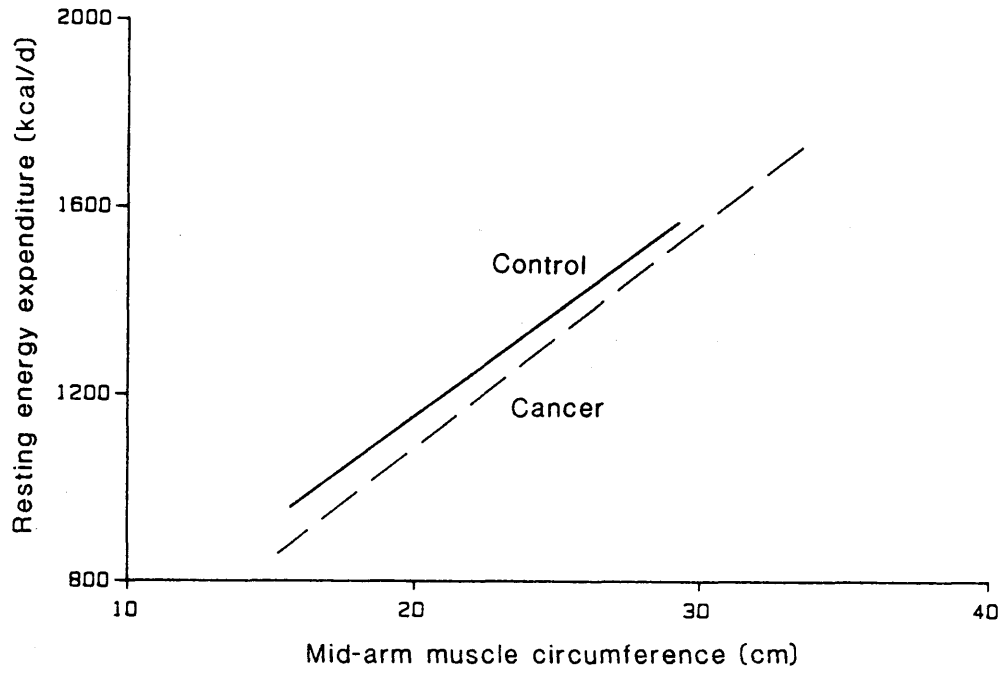


Figure 7

The relationship between resting energy expenditure and mid-arm muscle circumference in all cancer patients and all controls

Cancer	y = 240 + 49.3x
n = 98; r = 0.670; P<0.01	95% CI (38.2,60.4)
Control	y = 277 + 45.4x
n = 44; r = 0.619; P<0.01	95% CI (27.6,63.2)

No significant differences between the slopes.

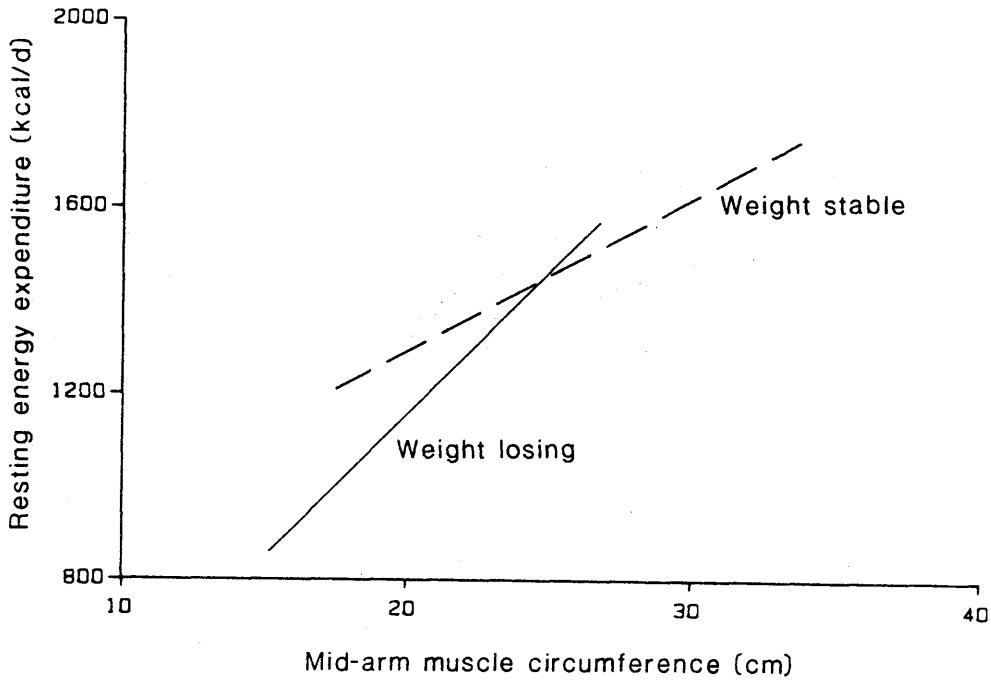


Figure 8

The relationship between resting energy expenditure and mid-arm muscle circumference in all weight stable patients and all weight losing patients

Weight stable	y = 518 + 36.8x
n = 81; r = 0.513; P<0.01	95% CI (23.0,50.6)
Weight losing	y = -108 + 65.3x
n = 61; r = 0.741; P<0.01	95% CI (49.9,80.7)

The weight stable slope is significantly different from the weight losing slope (P<0.01).

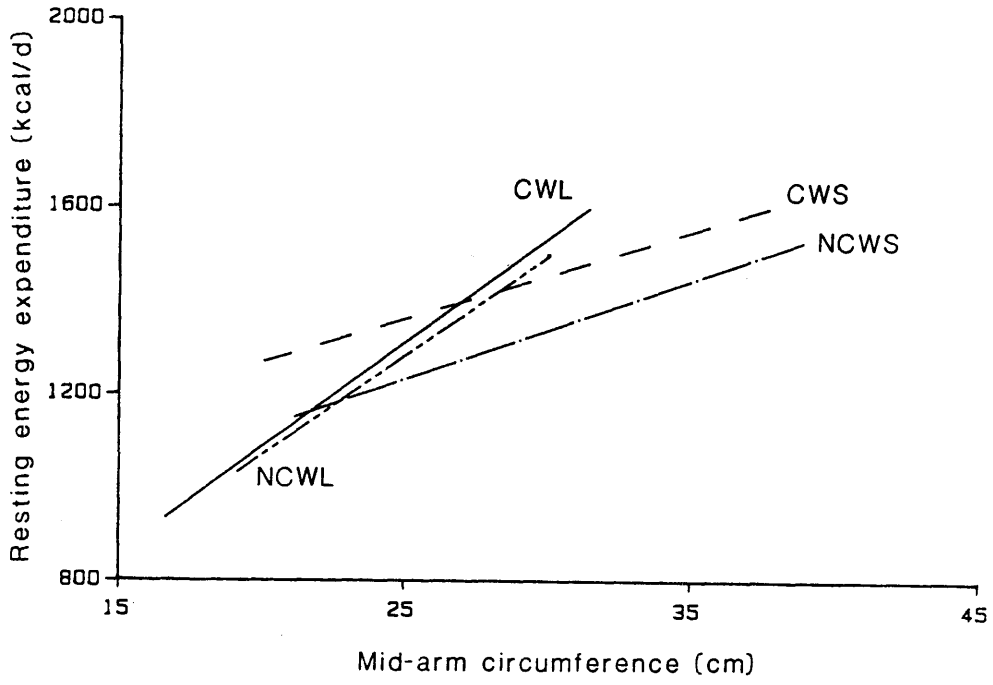


Figure 9

The relationship between resting energy expenditure and mid-arm circumference in each of the groups

CWL (cancer weight losing)	y = 178 + 45.4x
n = 44, r = 0.659; P<0.01	95% CI (29.4,61.4)
CWS (cancer weight stable)	y = 890 + 19.0x
n = 54; r = 0.352; P<0.01	95% CI (5.0,33.0)
NCWL (control weight losing)	y = 205 + 43.1x
n = 17; r = 0.667; P<0.01	95% CI (18.2,68.0)
NCWS (control weight stable)	y = 698 + 21.4x
n = 27; r = 0.444; P<0.05	95% CI (4.1,38.7)

The CWL slope is significantly different from the CWS slope (P<0.05).

Control weight stable: $r = 0.486$, 95% CI (1.4,9.0)
$P<0.05$

Control weight losing: $r = 0.726$, 95% CI (3.9,11.5)
$P<0.01$

where CI = confidence interval

REE correlated significantly with body weight, body weight$^{0.75}$ and LBM for each group (Table 17). No significant correlation was found when TST was related to either REE or $\dot{V}O_2$.

TABLE 17 CORRELATION BETWEEN RESTING ENERGY EXPENDITURE (REE) AND DIFFERENT INDICES OF BODY SIZE IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
REE related to:	Weight stable	Weight losing	Weight stable	Weight losing
Body weight	0.646 (6.9, 13.5)	0.804 (15.3, 19.3)	0.750 (7.2, 15.0)	0.772 (8.1, 19.9)
Body weight$^{0.75}$	0.645 (25.9, 51.3)	0.811 (49.2, 77.2)	0.706 (24.3, 56.9)	0.778 (29.7, 72.3)
Lean body mass	0.559 (5.1, 13.1)	0.845 (17.4, 26.4)	0.874 (13.5, 20.9)	0.887 (16.4, 28.6)

correlation coefficient
(95% confidence interval)

$P<0.01$ for all values

DISCUSSION

This study demonstrates a significant correlation between mid-arm muscle circumference (MAMC) and resting energy expenditure (REE) in both weight stable and weight losing patients with benign or malignant disease. Although the correlations between REE and body weight, body weight$^{0.75}$ and LBM were even closer than that between REE and MAMC, it is often impractical to weigh bed-bound patients, and the estimation of LBM requires the use of isotope dilution techniques (214) or total body potassium measurements (239).

The reason for assessing the value of anthropometric measurements in estimating REE is based on the observation that skeletal muscle mass relates well to basal heat production (240). Furthermore, it is less susceptible to the changes in extracellular fluid volume which occur in malnutrition (241). The arm is á useful site for anthropometry, as it is easily accessible and less affected by subcutaneous oedema than is the lower limb or subscapular region (242).

Brown and colleagues (242) reported a closer correlation when whole body oxygen consumption ($\dot{V}O_2$) rather than REE was related to MAMC. In the present study, although MAMC did correlate significantly with

$\dot{V}O_2$, the correlation was not as close as that between REE and MAMC. The uncorrected measurement of mid-arm circumference (MAC) also correlated significantly with REE, but less so than did MAMC, which takes account of mid-arm fat stores. Measurements of MAC have been shown by others (243) to be more reproducible and to correlate with weight change better than MAMC, and it has been suggested that the error margin associated with TST measurement is responsible for the poorer performance of MAMC. However, in the present study, MAMC has been shown to correlate more closely with REE than does MAC.

A significant finding in the present study is the altered relationship between REE and MAMC in the presence of significant weight loss. The correlation coefficients were considerably higher in both the weight losing groups compared with the weight stable groups. Since both the weight losing groups had smaller TST values than the weight stable groups, it may be that the inaccuracy caused by the presence of mid-arm fat stores was responsible for this difference in correlation.

The significant difference in the slopes of the regression lines for all weight stable and all weight losing patients (Figure 8) should be noted. The significantly steeper slope of the weight losing patients may imply that at low arm muscle

circumferences these patients are able to lower their REE to a greater extent than can weight stable patients. This interpretation is consistent with the theory put forward in Chapter 4, where REE was correlated with LBM.

In the present study, malignant disease did not appear to alter the relationship between MAMC and REE (Figure 7), suggesting that skeletal muscle is unlikely to play a major role in any alteration in REE seen in cancer patients. The regression lines in Figures 7 and 8 are very similar to those in Figures 4 and 5 (Chapter 4). This finding indicates that MAMC measurements reflect the metabolically active portion of the body.

It should be remembered that this study has been performed in patients who were largely unstressed, with no evidence of sepsis. Brown and colleagues (242) showed that the relationship between MAMC and whole body oxygen consumption was much poorer in the septic patient. Allowances will therefore have to be made for patients who have been stressed by trauma or surgery, and those who display any evidence of sepsis.

In conclusion, it would appear that mid-arm muscle circumference can be used to estimate resting energy expenditure in patients with benign or malignant

disease, although different relationships exist depending on whether the patient has or has not lost weight. This simple, easily performed measurement may therefore be of value in estimating the resting energy requirements of patients where access to indirect calorimetry facilities are unavailable. However, prospective evaluation of the accuracy of these regression equations is required.

CHAPTER 7

THE EFFECTS OF DIFFERENT TUMOUR TYPES ON RESTING ENERGY EXPENDITURE

INTRODUCTION

In the large group of cancer patients studied in Chapter 4, the type of tumour present did not appear to influence REE significantly. It was noted, however, that patients with non-small cell bronchial cancer appeared to show a trend towards a slightly higher REE than that of patients with colorectal and gastric cancer.

Since some authors (39) have suggested that differing tumour types may modify REE in different ways it is necessary to subdivide the heterogeneous group of cancer patients described in Chapter 4. This chapter therefore contains a closer study of the relationship between REE and separate groups of patients with colorectal, gastric or non-small cell bronchial cancer. This study includes some of the patients investigated in Chapter 3 as well as some new patients.

PATIENTS & METHODS

Eighty four patients with recently diagnosed, histologically proven cancer were included in the study. Patients were divided into three groups depending on the type of cancer present. Fifty one patients had colorectal cancer, 22 had gastric cancer and 11 had non-small cell bronchial cancer. The presence or absence of hepatic metastases was assessed by ultrasound and computerised tomography. Patients with colorectal or gastric cancer found to have hepatic metastases had these confirmed histologically at subsequent laparotomy.

The methods used are as described in Chapter 3.

RESULTS

Clinical details are shown in Table 18. There was no significant difference in mean age between patients in the different tumour groups. There were, however, more males than females in each group. No significant differences were found between the groups with respect to mean body weight, mean LBM and mean percentage weight loss. Hepatic metastases were present in 13 patients (25.5%) with colorectal cancer, five patients (22.7%) with gastric cancer and 2 patients (18.2%) with bronchial cancer. There were no significant differences in the incidence of hepatic metastases between the groups.

REE has been expressed as kcal/kg body weight/day and as kcal/kg LBM/day (Table 19). When expressed as kcal/kg body weight/day the REE of bronchial cancer patients is significantly increased when compared with the other two groups. However, there is no significant difference between the groups when REE is corrected for LBM.

Significant correlations are shown between REE and LBM for each tumour type studied (Figures 10-12). The gradient of the lung cancer regression line is significantly steeper than that of the other two groups when REE is plotted against LBM (Figure 13). REE also correlates significantly with body weight for

TABLE 18 CLINICAL DETAILS OF PATIENTS WITH COLORECTAL, GASTRIC AND BRONCHIAL CANCER

	Colorectal	Gastric	Bronchial
n	51	22	11
Male : Female	29 : 22	14 : 8	9 : 2
Age (years)	67 ± 1.6	67 ± 2.1	61 ± 3.5
Body weight (kg)	60.8 ± 1.5	55.7 ± 3.2	55.9 ± 5.2
Lean body mass (kg)	49.2 ± 1.5	46.5 ± 2.3	48.8 ± 4.3
Weight loss (%)	8 ± 1.1	13 ± 2.1	10 ± 3.0

mean ± s.e.m.

No significant differences between the groups

TABLE 19 RESTING ENERGY EXPENDITURE (REE) IN PATIENTS WITH COLORECTAL, GASTRIC AND BRONCHIAL CANCER

Expression of REE	Colorectal	Gastric	Bronchial
kcal/kg/day	23.1 ± 0.4	23.3 ± 0.7	26.2 ± 0.9[a]
kcal/kg LBM/day	29.1 ± 0.8	27.7 ± 0.8	29.9 ± 0.8

mean ± s.e.m.

a = P<0.01 versus Colorectal cancer patients

a = P<0.05 versus Gastric cancer patients

each tumour type (Figure 14). In this case the lung cancer regression line is significantly steeper than the gastric cancer regression line, but not the colorectal cancer regression line.

There were no apparent differences in REE between patients with or without hepatic metastases, irrespective of the way in which REE was expressed (Table 20). However, some of the subgroups were too small to allow statistical analysis.

Measured and predicted REE are shown in Table 21. The Harris-Benedict formula underestimated REE for each tumour type.

Table 22 shows details of dietary intake, anthropometry and serum proteins. There were no significant differences in mean energy and protein intakes between the groups. Mean MAMC and TST measurements were all less than the expected normal values, indicating a loss of both muscle and fat in these patients. Mean serum protein levels were all within normal limits with the exception of the gastric cancer patients who had a low mean serum albumin.

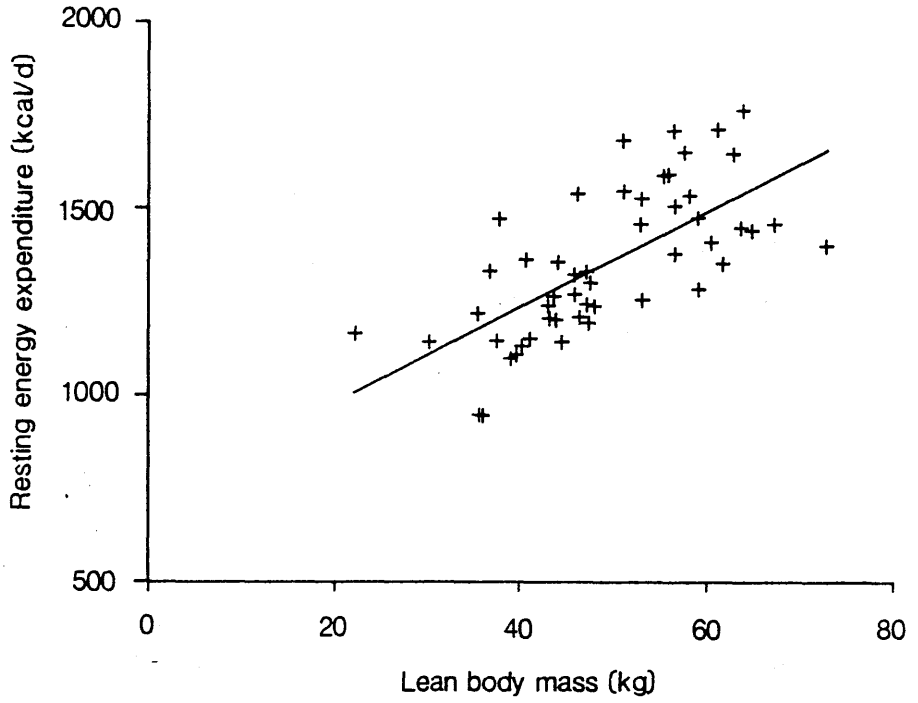


Figure 10

The relationship between resting energy expenditure and lean body mass in colorectal cancer patients

n = 51; r = 0.682; P<0.01 y = 728 + 13.5x

95% CI (9.3,17.7)

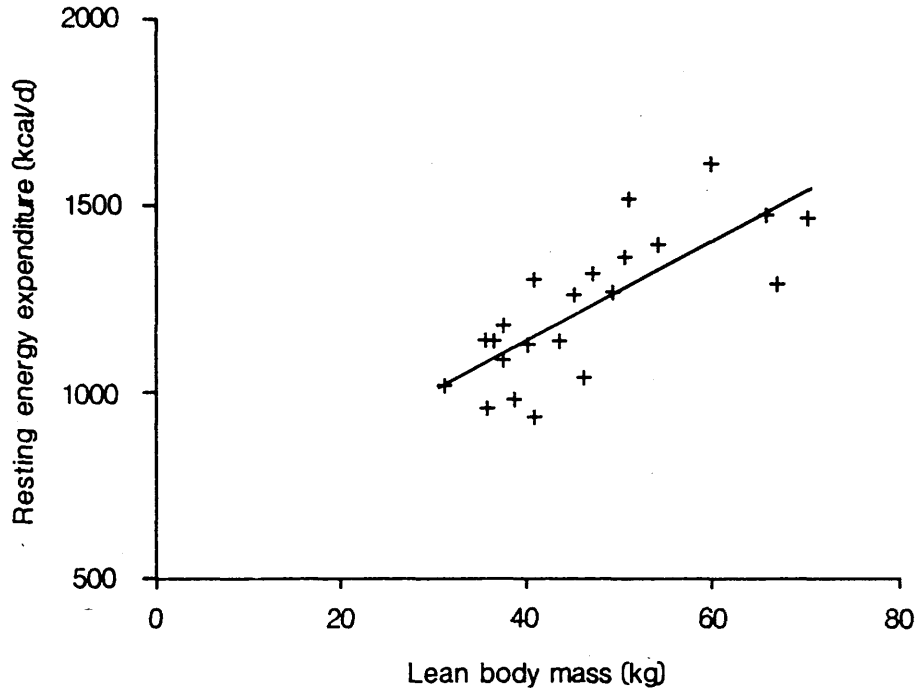


Figure 11

The relationship between resting energy expenditure and lean body mass in gastric cancer patients

n = 22; r = 0.767; P<0.01 y = 603 + 14.1x

95% CI (8.8,19.4)

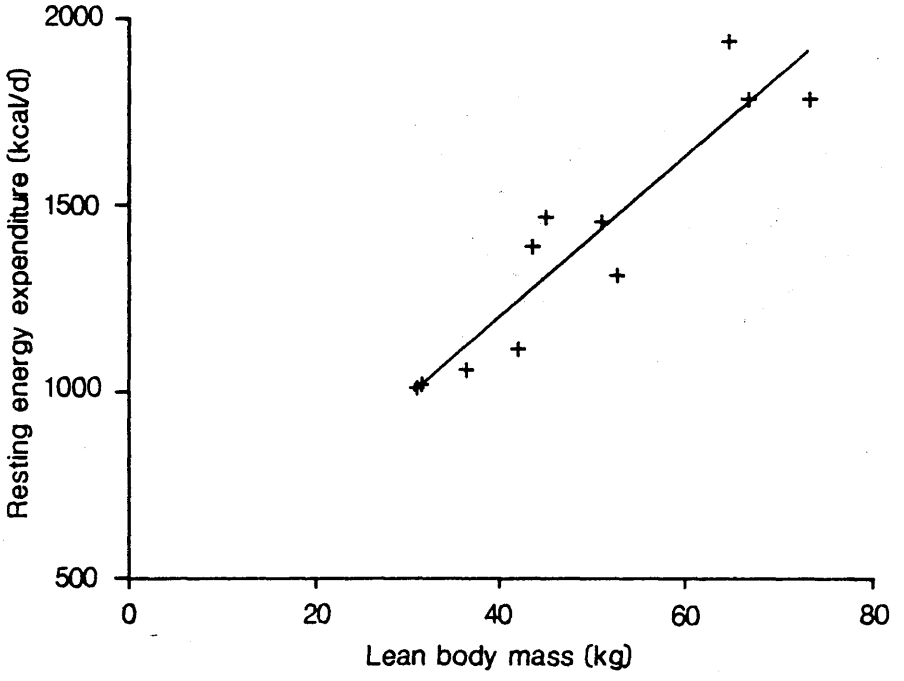


Figure 12

The relationship between resting energy expenditure and lean body mass in bronchial cancer patients

n = 11; r = 0.931; P<0.01 y = 320 + 22.9x

95% CI (16.9,28.9)

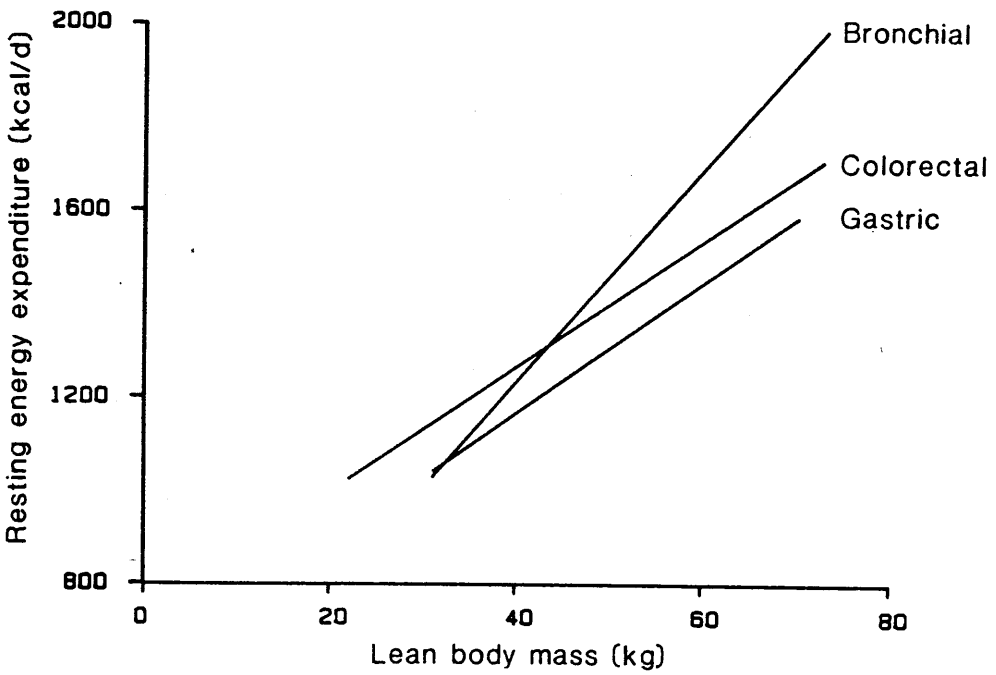


Figure 13

The relationship between resting energy expenditure and lean body mass in tumour group

(See Figs. 10-12 for group data)

The bronchial cancer slope is significantly different from the colorectal cancer slope ($P<0.05$) and the gastric cancer slope ($P<0.05$).

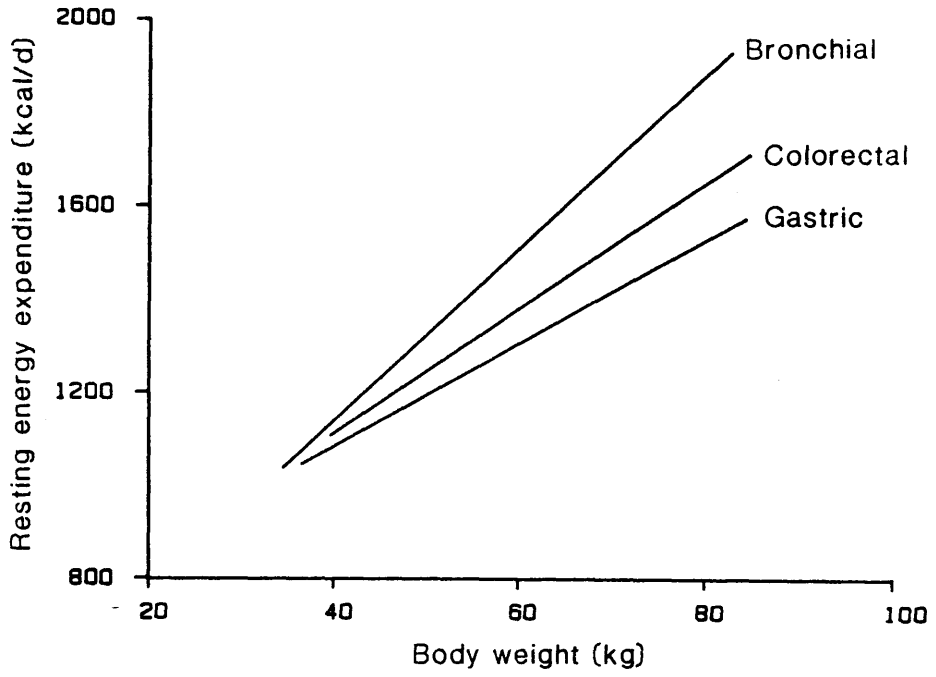


Figure 14

The relationship between resting energy expenditure and body weight in each tumour group

Colorectal	y = 571 + 13.6x
n = 51, r = 0.685; P<0.01	95% CI (9.4,17.8)
Gastric	y = 636 + 11.2x
n = 22; r = 0.685; P<0.01	95% CI (8.0,14.4)
Bronchial	y = 391 + 18.7x
n = 11; r = 0.923; P<0.01	95% CI (13.5,23.9)

The bronchial cancer slope is significantly different from the gastric cancer slope (P<0.05).

TABLE 20 RESTING ENERGY EXPENDITURE (REE) IN PATIENTS WITH COLORECTAL, GASTRIC AND BRONCHIAL CANCER WITH AND WITHOUT HEPATIC METASTASES

Expression of REE		Colorectal (n = 38)	Gastric (n = 17)	Bronchial (n = 9)
	kcal/kg/day	23.3 ± 0.4	23.1 ± 0.8	25.6 ± 1.0
No metastases				
	kcal/kg LBM/day	29.7 ± 1.0	27.3 ± 1.0	29.7 ± 1.0
		(n = 13)	(n = 5)	(n = 2)
	kcal/kg/day	22.7 ± 0.6	23.9 ± 1.2	29.3 ± 2.1
Metastases				
	kcal/kg LBM/day	27.5 ± 0.6	29.1 ± 1.2	31.2 ± 1.4

mean ± s.e.m.

No significant differences between the groups tested

TABLE 21 COMPARISON OF MEASURED AND PREDICTED (HARRIS-BENEDICT) RESTING ENERGY EXPENDITURE (REE) IN PATIENTS WITH COLORECTAL, GASTRIC AND BRONCHIAL CANCER

	Colorectal	Gastric	Bronchial
Measured REE (kcal/day)	1403 ± 29.9[a]	1266 ± 45.0	1438 ± 105.2
Predicted REE (kcal/day)	1280 ± 24.3	1214 ± 44.3	1260 ± 90.1

mean ± s.e.m.

a = $P<0.01$ versus predicted REE (Colorectal cancer patients)

TABLE 22 DIETARY INTAKE, ANTHROPOMETRY AND SERUM PROTEINS IN PATIENTS WITH COLORECTAL, GASTRIC AND BRONCHIAL CANCER

	Colorectal	Gastric	Bronchial
Energy intake (kcal/day)	1876 ± 87.9	1450 ± 120.8	1723 ± 218.2
Protein intake (kcal/day)	72.5 ± 3.0	60.2 ± 5.1	66.7 ± 7.6
MAMC (% expected)	94.2 ± 1.1	92.3 ± 3.5	88.2 ± 4.1
TST (% expected)	93.9 ± 4.5	76.9 ± 11.4	72.0 ± 10.2
Serum albumin (g/l)	36.8 ± 0.8	33.1 ± 1.2[a]	35.4 ± 1.3
Serum transferrin (g/l)	2.4 ± 0.1	2.2 ± 0.1	2.2 ± 0.2

mean ± s.e.m.

a = $P<0.01$ versus Colorectal cancer patients

DISCUSSION

Most studies of resting energy expenditure (REE) in cancer have involved investigation of cancer groups consisting of a variety of tumour types of widely differing sites and histological characteristics (8,11,27,34,35). These different tumours can cause a wide variety of symptoms and clinical effects. For example, an oesophageal neoplasm can affect the ability to ingest food due to mechanical blockage, whereas a sarcoma of the lower limb will have no direct effect on the gastrointestinal tract. These differences may be important, as both dietary intake (45) and weight loss (35) are known to influence REE. Despite these obvious difficulties, many workers have used heterogeneous groups of cancer patients for study and most have concluded that patients with cancer have an increased REE which may contribute to the development of cancer cachexia (6-8,11,27,34,35,225).

Mullen and colleagues (39) measured REE in 173 patients with gastrointestinal malignancies in an attempt to establish if there was a relationship between REE and tumour type. They concluded that patients with pancreatic and hepatobiliary cancer tended to have a decreased REE, whereas gastric cancer patients tended to have an increased REE. In contrast, the patients with colorectal or oesophageal cancer appeared to have a normal distribution of REE.

Unfortunately, these conclusions were reached by expressing measured REE as a percentage of predicted REE using the Harris-Benedict formula, the limitations of which have been highlighted in Chapter 5. In the present study, when REE was compared with the values predicted by the Harris-Benedict formula, mean predicted REE was lower than measured REE in each of the tumour types. Thus, had measured REE been expressed as a percentage of predicted REE, as in Mullen's study, each tumour type would have appeared to be associated with an increased REE, and colorectal cancer patients would appear to be hypermetabolic in these circumstances. Furthermore, the TST and MAMC measurements suggest that the gastric and bronchial cancer patients lost relatively more fat than muscle. This will alter body composition and can therefore lead to inaccuracies in prediction of REE when the formula used is dependent on total body weight.

In the present study, when REE is expressed in terms of kilograms of body weight, the bronchial cancer patients have an increased REE compared to the other groups. However, when REE is corrected for alterations in body composition and expressed in terms of lean body mass, there are no significant differences between the groups. Body composition therefore appears to be different depending on tumour type. Fat mass, calculated by subtracting lean body mass from body weight, was certainly lowest in the

bronchial cancer patients, and this is reflected in their TST measurement which was 28% less than the expected value.

An alternative method of comparing REE in different groups of patients would be to plot REE against either body weight or lean body mass for each tumour group and to compare the gradients of the resulting regression lines. The regression lines of the bronchial cancer patients (Figures 13 and 14) are steeper than that of the other groups, but the lines seem to converge as body weight and lean body mass falls. This finding supports the argument that some cancer patients can ultimately adapt their energy expenditure to the weight losing state (see Chapter 4). It would appear that the bronchial cancer patients are more liable to do this than the other groups studied.

The presence of hepatic metastases did not appear to alter REE in any of the tumour groups. This finding supports the conclusions of Chapter 4, but disagrees with other studies which suggest that patients with metastatic disease have an increased REE compared with patients who have localised malignancy (8,11,27).

Various metabolic abnormalities in cancer patients have been hypothesised to account for apparent alterations of REE in cancer patients. For example,

disordered cycling of substrates (51), increased Cori cycle activity (82), altered protein turnover (62) and the production by the tumour of proteins with metabolic effects (244) have all been offered as possible mechanisms for an elevation in REE. However, many of these studies have involved heterogeneous cancer groups (62,82), so it is not possible to attribute particular abnormalities to particular tumour types. In the present study, the differing relationships between REE and body size cannot readily be attributed to factors other than the type of tumour present. The tumour groups were well matched with respect to age, body weight and weight loss. No significant differences in energy and protein intakes were found, but it should be remembered that assessment of dietary intake by recall is subject to a considerable degree of error. The bronchial cancer patients had the lowest MAMC and TST measurements, but they were not significantly different from the other two groups. Serum albumin and transferrin levels in the bronchial cancer patients were within the normal range and were not significantly different from the other two groups.

In conclusion, in this study comparing patients with three different types of tumour, differing relationships between REE and indices of body size have been detected. These differences appear to be related to the type of tumour present, with bronchial

cancer having a different association between REE and body weight or lean body mass, when compared with colorectal or gastric cancer. Consequently, the use of heterogeneous cancer groups may be inappropriate in studies of resting energy expenditure and cancer.

CHAPTER 8

THE EFFECTS OF HEPATIC METASTASES ON RESTING ENERGY EXPENDITURE IN PATIENTS WITH COLORECTAL CANCER

INTRODUCTION

In Chapters 4 and 7 it was observed that patients with hepatic metastases had no significant differences in resting energy expenditure (REE) when compared with patients with localised malignancy. This conflicts with other reports which concluded that REE was increased in the presence of metastatic disease (11,27). For example, Macfie and colleagues (27) reported an increased REE in patients with metastases, while Arbeit and colleagues (11) suggested that REE was increased in patients with localised cancer, was greater still when metastases were present, and was reduced following surgical removal of the primary tumour.

In the present study 24 patients with colorectal cancer were studied before and after colorectal surgery in order to assess the effects of tumour removal or progression of metastatic disease on REE. In using each patient as his/her own control, the potential errors associated with the comparison of different groups of patients should be minimised. Furthermore, by comparing one group of patients who had been rendered "tumour free" with the other group who had progressive metastatic disease, any potential effect of tumour burden on REE should be maximised.

PATIENTS & METHODS

Twenty four patients with recently diagnosed, histologically proven colorectal cancer were studied preoperatively and again 3-10 months after recovery from surgical treatment of their tumours. All patients were assessed preoperatively with hepatic ultrasound and computerised tomography and nine were found to have hepatic metastases which were confirmed histologically at laparotomy (tumour bearing group). The remaining 15 patients had no evidence of hepatic metastases, and these patients had a "curative" resection (tumour free group). Hepatic ultrasound and computerised tomography were repeated in all patients at the time of the follow up study. None of the 15 tumour free patients had any clinical or radiological evidence of recurrence or progression of their disease. In all the tumour bearing patients, the presence of hepatic metastases was confirmed once again.

The methods used are as described in Chapter 3.

RESULTS

There were no significant differences in age, sex distribution and time to follow up between the groups (Table 23). The type of operation performed is shown in Table 24.

There were no significant differences in mean body weight between the groups either preoperatively or at follow up (Table 25). However, while the mean body weight of the tumour free patients remained virtually unchanged over the study period, the tumour bearing patients lost on average more than 4kg. There were no significant differences in preoperative mean LBM between the groups, and although both groups experienced a fall in mean LBM over the study period, this loss of LBM was small and not statistically significant.

REE and RQ are shown in Table 26. REE has been expressed as kcal/kg body weight/day and kcal/kg LBM/day. Irrespective of the method used to express REE, there were no significant differences in REE between the tumour free and tumour bearing patients either preoperatively or at follow up. There were also no significant differences in REE between the preoperative and follow up values within each group. The tumour free patients had a higher follow up RQ than the other groups but this was not statistically

TABLE 23 CLINICAL DETAILS OF THE TUMOUR FREE AND TUMOUR BEARING GROUPS OF COLORECTAL CANCER PATIENTS

	Tumour free	Tumour bearing
n	15	9
Male : Female	8 : 7	5 : 4
Age (years)	65.1 ± 2.9	67.7 ± 2.3
Time to follow up (months)	5.5 ± 0.6	4.6 ± 0.9

mean ± s.e.m.

No significant differences between the groups

TABLE 24 TYPE OF OPERATION PERFORMED IN THE TUMOUR FREE AND TUMOUR BEARING GROUPS OF COLORECTAL CANCER PATIENTS

Type of operation	Tumour free	Tumour bearing
Right hemicolectomy	3	1
Left hemicolectomy	2	-
Sigmoid colectomy	2	2
Anterior resection	1	1
A-P resection	4	2
Hartmann's procedure	3	1
Transverse loop colostomy	-	2

TABLE 25 CHANGES IN BODY WEIGHT AND LEAN BODY MASS (LBM) IN THE TUMOUR FREE AND TUMOUR BEARING GROUPS OF COLORECTAL CANCER PATIENTS

	Tumour free		Tumour bearing	
	Preoperative	Follow up	Preoperative	Follow up
Body weight (kg)	59.5 ± 2.0	60.2 ± 2.3	64.8 ± 3.8	60.4 ± 2.3
Change in body weight (kg)	+0.7 ± 0.9[a]		-4.4 ± 2.5	
LBM (kg)	45.1 ± 2.3	44.2 ± 1.3	51.7 ± 3.2	49.4 ± 1.9
Change in LBM (kg)	-0.9 ± 2.2		-2.3 ± 1.8	

mean ± s.e.m.

a = $P<0.05$ versus change in body weight in tumour bearing group

TABLE 26 PREOPERATIVE AND FOLLOW UP MEASUREMENTS OF RESTING ENERGY EXPENDITURE (REE) AND RESPIRATORY QUOTIENT (RQ) IN THE TUMOUR FREE AND TUMOUR BEARING GROUPS OF COLORECTAL CANCER PATIENTS

	Tumour free		Tumour bearing	
Expression of REE or RQ	Preoperative	Follow up	Preoperative	Follow up
kcal/kg/day	23.7 ± 0.8	25.1 ± 1.1	22.6 ± 0.8	24.2 ± 0.6
kcal/kg LBM/day	31.3 ± 1.2	33.3 ± 1.3	28.5 ± 1.4	29.6 ± 0.8
RQ	0.742 ± 0.019	0.838 ± 0.025	0.739 ± 0.055	0.722 ± 0.023

mean ± s.e.m.

No significant differences between the groups

significant.

Predicted REE using the Harris-Benedict formula has been compared with measured REE in Table 27. In each group, mean predicted REE was less than the measured REE. Only one patient (tumour bearing group, preop) had a predicted REE greater than the measured value.

There were no significant differences in MAMC and TST between the groups, although the tumour bearing patients had a mean TST 18% less than expected at follow up (Table 28). There were no significant differences in energy and protein intakes between the groups. Follow up serum albumin levels were higher in both groups compared to preoperative values, although this reached statistical significance in the tumour free patients only.

TABLE 27 COMPARISON OF MEASURED AND PREDICTED (HARRIS-BENEDICT) RESTING ENERGY EXPENDITURE (REE) IN THE TUMOUR FREE AND TUMOUR BEARING GROUPS OF COLORECTAL CANCER PATIENTS

	Tumour free		Tumour bearing	
	Preoperative	Follow up	Preoperative	Follow up
Measured REE (kcal/day)	1398 ± 48.9[a]	1498 ± 68.8[b]	1467 ± 80.9	1476 ± 77.4[c]
Predicted REE (kcal/day)	1249 ± 39.9	1255 ± 40.7	1323 ± 61.0	1263 ± 44.0

mean ± s.e.m.

a = P<0.05 versus predicted REE (tumour free - preoperative)

b = P<0.01 versus predicted REE (tumour free - follow up)

c = P<0.05 versus predicted REE (tumour bearing - follow up)

TABLE 28 PREOPERATIVE AND FOLLOW UP MEASUREMENTS OF ANTHROPOMETRY, DIETARY INTAKE AND SERUM ALBUMIN IN THE TUMOUR FREE AND TUMOUR BEARING GROUPS OF COLORECTAL CANCER PATIENTS

	Tumour free		Tumour bearing	
	Preoperative	Follow up	Preoperative	Follow up
MAMC (% expected)	92.4 ± 2.4	95.3 ± 2.7	95.6 ± 2.6	93.3 ± 2.6
TST (% expected)	94.2 ± 9.4	87.0 ± 11.1	94.2 ± 7.7	82.0 ± 5.0
Energy intake (kcal/day)	1845 ± 164	2150 ± 179	1953 ± 201	1792 ± 307
Protein intake (kcal/day)	69.6 ± 4.7	74.6 ± 6.8	74.7 ± 7.6	69.3 ± 13.8
Serum albumin (g/l)	35.1 ± 1.8[a]	43.3 ± 1.0	36.9 ± 1.6	41.2 ± 2.8

mean ± s.e.m.

a = $P<0.01$ versus tumour free - follow up group

DISCUSSION

In the present study 24 patients with colorectal cancer have been investigated preoperatively when all were tumour bearing, and again after surgery, by which time 15 were potentially tumour free and nine had a considerable tumour burden. Despite these two groups of patients having very different tumour burdens postoperatively, there is no evidence to support the belief that REE is affected by colorectal cancer, or that an increasing tumour load increases REE.

Arbeit and colleagues (11) have suggested that surgical excision of tumour bulk reduces REE in proportion to the mass of tumour excised, but the study involved only four patients and REE was expressed only in terms of body weight. This has not been seen in the present study, where there was an upwards trend in REE in both groups of patients during the study period (Table 27) irrespective of the way in which REE was expressed.

Mullen and colleagues (38,39), in studies of patients with gastrointestinal malignancies, concluded that REE was not dependent on tumour burden or the presence of hepatic metastases. However, they compared measured REE with that predicted from the Harris-Benedict formula which has been shown to be inaccurate in predicting REE in many patients (see

Chapter 5). Indeed, within the present study the Harris-Benedict formula consistently underestimated REE in each group, and in one patient, REE was underestimated by 34%.

Macfie and colleagues (27) reported an increase in REE of 289 kcal/day in patients with metastases (mainly hepatic) from gastrointestinal cancer. They calculated that this increment of REE could have led to the loss of almost 1 kg of fat per month. The tumour bearing patients in the present study lost on average 4.4 kg of body weight and this loss cannot be explained by an alteration in REE. An obvious explanation for the observed weight loss would be anorexia with consequent reduction in food intake. In the present study there were no significant differences in energy and protein intake between the groups. However, the slight increase in intake in the tumour free patients and the decrease in the tumour bearing patients over the study period are consistent with the observed changes in body weight and lean body mass, and are most likely to reflect an actual reduction in food intake by the tumour bearing patients. A small and insignificant increase in serum albumin levels has been observed in the tumour bearing group at follow up. This conflicts with other reports (11,150) and has failed to reflect the fall in body weight and lean body mass seen in these patients. It should be remembered, however, that many factors other

than nutritional status can affect serum albumin levels.

The low RQs in both groups preoperatively and in the tumour bearing group at follow up supports the evidence suggesting an increased utilisation of fat stores in cancer patients (11,245). Furthermore, TST measurements (reflecting fat stores) were less than expected in both groups and decreased over the study period, especially in the tumour bearing patients. No significant alteration was observed in MAMC measurements (reflecting muscle mass), although measurement of body weight and lean body mass suggests that tumour bearing patients lost predominantly fat together with a little lean tissue during the study period. This observation of loss of body fat warrants further investigation, especially in view of recent evidence that tumour necrosis factor or cachectin, produced by the host in response to the presence of cancer, may cause alterations in lipid metabolism (122,123).

In conclusion, REE and indices of body composition have been measured in patients before and after surgical treatment of colorectal cancer. Each patient therefore has acted as his/her own control, thus minimising the potential errors which can occur when different groups of patients are compared. It is concluded that neither surgical removal of the primary

tumour nor progression of metastatic hepatic disease significantly alters REE in patients with colorectal cancer. Thus if there is any increase in REE caused by the presence of cancer, it is within the limits of detection of indirect calorimetry and therefore is unlikely to be a significant cause of weight loss in these patients.

CHAPTER 9

THE EFFECTS OF CANCER AND WEIGHT LOSS ON THE OXIDATION OF BODY FUEL STORES

INTRODUCTION

The evidence of Chapters 5,7 and 8 suggesting that tumour bearing patients lose relatively more fat than lean tissue requires closer investigation. Alterations in fat and carbohydrate metabolism have been implicated in the development of cancer cachexia (9). For example, studies in rats have indicated increased endogenous fat utilisation in the presence of cancer (109,111,112), and although recent studies have shown an increase in fat utilisation in cancer patients compared with controls (10-12), some of the cancer groups have been very heterogeneous (11,12) and some control groups have been very small (12).

In the present study the effects of both cancer and weight loss on endogenous fat and carbohydrate oxidation rates have been investigated in patients with colorectal and gastric cancer, as well as in patients with nonmalignant illness.

PATIENTS & METHODS

Ninety three recently diagnosed patients were studied. Colorectal or gastric cancer was proven histologically in 70 patients, and a control group of 23 patients had nonmalignant illness (Table 29). Of the 70 cancer patients, 43 were weight stable and 27 were weight losing. The control group was similarly divided into 10 weight stable and 13 weight losing patients.

In the cancer patients, the presence or absence of hepatic metastases was assessed by ultrasound and computerised tomography and confirmed at subsequent laparotomy. Six of the weight stable patients and eight of the weight losing patients had hepatic metastases.

The methods used are as described in Chapter 3.

TABLE 29 CLINICAL DIAGNOSES IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

Diagnosis	Cancer	
	Weight stable (n = 43)	Weight losing (n = 27)
Colorectal cancer	31	17
Gastric cancer	12	10

	Control	
	Weight stable (n = 10)	Weight losing (n = 13)
Duodenal ulceration	2	5
Pyloric stenosis	-	1
Cholelithiasis	2	1
Benign colorectal polyp	4	2
Diverticular disease	1	2
Crohn's disease	-	2
Ulcerative colitis	1	-

RESULTS

There was no significant difference in mean age between the groups (Table 30). The weight losing cancer patients had a significantly lower mean body weight and LBM than their weight stable counterparts. The weight losing controls had a significantly lower mean body weight but no significant difference in LBM, compared with their weight stable counterparts. Both the weight losing groups had lost 15% or more of their pre-illness body weight.

Anthropometric and nutritional details are shown in Table 31. Mean MAMC and TST measurements were significantly lower in both weight losing groups compared with their weight stable counterparts. This was especially evident for the TST measurements which were almost 30% less than expected standard values for both the weight losing groups. The weight losing cancer patients had significantly lower mean serum albumin and transferrin levels compared with the other three groups. No significant differences were detected in mean energy intakes, but both cancer groups had a significantly reduced protein intake compared with the weight stable controls.

REE has been expressed as kcal/kg body weight/day and as kcal/kg LBM/day (Table 32). When REE is expressed in terms of body weight, both weight losing

TABLE 30 CLINICAL DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
n	43	27	10	13
Male : Female	28 : 15	12 : 15	2 : 8	7 : 6
Age (years)	65.1 ± 1.6	67.0 ± 2.3	59.1 ± 4.5	58.3 ± 4.8
Body weight (kg)	63.9 ± 2.1[b]	53.9 ± 2.2[a]	70.8 ± 5.0[b]	56.3 ± 2.8
Lean body mass (kg)	51.4 ± 1.9	45.4 ± 2.0[c]	51.5 ± 3.3	46.8 ± 2.4
Weight loss (%)	3 ± 0.5	17 ± 1.2[a]	2 ± 0.8	15 ± 1.4[a]

mean ± s.e.m.

a = P<0.01 versus weight stable cancer patients and weight stable controls

b = P<0.05 versus weight losing controls

c = P<0.05 versus weight stable cancer patients

TABLE 31 ANTHROPOMETRIC AND NUTRITIONAL DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
MAMC (% expected)	97.0 ± 1.8	90.7 ± 1.6[a]	106.1 ± 4.2[c]	93.5 ± 2.9[b]
TST (% expected)	104.3 ± 6.8	73.1 ± 5.3[a]	147.7 ± 18.1[c]	70.8 ± 6.8[b]
Serum albumin (g/l)	37.8 ± 0.8	33.2 ± 1.0[d]	39.6 ± 1.1	39.5 ± 1.2
Serum transferrin (g/l)	2.6 ± 0.1	2.2 ± 0.1[d]	2.7 ± 0.2	2.8 ± 0.2
Energy intake (kcal/day)	1865 ± 98.9	1587 ± 184.5	2314 ± 248.5	2172 ± 373.6
Protein intake (g/day)	70.3 ± 2.9	59.6 ± 6.2[b]	86.7 ± 7.0[c]	70.9 ± 6.3

mean ± s.e.m.

a = P<0.01 versus weight stable cancer patients and weight stable controls

b = P<0.01 versus weight stable controls

c = P<0.05 versus weight stable cancer patients

d = P<0.01 versus other three groups

TABLE 32 RESTING ENERGY EXPENDITURE (REE), RESPIRATORY QUOTIENT (RQ) AND URINARY NITROGEN IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
kcal/kg/day	22.7 ± 0.5[a]	24.6 ± 0.6[c]	20.6 ± 0.8	23.5 ± 0.8[b]
kcal/kg LBM/day	28.0 ± 1.0	29.3 ± 0.8	26.0 ± 1.6	28.2 ± 0.5
RQ	0.802 ± 0.009	0.786 ± 0.011	0.828 ± 0.017	0.806 ± 0.021
Urinary nitrogen (g/day)	5.4 ± 0.5	4.3 ± 0.3	5.2 ± 0.7	4.4 ± 0.5

mean ± s.e.m.

a = $P<0.05$ versus weight stable controls and weight losing cancer patients

b = $P<0.05$ versus weight stable controls

c = $P<0.01$ versus weight stable controls

groups have a significantly higher mean REE than their weight stable counterparts. However, there are no significant differences in REE between the groups when REE is expressed in terms of LBM. There were no significant differences in RQ or daily urinary nitrogen excretion between the groups.

Oxidation rates of endogenous fat and carbohydrate are shown in Table 33. As with REE, these oxidation rates have been expressed in terms of kg of body weight and kg of LBM to allow comparison between groups. When fat oxidation is expressed in terms of body weight, the weight losing cancer patients have a significantly increased mean fat oxidation rate compared with the other three groups. There are no significant differences between the groups when carbohydrate oxidation is expressed in terms of body weight. When fat and carbohydrate oxidation rates are expressed in terms of LBM, no significant differences are detected between the groups.

It is evident from Table 33 that both cancer groups have higher mean fat oxidation rates and lower mean carbohydrate oxidation rates than both control groups, irrespective of the way in which these rates are expressed. When fat and carbohydrate oxidation rates of all the cancer patients are compared with those of all controls (Table 34), mean fat oxidation rates are significantly higher and mean carbohydrate

TABLE 33 FAT AND CARBOHYDRATE OXIDATION RATES IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing
Fat oxidation:				
(g/kg/day)	1.39 ± 0.08	1.68 ± 0.12[a]	1.07 ± 0.16	1.27 ± 0.14
(g/kg LBM/day)	1.69 ± 0.13	2.02 ± 0.16	1.45 ± 0.19	1.54 ± 0.17
Carbohydrate oxidation:				
(g/kg/day)	1.79 ± 0.20	1.54 ± 0.22	2.10 ± 0.33	2.38 ± 0.47
(g/kg LBM/day)	2.47 ± 0.24	1.82 ± 0.27	2.88 ± 0.43	2.77 ± 0.51

mean ± s.e.m.

a = $P<0.05$ versus weight stable cancer patients and weight losing controls

a = $P<0.01$ versus weight stable controls

TABLE 34 FAT AND CARBOHYDRATE OXIDATION RATES COMPARING ALL CANCER PATIENTS WITH ALL CONTROLS

	Cancer (n = 70)	Controls (n = 23)	P
Fat oxidation:			
(g/kg/day)	1.50 ± 0.07	1.18 ± 0.10	<0.01
(g/kg LBM/day)	1.83 ± 0.10	1.50 ± 0.12	<0.05
Carbohydrate oxidation:			
(g/kg/day)	1.69 ± 0.14	2.25 ± 0.29	<0.05
(g/kg LBM/day)	2.20 ± 0.18	2.82 ± 0.33	<0.05

mean ± s.e.m.

oxidation rates significantly lower in the cancer patients. Furthermore, patients with hepatic metastases have significantly higher fat oxidation rates and significantly lower carbohydrate oxidation rates than those cancer patients without hepatic metastases (Table 35). Patients with localised cancer have significantly higher mean fat oxidation rates ($P<0.05$) and significantly lower mean carbohydrate oxidation rates ($P<0.05$) than controls. No significant correlation was found between fat oxidation rates and the degree of weight loss for any of the groups.

TABLE 35 FAT AND CARBOHYDRATE OXIDATION RATES IN CANCER PATIENTS WITH AND WITHOUT HEPATIC METASTASES

	Metastases (n = 14)	No metastases (n = 56)	P
Fat oxidation:			
(g/kg/day)	1.89 ± 0.17	1.40 ± 0.07	<0.01
(g/kg LBM/day)	2.25 ± 0.23	1.71 ± 0.11	<0.05
Carbohydrate oxidation:			
(g/kg/day)	1.04 ± 0.28	1.85 ± 0.16	<0.01
(g/kg LBM/day)	1.20 ± 0.33	2.48 ± 0.20	<0.01

mean ± s.e.m.

DISCUSSION

This study demonstrates that patients with colorectal or gastric cancer have increased rates of body fat oxidation compared with patients who have nonmalignant illness. This increase in fat oxidation is especially evident in those cancer patients who have lost weight and those who have hepatic metastases. These findings are consistent with the observations made in previous chapters, where the body fat stores of cancer patients appeared to be more depleted than lean tissue stores, and support the findings of Watson and Sammon (233), referred to in Chapter 5.

Abnormalities of fat metabolism, including lipaemia (112) and loss of body fat stores (109,113), have been reported in experimental animals (see Historical Review). However, studies of fat metabolism in tumour-bearing patients have been less well controlled. In 1917 Murphy and colleagues (29) reported an increased resting energy expenditure in a patient with leukaemia, and concluded that most of the calories were supplied by fat. More recently, various workers have reported abnormalities in fat metabolism in cancer patients. For example, Waterhouse and Kemperman (10) showed diminished suppression of free fatty acid oxidation in response to a glucose load in five metastatic cancer patients compared with

controls. Other workers (11,106) have reported increased lipolysis and increased fat oxidation rates in cancer patients. For example, Arbeit and colleagues (11) reported an increased fat oxidation rate in four cancer patients with diffuse metastatic disease compared with 11 controls. They also reported increased fat oxidation rates in patients with metastatic cancer compared with controls, but found no significant difference between patients with localised cancer and controls. They found no significant difference between patients with metastatic and localised cancer. In contrast, patients with hepatic metastases in the present study had significantly increased fat oxidation rates and significantly decreased carbohydrate oxidation rates compared with patients with localised cancer.

Apart from the present study, only one other group of investigators has attempted to compare both weight stable and weight losing patients with cancer and nonmalignant illness. Edén and colleagues (12) showed that weight losing cancer patients had significantly increased glycerol turnover and concluded that this probably indicated an increased whole body lipolysis. However, their study involved only 20 patients with a wide variety of tumour types. Furthermore, their weight losing control group was not strictly comparable in that four of the six patients had lost weight several months or years previously and

therefore were not actively losing weight. In the present study fat and carbohydrate oxidation rates have been investigated in large groups of patients who were well matched with respect to age and weight as well as the degree and rate of weight loss. Only two tumour types have been studied, namely colorectal and gastric cancer, which have been shown to behave similarly with respect to resting energy expenditure (see Chapter 7). The use of heterogeneous cancer groups should be viewed with caution as differences in the metabolic behaviour of various tumour types have been reported (39 + Chapter 7). In the present study, there were no significant differences in fat or carbohydrate oxidation rates between the colorectal and gastric cancer patients.

The low triceps skinfold thickness (TST) measurements in the weight losing cancer patients are in keeping with the observed increase in endogenous fat oxidation in these patients. It should be noted, however, that the weight losing controls, while having a similar TST measurement, had normal fat oxidation rates. This may indicate an altered pattern of weight loss, with the controls having an initial rapid loss of body fat whereas the cancer patients have a more prolonged but less rapid loss.

Various workers (47,78,82) have reported altered carbohydrate metabolism in cancer patients. An

increased rate of anaerobic glycolysis with lactate production has been demonstrated in tumour cells (47,78), and increased glucose turnover has been found in tumour-bearing patients (82). These observations are compatible with the findings of the present study, since the observed decrease in carbohydrate oxidation rate in tumour-bearing patients could still occur against a background of increased Cori cycle activity and increased gluconeogenesis.

The inaccuracies associated with the assessment of dietary intake are most likely responsible for the lack of statistical significance between the low mean energy intakes in the cancer groups compared with the controls. Nevertheless, mean energy intake in the weight losing controls was greater than that of both the cancer groups. This suggests a degree of anorexia even in those cancer patients who had not lost weight and perhaps reflects the ability of the tumour-bearing host to compensate for a decreased food intake, at least in the early stages of the disease. The reduced serum albumin and transferrin levels in the weight losing cancer patients are similar to the findings of other studies (11,150).

REE measurements in this study are similar to those in Chapter 4, whereby no significant differences in REE are seen when REE is corrected for differences in LBM. No significant differences were found between

the groups in terms of RQ, a finding similar to that of others (11,27,35). However, in both this study and that of others (11,35) the respiratory quotients of the cancer groups have been consistently lower than those of the controls.

At present, no firm explanation as to the mechanisms responsible for altering fat metabolism in cancer patients can be offered. It is likely that it is hormonally mediated and changes in insulin, glucagon, cortisol and catecholamine levels may deserve further study. However, recent reports that macrophage-derived substances such as tumour necrosis factor or cachectin (122,123) interfere with fat metabolism suggest that this putative 'defense' against the tumour-bearing state may be involved in the development of cancer cachexia.

CHAPTER 10

THE RELATIONSHIP BETWEEN RESTING ENERGY EXPENDITURE AND WHOLE BODY PROTEIN TURNOVER IN PATIENTS WITH BENIGN AND MALIGNANT DISEASE

INTRODUCTION

In the previous chapter abnormalities of fat and carbohydrate metabolism have been demonstrated in patients with cancer. Abnormal protein metabolism in cancer patients has been reported by some workers (62,66,67), although there is conflicting evidence in the literature (68,69).

Whole body protein turnover (WBPT) has been estimated to account for up to 50% of resting energy expenditure (REE) in man (51). Consequently, abnormalities of WBPT may be reflected in alterations in REE. Few studies, however, have compared WBPT and REE in the same individuals.

The aim of this study was to assess the effects of cancer and weight loss on WBPT. The relationship between WBPT and REE has also been investigated. WBPT and REE have been measured simultaneously in weight stable and weight losing patients with colorectal, gastric and non-small cell bronchial cancer, as well as in patients with nonmalignant illness.

PATIENTS AND METHODS

Ninety six recently diagnosed patients were included in the study. Cancer was proven histologically in 74 patients, and a control group of 22 patients had nonmalignant illness. The pathological diagnoses and distribution of patients according to weight status are shown in Table 36.

The presence of hepatic metastases in the cancer patients was assessed by ultrasound and computerised tomography and confirmed histologically in those patients who underwent laparotomy. Seven patients (three weight stable, four weight losing) with colorectal cancer, four patients (one weight stable, three weight losing) with gastric cancer and five patients (all weight losing) with bronchial cancer had hepatic metastases.

The methods used are as described in Chapter 3.

TABLE 36 PATHOLOGICAL DIAGNOSES IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

Diagnosis	Cancer	
	Weight stable (n = 40)	Weight losing (n = 34)
Colorectal cancer	24	14
Gastric cancer	8	8
Bronchial cancer	8	12

	Control	
	Weight stable (n = 10)	Weight losing (n = 12)
Duodenal ulceration	2	5
Pyloric stenosis	-	1
Cholelithiasis	2	1
Diverticular disease	1	1
Benign colorectal polyp	4	2
Ulcerative colitis	1	-
Crohn's disease	-	2

RESULTS

There was no significant difference in mean age between the groups (Table 37). The weight losing gastric cancer, bronchial cancer and control patients had a significantly lower mean body weight and LBM than that of their weight stable counterparts. There were no significant differences between the weight losing and weight stable colorectal cancer patients with respect to body weight and LBM, although the weight losing colorectal cancer patients had lost more than 15% of their pre-illness body weight. The degree of weight loss was similar in each of the weight losing groups.

Rates of whole body protein synthesis and whole body protein degradation (which is equivalent to whole body protein turnover since patients were studied in the fasting state) are shown in Table 38. Results have been expressed in terms of the isotopic enrichment of both urinary ammonia and urinary urea. Rates of protein degradation were all greater than the corresponding rates of protein synthesis because patients were studied following an overnight fast.

Rates of protein synthesis and degradation were not affected significantly by the presence of weight loss in any of the cancer patients or controls, although in most cases mean rates of synthesis and

TABLE 37 CLINICAL AND NUTRITIONAL DETAILS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Colorectal cancer		Gastric cancer		Bronchial cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing	Weight stable	Weight losing	Weight stable	Weight losing
n	24	14	8	8	8	12	10	12
Male : Female	16:8	5:9	5:3	5:3	8:0	10:2	2:8	6:6
Age (years)	62±2.1	69±2.4	65±2.6	62±3.8	62±3.7	58±3.9	59±4.5	58±4.8
Body weight (kg)	60.4±3.2	56.3±1.9	68.1±5.1	50.7±2.8[a]	67.3±3.8	53.4±4.9[b]	70.8±5.8	55.5±3.3[c]
Lean body mass (kg)	44.2±1.9	47.1±2.1	53.7±2.6	42.8±2.3[a]	53.5±2.9	46.1±2.7[b]	51.3±2.9	46.2±3.1
Weight loss (%)	3±1.1	17±2.4[d]	3±1.1	20±2.8[a]	0.4±0.3	21±2.9[b]	2±1.3	15±2.1[c]
Serum albumin (g/l)	38.2±1.2	36.2±1.1	35.2±1.8	31.4±2.1[a]	37.3±1.6	32.4±2.0[b]	39.5±1.8	38.1±1.7

mean ± s.e.m.

a = P<0.01 versus weight stable gastric cancer patients

b = P<0.01 versus weight stable bronchial cancer patients

c = P<0.01 versus weight stable controls

d = P<0.01 versus weight stable colorectal cancer patients

TABLE 38 WHOLE BODY PROTEIN KINETICS OF WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Colorectal cancer		Gastric cancer		Bronchial cancer		Control	
Protein kinetics	Weight stable	Weight losing	Weight stable	Weight losing	Weight stable	Weight losing	Weight stable	Weight losing
Protein synthesis (gP/kg/day):								
ammonia	3.12±0.36[b]	3.69±0.33[b]	1.84±0.33	2.12±0.24	4.11±0.65[a]	4.04±0.65[a]	2.20±0.21	2.81±0.47
urea	4.20±0.41[b]	4.39±0.35[b]	2.81±0.39	3.66±0.47	5.14±0.51[a]	5.44±0.72[a]	3.04±0.38	4.02±0.54
Protein turnover (degradation) (gP/kg/day)								
ammonia	3.62±0.44[b]	4.19±0.27[b]	2.28±0.33	2.66±0.27	4.61±0.70[a]	4.71±0.56[a]	2.66±0.20	3.30±0.45
urea	4.70±0.39[b]	4.89±0.33[b]	3.25±0.38	4.20±0.47	5.65±0.57[a]	6.13±0.75[a]	3.49±0.34	4.53±0.49

mean ± s.e.m.

a = P<0.01 versus weight stable and weight losing gastric cancer patients and controls

b = P<0.01 versus weight stable and weight losing gastric cancer patients

degradation were slightly higher in the weight losing patients. Patients with bronchial cancer had significantly higher rates of protein synthesis and degradation than gastric cancer patients and controls. Patients with colorectal cancer had significantly higher rates of protein synthesis and degradation than patients with gastric cancer. There were no significant differences in protein synthesis and degradation rates between gastric cancer patients and controls. The pattern and significance of results were similar whether ammonia or urea values were used.

When WBPT and REE were expressed in terms of LBM (Table 39), the pattern of results was similar to that shown in Table 38. There were no significant differences in REE between the groups. The presence of hepatic metastases had no significant effect on protein synthesis and degradation rates (Table 40), although most patients with hepatic metastases had higher mean rates compared with those patients who had localised disease.

There was no correlation between WBPT and REE in any of the groups (Figure 15). There was also no correlation between WBPT and weight loss (Figure 16).

TABLE 39 WHOLE BODY PROTEIN TURNOVER AND RESTING ENERGY EXPENDITURE (REE) IN WEIGHT STABLE AND WEIGHT LOSING CANCER PATIENTS AND CONTROLS

	Colorectal cancer		Gastric cancer		Bronchial cancer		Control	
	Weight stable	Weight losing	Weight stable	Weight losing	Weight stable	Weight losing	Weight stable	Weight losing
Protein turnover (gP/kg LBM/day):								
ammonia	4.95±0.64	5.01±0.32	2.89±0.44[a]	3.15±0.25[a]	5.80±0.90[b]	5.46±0.64[b]	3.67±0.31	3.96±0.51
urea	6.36±0.69	5.83±0.41	4.10±0.47[a]	5.00±0.49[a]	7.10±0.69[b]	7.10±0.84[b]	4.80±0.49	5.51±0.64
REE (kcal/kg LBM/day)	30.8±1.9	28.3±1.1	27.8±1.8	30.8±1.7	29.2±1.8	30.9±1.3	28.2±1.2	28.4±0.6

mean ± s.e.m.

a = P<0.01 versus weight stable and weight losing bronchial and colorectal cancer patient.

b = P<0.05 versus weight stable and weight losing controls

TABLE 40 WHOLE BODY PROTEIN KINETICS IN CANCER PATIENTS WITH AND WITHOUT HEPATIC METASTASES

	Colorectal cancer		Gastric cancer		Bronchial cancer	
	Metastases	No metastases	Metastases	No metastases	Metastases	No metastases
Protein synthesis (gP/kg/day):						
ammonia	4.00±0.49	3.15±0.26	2.62±0.51	1.77±0.18	4.62±0.62	3.88±0.50
urea	4.52±0.66	4.21±0.29	3.77±0.68	3.06±0.36	6.00±0.66	5.10±0.59
Protein turnover (gP/kg/day):						
ammonia	4.50±0.61	3.67±0.27	3.28±0.44	2.20±0.19	5.40±0.65	4.43±0.52
urea	5.06±0.65	4.70±0.30	4.44±0.62	3.49±0.36	6.78±0.74	5.65±0.61
Protein turnover (gP/kg LBM/day):						
ammonia	5.64±0.87	4.82±0.40	3.76±0.40	2.77±0.27	6.15±0.76	5.41±0.64
urea	6.16±1.00	6.18±0.45	5.10±0.64	4.35±0.41	7.67±0.71	6.91±0.72

mean ± s.e.m.

No significant differences due to the presence of metastases

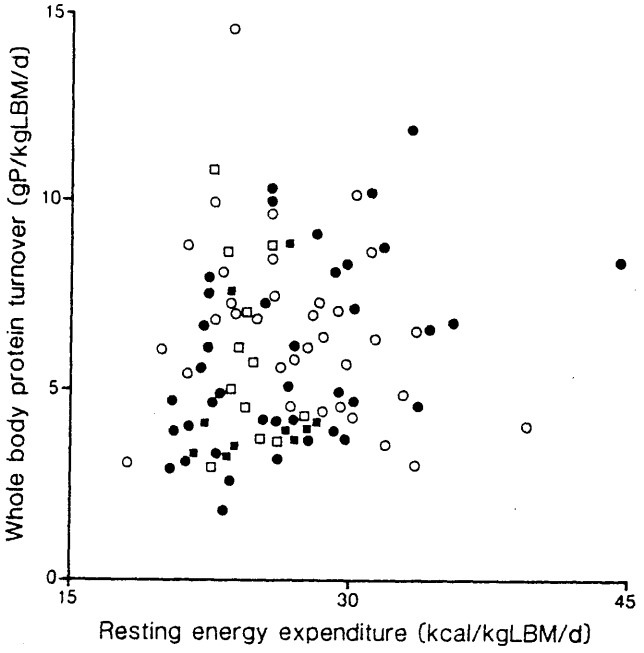


Figure 15

The relationship between resting energy expenditure and whole body protein turnover in weight stable and weight losing cancer patients and controls

weight stable cancer patients - solid circle

weight losing cancer patients - open circle

weight stable controls - solid square

weight losing controls - open square

There are no significant correlations in any of the groups.

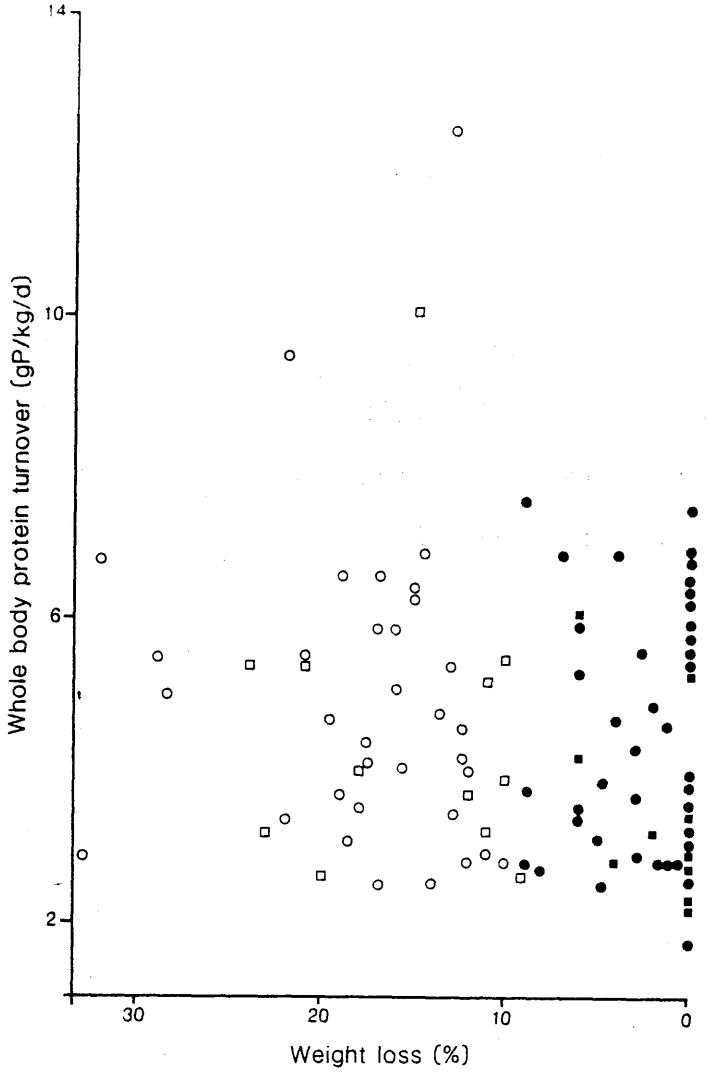


Figure 16

The relationship between weight loss and whole body protein turnover in weight stable and weight losing cancer patients and controls

weight stable cancer patients - solid circle

weight losing cancer patients - open circle

weight stable controls - solid square

weight losing controls - open square

There are no significant correlations in any of the groups.

DISCUSSION

The present study has demonstrated that patients with colorectal or non-small cell bronchial cancer tend to have elevated rates of WBPT compared with patients who have gastric cancer or nonmalignant illness. These findings were unaffected by weight loss and were consistent, irrespective of whether WBPT was expressed with reference to the patients' total body weight or lean body mass. Thus, independent of weight loss or altered body composition WBPT was increased in patients with bronchial and colorectal cancer.

Edén and colleagues (67) suggested that elevated WBPT may increase energy expenditure in the cancer patient and thus initiate or worsen a negative energy balance. In the present study no correlation was found between rates of WBPT and REE for any of the patient groups examined. Furthermore, there were no significant differences in the rates of REE between the groups of cancer patients and controls. Thus, although patients with colorectal and bronchial cancer had an elevated rate of WBPT, this was not associated with a detectable increase in REE. In Chapter 7 it was noted that the relationship between REE and various indices of body size was similar for patients with colorectal and gastric cancer, yet in the present study patients with colorectal cancer had WBPT rates which were more than 50% greater than those of the

gastric cancer patients. This finding supports the contention that changes in WBPT do not affect REE measureably.

It should be remembered that in the present study measurements of protein turnover and energy expenditure represent whole body rates. It is possible that in the presence of an increased WBPT, certain energy-requiring processes are reduced to compensate for the energy cost incurred, thereby maintaining a normal REE. It is also possible that although certain patients have an elevated rate of tracer flux, this may represent regional changes of protein turnover rather than a uniformly elevated rate throughout the body. It has been demonstrated that protein synthesis can be depressed in skeletal muscle and elevated in the liver of patients with cancer (63,68,70). Furthermore, the efficiency of energy conversion and of protein synthesis may vary from one tissue to another. Thus, since WBPT and REE are measurements derived from all tissues of the body it would be wrong to assume that these two variables should necessarily change in parallel.

Rates of protein turnover have been shown to decrease during uncomplicated starvation (62,246) and it has been proposed that this may be one mechanism of energy conservation. Since anorexia and decreased food intake are a major cause of weight loss in cancer

patients (3) it might be expected that protein turnover would show an adaptive fall with increasing weight loss. A recent study by Edén and colleagues (67) suggested that rates of WBPT were inversely related to the severity of weight loss in patients with cancer. However, the opposite result was obtained by Heber and colleagues (66) who showed a direct correlation between increased rates of WBPT and increasing weight loss. The small numbers of patients with different types of cancer, and the different labelled amino acids infused, may account for these contradictory results. The results of the present study indicate that there is no correlation between WBPT and weight loss in patients with colorectal, gastric and bronchial cancer, or in controls. If the patients' weight loss was predominantly due to a decrease in their food intake this study suggests that the normal adaptation to semistarvation is compromised in the presence of malignant disease.

Carmichael and colleagues (52), in a study of 11 patients with colorectal cancer, claimed that protein turnover, synthesis and degradation increased with advancing disease, while Ward and colleagues (247) demonstrated a similar finding in the immediate postoperative period in patients with disseminated cancer and hepatic metastases. In the present study, patients with hepatic metastases showed a small but insignificant increase in protein turnover, synthesis

and degradation compared with those patients without hepatic metastases.

It is possible that a small rise in REE may occur in the presence of an elevated WBPT, but that this may not be detected by the methods used. From stochiometry it can be estimated that the minimum energy required for the synthesis of 1 gram of protein is about 0.86 kcal (248). Using the isotopic enrichment of urinary urea to calculate rates of protein synthesis, the mean rate of protein synthesis for the colorectal and bronchial cancer patients was 5.0gP/kg/day compared with 3.6gP/kg/day for controls. This represents an increase of 1.4gP/kg/day. Since the mean weight of the patients was about 60kg, these cancer patients were synthesising approximately 84g more protein per day. This extra protein synthesis would require the expenditure of 72.2 kcal which represents approximately 5% of the patients' mean REE. A change of this magnitude would be at the limit of detection of the method used to measure REE. Moreover, REE can vary between normal individuals by up to 50% (249). Thus, if the above minimum estimates for the energy cost of protein synthesis are correct, the expected increase in REE may be undetectable.

Trauma and sepsis are the two main pathological states normally associated with increased whole body protein flux (250). In the present study WBPT rates

in the colorectal and bronchial cancer patients were up to 80% greater than those of the control patients, yet none of the patients had evidence of trauma or sepsis. The rate of protein synthesis in human tumours is approximately the same as the tissue of origin (251), and human cancers rarely exceed 1% of body mass (252). Thus, it is unlikely that the tumour itself could have caused the observed increase in WBPT. One possible explanation for the increased rates of WBPT may be the presence of an inflammatory response in these cancer patients.

An acute phase protein response can be demonstrated in the majority of individuals with progressive neoplasia (253,254). The acute phase protein response is a characteristic alteration in the serum concentration of certain circulating proteins which usually accompanies the body's inflammatory response to injury (255). Tumour necrosis, destruction of normal tissue, and infection of adjacent tissue are some of the factors independent of tumour type that could elicit such an acute phase protein response. The synthesis of acute phase proteins is thought to be mediated by the peptide monokine interleukin-1 (256). Recent studies have also suggested that circulating peptides which may be cleavage products of interleukin-1 can influence the protein metabolism of skeletal muscle (257). Thus, the immune response of the host may participate in the production of some of

the metabolic abnormalities seen in the tumour-bearing host.

In conclusion, WBPT appears to be elevated in patients with certain tumour types. This abnormal protein metabolism does not appear to be related to weight loss and has no detectable effect on REE. The possibility of an acute phase protein response contributing to an elevated WBPT requires further investigation.

CHAPTER 11

THE EFFECTS OF PERIPHERALLY-ADMINISTERED INTRAVENOUS NUTRITION ON THE METABOLIC RESPONSE TO TRAUMA IN PATIENTS FOLLOWING SURGERY FOR COLORECTAL CANCER

INTRODUCTION

In the preceding chapters various abnormalities in the substrate metabolism of patients with cancer have been demonstrated, and their possible relationship to the development of cancer cachexia has been discussed. There is evidence to suggest that debilitated patients who have lost weight have increased morbidity and mortality following surgical procedures (13,14,258-260). Thus, attempts to minimise the postoperative loss of body protein which is characteristic of the metabolic response to trauma (144,145) may be of value in debilitated cancer patients.

In this and the following two chapters, the metabolic response to surgery has been investigated in patients undergoing surgery for colorectal or gastric cancer. Attempts to modify this response using nutritional support (Chapters 11 and 12) and pharmacological manipulation (Chapters 12 and 13) are reported.

In the first of these studies, three peripherally-administered intravenous regimens have been compared in patients following surgery for colorectal cancer. A standard dextrose-saline regimen has been compared with an amino acid regimen as well as a more complete nutritional mixture containing

glucose, amino acids and fat. The effects of these regimens on postoperative fat and carbohydrate oxidation rates and nitrogen balance is reported.

PATIENTS & METHODS

Forty two patients about to undergo elective surgery for colorectal cancer were randomised to receive on the first four postoperative days one of the following fluid regimens:

(1) Dextrose-saline (DS) - consisting of 2 litres dextrose 5% and 1 litre normal saline per day.

(2) Amino acid (AA) - consisting of 1.5 litres of Vamin N (Kabi-Vitrum) diluted with 1.5 litres sterile water.

(3) Glucose-amino acid-fat (GAF) - Vitrimix (Kabi-Vitrum).

Solution (3) consists of 750ml Vamin Glucose which is mixed with 250ml Intralipid 20% in the ward using a simple vacuum device supplied with the solutions (Figure 17). Two litres of this solution were administered over each 24 hour period, in addition to 0.5 litres of dextrose 5% and 0.5 litres of normal saline. The amino acid profiles of the AA and GAF solutions were identical. Potassium supplements were added to each solution to provide 50mmol of potassium per day. Each regimen was infused continuously so that the delivery of amino acids, fat or carbohydrate remained constant over each 24 hour period. The calorie and nitrogen content of each of these fluid

Figure 17

The contents of the two bottles which constitute the glucose-amino acid-fat (GAF) regimen are mixed in the ward immediately prior to administration

regimens are shown in Table 41. Of the 1700 non-protein kcals in the GAF group, 1000 kcal were provided by fat (Intralipid 20%; Kabi-Vitrum) and 700 kcal were provided by carbohydrate. These solutions were administered through a peripheral vein via a peristaltic infusion pump. On the day of operation, fluid balance was maintained with blood products and crystalloid solutions as required. Fluid requirements in excess of 3 litres/day were provided in the form of either blood products or normal saline.

Preoperatively and on each of the first four postoperative days a 24 hour urine collection was obtained for total urinary nitrogen, urea, ammonia and 3-methylhistidine estimation, and blood samples were obtained for urea and electrolytes, liver function tests, plasma glucose, plasma insulin, serum albumin and serum transferrin. Approximate nitrogen balance was calculated by subtracting daily urinary nitrogen excretion from intravenous nitrogen input. This value was corrected for changes in total body urea nitrogen which occurred during the study period. Total body urea was calculated from blood urea and total body water measurements (see below) preoperatively and on the 4th postoperative day. A record of fluid input and output was made for each study day. No allowance was made for non-urinary loss of nitrogen, which was assumed to be constant in each group, since no patient had excessive nasogastric or drain losses.

TABLE 41 ENERGY AND NITROGEN CONTENT OF THE POSTOPERATIVE FLUID REGIMENS

	Dextrose-saline	Amino acid	Glucose-amino acid-fat
Energy (nonprotein kcal/day)	400	-	1700
Nitrogen (g/day)	-	14.1	14.1

Resting energy expenditure (REE) and respiratory quotient (RQ) were measured between 09.00 and 12.00 hours on the first preoperative day and on the second and fourth postoperative days as described in Chapter 3. Carbohydrate and fat oxidation rates were calculated using the formulae of Frayn (see Chapter 3).

Lean body mass (LBM) was derived from measurements of total body water made during the preoperative and fourth postoperative day calorimetry runs (see Chapter 3).

Peripheral venous cannulae sites were examined daily and the cannula was moved to another site if signs of inflammation were detected. Episodes of inflammation or phlebitis were recorded for each regimen.

RESULTS

Sixteen patients received the dextrose-saline (DS) regimen, 12 received the amino acid (AA) regimen and 14 received the glucose-amino acid-fat (GAF) regimen. There were no significant differences between the groups with respect to mean age, body weight, percentage weight loss and lean body mass (Table 42). The types of operation performed are shown in Table 43.

There were no significant differences in preoperative urinary nitrogen excretion between the groups (DS = 4.8 ± 0.4gN/d, AA = 7.1 ± 1.3gN/d, GAF = 4.5 ± 0.4gN/d). The cumulative nitrogen balance for the four postoperative days in the AA group (-10.3 ± 3.8gN) was significantly better than the DS group (-25.3 ± 3.1gN, $P<0.01$), while that of the GAF group (+7.7 ± 2.3gN) was significantly better than both the AA and DS groups ($P<0.01$). Nitrogen balance for each of the postoperative days is shown in Figure 18. Nitrogen balance in the AA group was significantly better than the DS group on the first ($P<0.01$) and second ($P<0.01$) postoperative days only. Nitrogen balance in the GAF group was significantly better than the AA group on the second, third and fourth postoperative days ($P<0.01$), and significantly better than the DS group on each of the postoperative days ($P<0.01$). There was a significant fall in nitrogen

TABLE 42 CLINICAL DETAILS OF PATIENTS IN THE DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT GROUPS

	Dextrose-saline	Amino acid	Glucose-amino acid-fat
n	16	12	14
Male : Female	7 : 9	9 : 3	8 : 6
Age (years)	64.5 ± 2.9	67.6 ± 2.7	63.8 ± 2.8
Body weight (kg)	59.3 ± 3.5	63.8 ± 3.8	61.5 ± 3.3
Weight loss (%)	7.9 ± 1.5	7.5 ± 2.3	9.1 ± 2.2
LBM (kg)	44.2 ± 2.6	53.5 ± 3.3	50.2 ± 3.1

mean ± s.e.m.

No significant differences between the groups

TABLE 43 TYPE OF OPERATION PERFORMED ON PATIENTS IN THE DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT GROUPS

Type of operation	Dextrose-saline	Amino acid	Glucose-amino acid-fat
Right hemicolectomy	4	2	1
Left hemicolectomy	1	1	-
Sigmoid colectomy	4	1	4
Anterior resection	4	1	3
A-P resection	1	5	2
Transverse loop colostomy	-	-	1
Hartmann's procedure	2	2	3

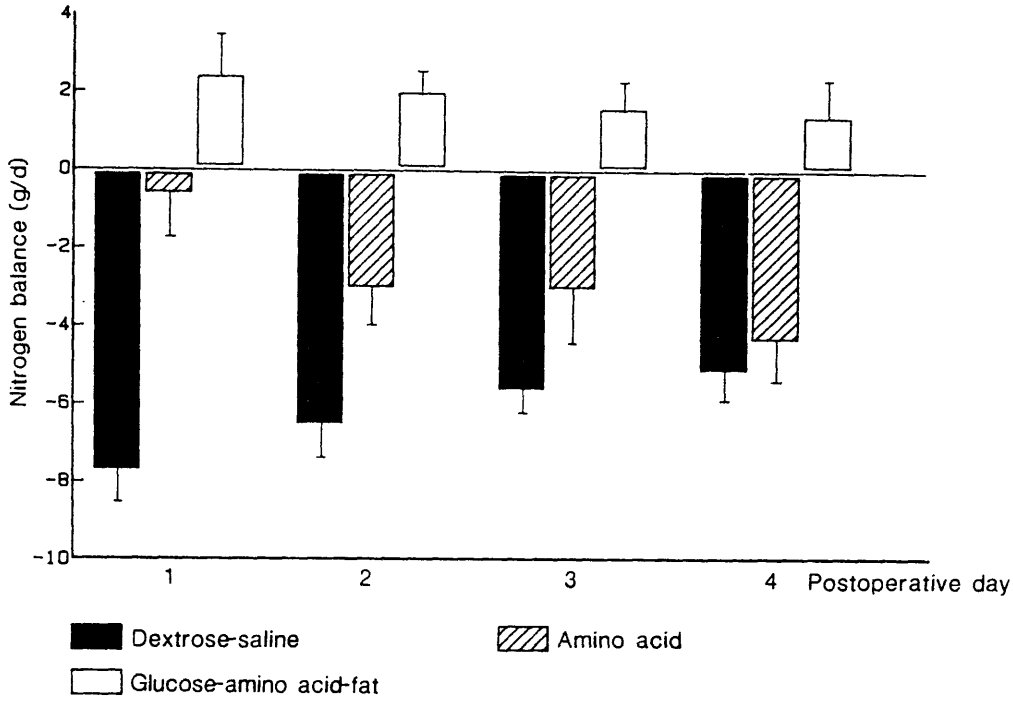


Figure 18

Mean daily nitrogen balance (± s.e.m.) for the first four postoperative days in patients receiving dextrose-saline, amino acid or glucose-amino acid-fat

balance in the AA group ($P<0.05$) and a significant improvement in the DS group ($P<0.01$) between the first and fourth postoperative days.

There were no significant differences between the groups in preoperative REE (Figure 19) and RQ (Figure 20). Postoperatively, REE increased significantly in the AA ($P<0.01$) and GAF ($P<0.01$) groups. On the second postoperative day, REE in the AA group was significantly greater than in the other two groups ($P<0.05$). RQ fell significantly on the second ($P<0.05$) and fourth ($P<0.01$) postoperative days in the AA group.

There were no significant differences between the groups in preoperative fat and carbohydrate oxidation rates. Carbohydrate oxidation rates are shown in Figure 21. The trends in this figure are very similar to those of Figure 20. Carbohydrate oxidation fell significantly ($P<0.01$) in the AA group postoperatively. Six patients in this group had negative values of carbohydrate oxidation on the second and fourth postoperative days. Carbohydrate oxidation was significantly lower in the AA group compared with the other two groups on the fourth postoperative day ($P<0.01$). Fat oxidation increased significantly ($P<0.05$) in the AA group postoperatively (Figure 22). On the second and fourth postoperative days, fat oxidation was significantly lower in the GAF

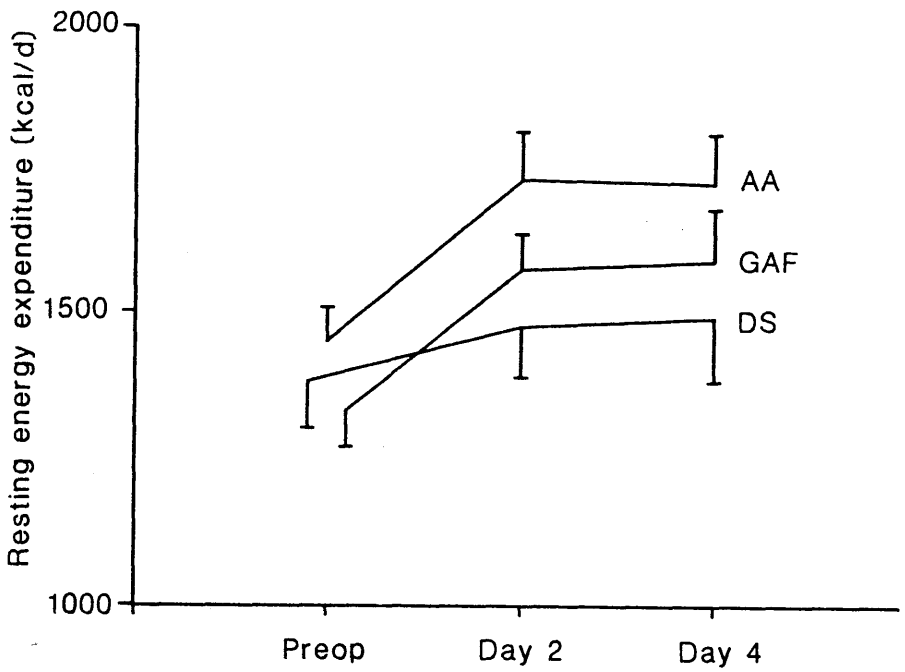


Figure 19

Mean resting energy expenditure (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

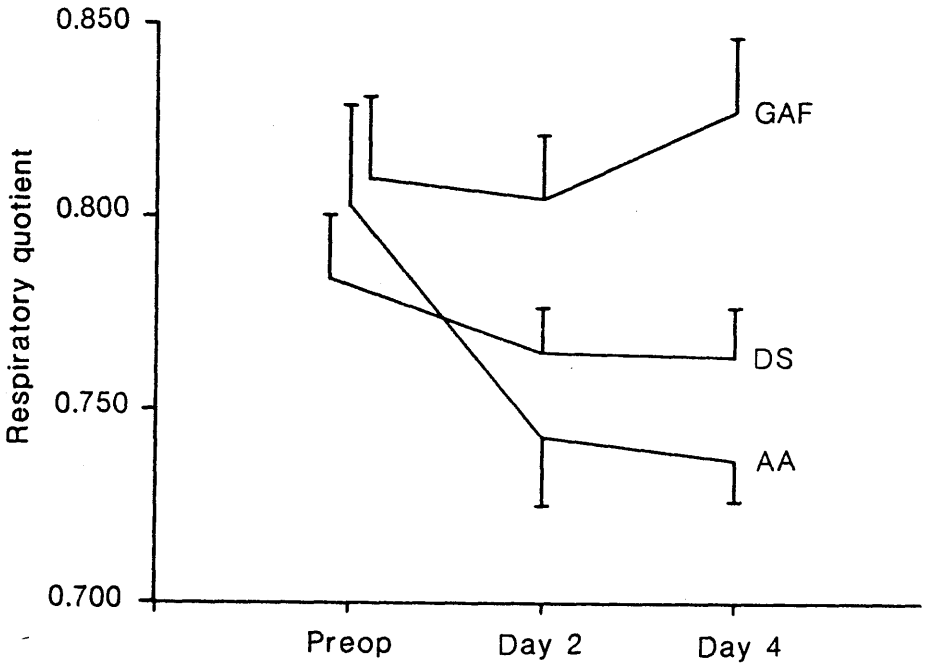


Figure 20

Mean respiratory quotient (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

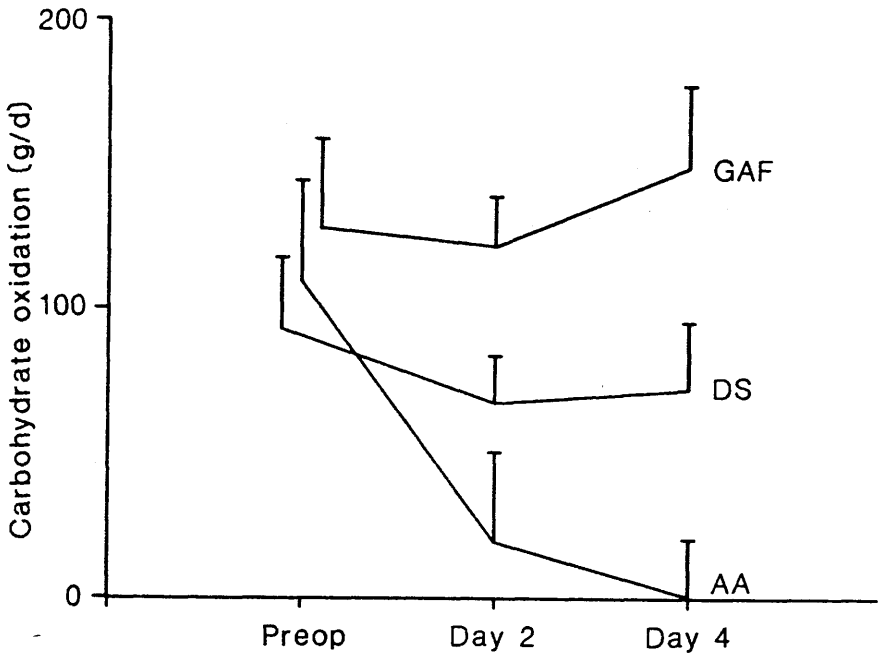


Figure 21

Mean carbohydrate oxidation rates (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

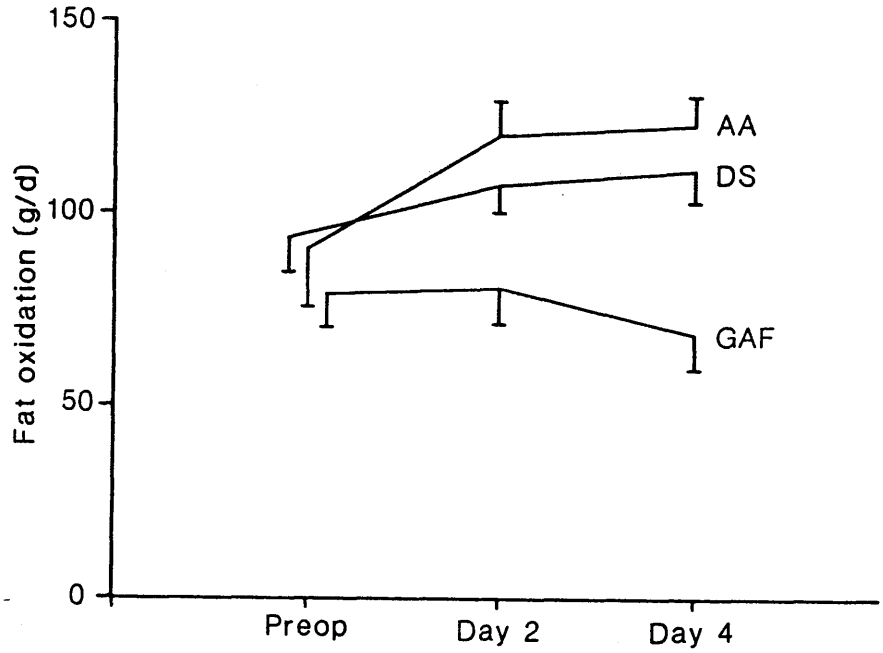


Figure 22

Mean fat oxidation rates (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

group compared with the other two groups ($P<0.01$).

Measured fluid balance for each of the postoperative days is shown in Figure 23. There were no significant differences in fluid balance between the groups. The cumulative fluid balance over the four postoperative days was significantly higher in the GAF group (+5.2 ± 0.62 litres) compared with the DS group (+3.4 ± 0.58 litres; $P<0.05$). Fluid balance in the AA group (+4.2 ± 0.44 litres) was not significantly different from the other two groups. This contrasts with the total body water measurements which showed a fall between the preoperative and postoperative measurements in the AA group (-2.07 ± 0.71 litres) which was significantly different from the DS (+1.94 ± 0.59 litres; $P<0.01$) and GAF (+1.30 ± 0.85 litres; $P<0.01$) groups. The number of patients requiring postoperative diuretic therapy was not significantly different between the groups (DS = 2 patients, AA = 1 patient, GAF = 2 patients).

Preoperatively there were no significant differences between the groups with respect to the urinary excretion of the metabolites shown in Table 44. Postoperatively, urinary nitrogen and urea excretion in the DS group was significantly lower than in the other two groups ($P<0.01$). Urinary nitrogen and urea excretion in the AA group was significantly higher than in the GAF group ($P<0.01$). There were no

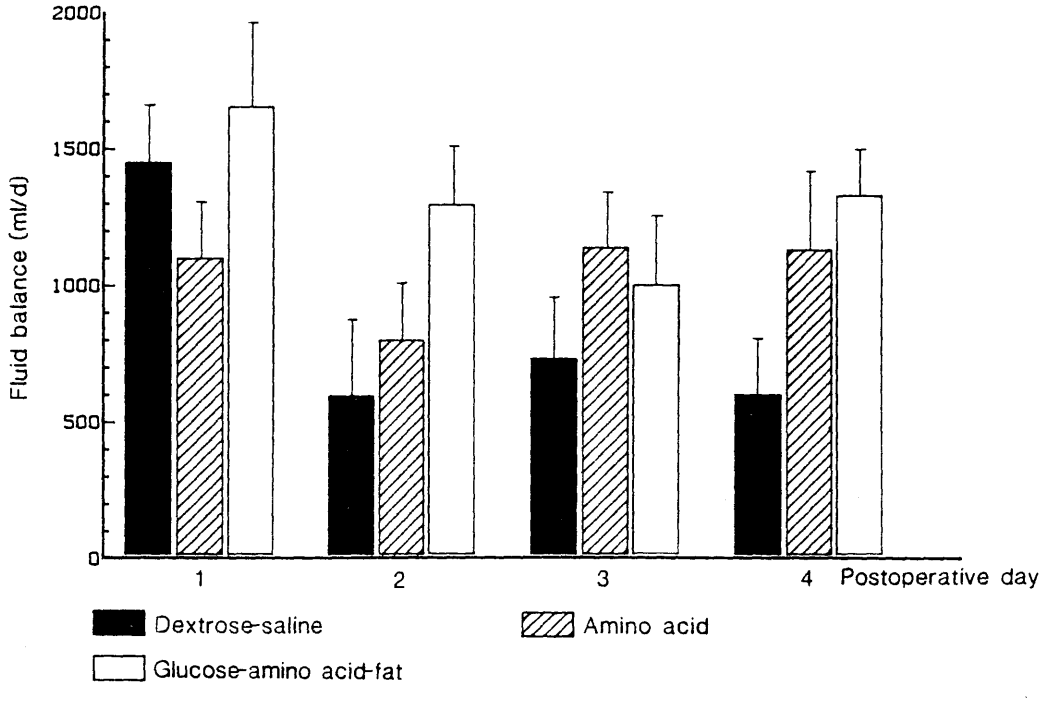


Figure 23

Mean daily fluid balance (± s.e.m.) for the first four postoperative days in patients receiving dextrose-saline, amino acid or glucose-amino acid-fat

TABLE 44 URINARY EXCRETION OF NITROGEN, UREA, AMMONIA AND 3-METHYLHISTIDINE IN PATIENTS IN THE DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT GROUPS

	Dextrose- saline	Amino acid	Glucose-amino acid-fat
Nitrogen: Preop (mmol/24hours)	339 ± 32.5	511 ± 92.2	328 ± 27.2
Postop (mmol/96hours)	1856 ± 197	4637 ± 260	3350 ± 117
Urea: Preop (mmol/24hours)	142 ± 16.8	219 ± 36.0	133 ± 12.3
Postop (mmol/96hours)	721 ± 103	1989 ± 114	1375 ± 62.8
Ammonia: Preop (mmol/24hours)	21.3 ± 3.0	26.7 ± 7.7	20.5 ± 2.7
Postop (mmol/96hours)	191 ± 21.0	291 ± 23.4	270 ± 17.1
Non-urea non-ammonia nitrogen:			
Preop (mmol/24hours)	33.7 ± 7.1	46.3 ± 15.4	41.5 ± 6.6
Postop (mmol/96hours)	223 ± 34.0	368 ± 92.1	330 ± 42.2
Urea (as % of nitrogen): Preop (%)	82.7 ± 3.8	87.5 ± 6.2	80.4 ± 2.0
Postop (%)	75.0 ± 3.1	85.8 ± 1.7	81.7 ± 1.6
Ammonia (as % of nitrogen): Preop (%)	6.6 ± 1.0	4.8 ± 0.7	6.8 ± 1.1
Postop (%)	11.1 ± 1.3	6.4 ± 0.6	8.1 ± 0.5
3-methylhistidine:			
Preop (umol/mmol creatinine/24hours)	13.8 ± 1.4	16.9 ± 1.6	17.7 ± 1.3
Postop (umol/mmol creatinine/96hours)	29.6 ± 1.2	30.4 ± 1.6	28.6 ± 1.8

mean ± s.e.m.

significant differences between the groups in the urinary excretion of nitrogen in forms other than that of urea and ammonia, nor in 3-methylhistidine excretion.

There were no significant differences between the groups with respect to preoperative serum urea and pre- and postoperative serum creatinine (Table 45). Postoperatively, serum urea fell significantly in the DS group ($P<0.01$) and increased in the other two groups ($P<0.01$).

Preoperatively, there were no significant differences between the groups with respect to plasma glucose and insulin (Table 45). Postoperatively plasma glucose increased significantly in the DS ($P<0.01$) and GAF ($P<0.01$) groups, and was significantly higher than that of the AA group ($P<0.01$), while plasma insulin increased significantly in all three groups ($P<0.01$). There were no significant differences in plasma insulin between the DS and AA groups, but plasma insulin levels in the GAF group were significantly greater than those of the other two groups ($P<0.05$).

Serum albumin and serum transferrin (Table 46) fell postoperatively in each group ($P<0.01$), and haematocrit fell in the DS ($P<0.05$) and GAF ($P<0.01$) groups.

TABLE 45 SERUM UREA AND CREATININE, PLASMA GLUCOSE AND INSULIN IN PATIENTS IN THE DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT GROUPS

	Dextrose-saline	Amino acid	Glucose-amino acid-fat
Serum urea (mmol/l):			
Preop	3.9 ± 0.3	4.8 ± 0.6	4.4 ± 0.3
Day 2	3.2 ± 0.3	6.4 ± 0.4	6.1 ± 0.5
Day 4	2.7 ± 0.4	7.7 ± 0.6	6.0 ± 0.7
Serum creatinine (umol/l):			
Preop	80 ± 3.4	80 ± 4.1	95 ± 8.6
Day 2	72 ± 4.2	77 ± 3.8	81 ± 8.1
Day 4	70 ± 4.7	72 ± 4.2	67 ± 6.4
Plasma glucose (mmol/l):			
Preop	5.5 ± 0.2	5.3 ± 0.3	5.4 ± 0.2
Day 2	6.9 ± 0.3	4.9 ± 0.1	6.4 ± 0.3
Day 3	7.0 ± 0.4	5.2 ± 0.3	6.4 ± 0.3
Day 4	5.9 ± 0.2	5.5 ± 0.5	6.2 ± 0.3
Plasma insulin (mU/l):			
Preop	10.1 ± 1.8	8.3 ± 0.9	13.0 ± 1.8
Day 2	14.1 ± 2.0	12.3 ± 1.5	51.5 ± 11.1
Day 3	15.4 ± 2.0	11.2 ± 1.7	36.8 ± 7.4
Day 4	11.3 ± 1.6	10.2 ± 2.3	31.7 ± 6.6

mean ± s.e.m.

TABLE 46 SERUM ALBUMIN, SERUM TRANSFERRIN AND HAEMATOCRIT IN PATIENTS IN THE DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT GROUPS

	Dextrose-saline	Amino acid	Glucose-amino acid-fat
Serum albumin (g/l):			
Preop	37.9 ± 1.3	37.3 ± 1.4	37.6 ± 1.5
Day 2	31.1 ± 0.9	33.1 ± 1.0	30.0 ± 1.2
Day 4	28.7 ± 0.8	32.2 ± 1.3	29.2 ± 1.3
Serum transferrin (g/l):			
Preop	2.3 ± 0.2	2.4 ± 0.1	2.6 ± 0.2
Day 2	1.7 ± 0.1	1.9 ± 0.1	1.7 ± 0.1
Day 4	1.6 ± 0.1	1.9 ± 0.1	1.7 ± 0.1
Haematocrit (%):			
Preop	39.0 ± 1.2	40.4 ± 1.2	39.2 ± 1.2
Day 2	34.5 ± 1.0	38.0 ± 1.5	33.9 ± 1.1
Day 4	32.0 ± 1.3	37.0 ± 1.6	31.6 ± 1.7

mean ± s.e.m.

Ten episodes of cannula site inflammation or mild phlebitis occurred in the GAF group compared with four in the AA group and three in the DS group (no significant differences). There were no significant differences between the groups with respect to postoperative complications and hospital stay (Table 47).

TABLE 47 POSTOPERATIVE COMPLICATIONS IN PATIENTS IN THE DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT GROUPS

Complication	Dextrose-saline	Amino acid	Glucose-amino acid-fat
Wound infection	2	3	3
Intra-abdominal abscess	1	-	-
Chest infection	2	5	2
Urinary infection	5	4	3
Septicaemia	2	-	1
Death	-	1	-
Diuretic therapy	2	1	2
Postoperative stay (days)*	16 ± 1.8	17 ± 2.4	14 ± 1.6

* mean ± s.e.m.

DISCUSSION

In 1973, Blackburn and colleagues (165) claimed that the infusion of amino acid solutions in the absence of glucose could improve nitrogen balance and conserve visceral proteins. Isotonic dextrose solutions had previously been shown to spare nitrogen (163,164), but Blackburn hypothesised that infused glucose stimulated insulin secretion and hence inhibited lipolysis. He suggested that the infusion of amino acids alone resulted in reduced insulin production with consequent enhancement of fat mobilisation and ketone production, thereby sparing the body's protein stores. However, various workers (166-168), comparing amino acid infusions alone with amino acid plus dextrose, have shown that the protein sparing effects of peripheral amino acids are due to the infused amino acids themselves, and are independent of plasma insulin levels and ketosis.

In the present study, the patients receiving amino acids alone (AA group) had a significantly improved nitrogen balance compared with those patients receiving dextrose-saline (DS group). This improvement, however, was apparent only on the first and second postoperative days, after which there was no significant difference in nitrogen balance between these two groups. This finding is similar to that of Garden and colleagues (170), who reported a

significant improvement in nitrogen balance on only the first postoperative day in patients receiving amino acid infusions providing 10g of nitrogen per day compared with patients receiving dextrose-saline. Other studies have shown a more prolonged improvement in nitrogen balance in patients receiving amino acid solutions containing 10-14g nitrogen per day(169,171). In these studies, the mean daily nitrogen balance was approximately -7g nitrogen per day. In the present study, mean daily nitrogen balance was less than -3g nitrogen per day. The type of amino acid solution used, and the balance of essential to non-essential amino acids, may be partly responsible for these differences in nitrogen balances.

A finding of note in the present study was the significant improvement in nitrogen balance with time in those patients receiving dextrose-saline, while nitrogen balance became more negative in the patients receiving amino acids. There was also a deterioration in nitrogen balance with time in those patients receiving a combination of glucose, amino acids and fat. The provision of this more complete nutrient mixture, however, resulted in a positive nitrogen balance on each of the study days. Even when allowances are made for non-urinary nitrogen loss of approximately 2g/day, these patients were virtually in nitrogen balance throughout the study period. 3-methylhistidine excretion reflects skeletal muscle

breakdown (261), although it has been shown that it is released from tissues other than skeletal muscle (262). In the present study, the similar postoperative excretion of 3-methylhistidine in each group suggests that any effect on nitrogen sparing is due to improved protein synthesis rather than decreased breakdown.

The significant postoperative rise in fat oxidation and fall in carbohydrate oxidation and RQ in the patients receiving amino acids, together with the significantly lower plasma glucose levels, appear initially to support the fat mobilisation theory of Blackburn (165). However, the similar postoperative plasma insulin levels in the DS and AA groups suggest that any nitrogen sparing effect of the amino acids occurs independently of plasma insulin levels, a finding supported by the work of Greenberg and colleagues (166). It should also be noted that there were no significant differences in postoperative RQ or fat oxidation between patients receiving amino acids and those receiving dextrose-saline. The negative carbohydrate oxidation rates in the amino acid group most probably represent gluconeogenesis, which might be expected to occur in the absence of infused glucose. It is unlikely, however, that these patients receiving amino acids were in a state of net glucose production throughout each 24 hour period. A possible explanation lies in the timing of the indirect

calorimetry measurement. It may be that following a period of sleep when REE would be lowest, these patients were in a state of maximal fat mobilisation and amino acid utilisation, with net glucose production. The stress associated with the nursing and physiotherapy activities which followed the calorimetry measurement may return these patients into a state of net glucose oxidation. This hypothesis would seem reasonable, as a persistent state of net glucose production would result in glycogenesis, which would be unlikely to occur in these patients.

The carbohydrate oxidation rates in the dextrose-saline and glucose-amino acid-fat groups were similar to the daily amount of infused glucose (see Figure 21). The high fat oxidation rates in the amino acid and dextrose-saline groups, in the absence of infused fat, indicate mobilisation of body fat stores. In contrast, those patients receiving 110g fat/day (GAF group) had fat oxidation rates which were significantly lower (60-75g/day). Thus, the amount of fat administered may be in excess of requirements.

The significant increase in postoperative REE in the AA and GAF groups (18-19% of preoperative REE) most probably reflects a combination of the postoperative metabolic response to trauma and the specific dynamic action of the infused nutrients (182,263). This increase was greatest in the AA group

and may reflect the energy cost associated with the metabolism of these amino acids. This high energy cost may contribute to the poor nitrogen balance in this group. The postoperative rise in REE of only 7% in the DS group is similar to the 9% rise reported by Harris and colleagues (182) whose patients received a similar low calorie fluid regimen.

The increases in serum and urine urea in the AA and GAF groups, together with the similar values for the non-urea non-ammonia urinary nitrogen, indicate that most of the infused amino acids in these groups has been metabolized and not simply excreted in the urine.

The discrepancy between the fluid balance and total body water measurements emphasises the fluid shifts which occur in the perioperative period. The fluid balance data commence on the first postoperative day and therefore do not take account of fluid administration on the day of surgery, so a comparison with the total body water measurements is not strictly justified. The mean daily fluid balance for each group was approximately +1 litre/day, a proportion of which will have been lost as insensible water loss. The fall in serum albumin and transferrin is mirrored by the fall in haematocrit, which reflects the positive fluid balance in each group.

The achievement of positive nitrogen balance using a peripherally-infused combination of glucose, amino acids and fat is important. Similar results have been obtained using a peripheral regimen containing 14.1g nitrogen and more than 3000 non-protein calories per day (173). The patients in that study, however, had not been subjected to major surgery immediately prior to commencing the nutritional support. Furthermore, although the solution was described as one for peripheral administration, half the patients received the solution through central venous cannulae. In the present study, the GAF regimen contained no additional trace elements or vitamins. If peripheral vein feeding were to continue for more than 3-4 days, these additives should be included. The stability of the mixture is unlikely to be affected, but this would require further investigation.

The episodes of mild phlebitis which occurred in all groups probably would be minimised by the daily resiting of peripheral venous cannulae. Messing and colleagues (264) demonstrated a reduction in venous complications due to the peripheral infusion of a similar GAF regimen (osmolarity 960 mOsm/l) when heparin was added to the solution. They also recommended daily resiting of the cannulae. The infusion of amino acids, with or without fat and glucose calories, is best given via the larger forearm veins, where few phlebitic episodes occurred in the

present study.

It is not surprising that there were no significant differences between the groups in postoperative morbidity and mortality. This study was designed to investigate the effects of different fluid regimens on the metabolic and biochemical changes which occur in the early postoperative period. The provision of calories and nitrogen for such a short duration would not be expected to have a demonstrable effect on clinical outcome.

In conclusion, this study demonstrates that a combination of glucose, amino acids and fat administered via a peripheral vein in the postoperative period can result in positive nitrogen balance. The infusion of amino acids alone only transiently improves postoperative nitrogen balance and has little to offer compared with the standard dextrose-saline regimen. Where the provision of peripheral intravenous nutritional support is desired, the use of a more complete nutritional mixture, namely, a combination of amino acids and both glucose and fat calories, is recommended.

CHAPTER 12

THE EFFECTS OF AN ANABOLIC STEROID AND PERIPHERALLY-ADMINISTERED INTRAVENOUS NUTRITION ON THE METABOLIC RESPONSE TO TRAUMA IN PATIENTS FOLLOWING SURGERY FOR COLORECTAL CANCER

INTRODUCTION

Various attempts have been made to manipulate the metabolic response to surgery by pharmacological agents. For example, the administration of insulin (188,189), growth hormone (20), naftidrofuryl (21) and anabolic steroids (196) each have been shown to influence postoperative nitrogen losses but not all studies have demonstrated this effect (190,191,197). In some studies a combination of intravenous nutrition and an anabolic steroid have resulted in a reduction in nitrogen excretion (192,193), while in others no effect on nitrogen balance was seen (197).

In the present study, the anabolic steroid stanozolol was given to determine its effect on the metabolic response to surgery in patients with colorectal cancer. The effects of combining the anabolic steroid with each of the postoperative nutritional regimens descibed in the previous chapter has also been investigated.

PATIENTS & METHODS

Sixty patients about to undergo elective surgery for colorectal cancer were included in the study. The study was stratified to include equal numbers of males and females in each treatment group. They were randomised to receive either a single intramuscular injection of 50mg stanozolol (Stromba, Sterling Research Laboratories) 24 hours prior to surgery or to a control group which received no injection. The patients were further randomised to receive on the first four postoperative days one of the fluid regimens described in Chapter 11, namely, dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF).

The methods used are as described in Chapters 3 and 11.

RESULTS

Each of the six groups consisted of five male and five female patients. There were no significant differences between the groups with respect to mean age, body weight, percentage weight loss and lean body mass (Table 48). The types of operation performed are shown in Table 49.

There were no significant differences in preoperative urinary nitrogen excretion between the groups (DS/stanozolol = 4.4 ± 0.4gN/d, DS/control = 5.3 ± 0.8gN/d; AA/stanozolol = 6.5 ± 1.5gN/d, AA/control = 5.3 ± 0.9gN/d; GAF/stanozolol = 4.1 ± 0.6gN/d, GAF/control = 4.2 ± 0.3gN/d). The cumulative nitrogen balance for the four postoperative days is shown in Figure 24. Nitrogen balance in those patients receiving amino acids alone was significantly improved ($P<0.05$) by the administration of stanozolol. Stanozolol did not significantly influence the cumulative nitrogen balance in those patients receiving either the dextrose-saline or glucose-amino acid-fat regimens. The cumulative nitrogen balance in both the AA groups was significantly better than that of both the DS groups ($P<0.01$), and that of the two GAF groups was significantly better than in the two AA and the two DS groups ($P<0.01$).

Cumulative nitrogen balance, displayed separately

TABLE 48 CLINICAL DETAILS OF THE STANOZOLOL AND CONTROL GROUPS OF PATIENTS RECEIVING DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT

	Dextrose-saline		Amino acid		Glucose-amino acid-fat	
	stanozolol	control	stanozolol	control	stanozolol	control
n	10	10	10	10	10	10
Male : Female	5 : 5	5 : 5	5 : 5	5 : 5	5 : 5	5 : 5
Age (years)	61.9±3.8	69.4±2.8	68.9±1.8	69.6±4.1	65.3±4.5	69.3±2.1
Body weight (kg)	62.3±4.7	61.2±4.1	63.1±4.4	60.4±2.6	59.2±3.9	59.1±3.9
Weight loss (%)	6.1±1.4	7.6±2.2	4.3±2.0	9.1±2.4	8.2±2.7	13.1±2.6
LBM (kg)	45.1±4.1	47.6±3.0	48.8±4.0	51.1±3.3	46.2±3.2	50.2±3.7

mean ± s.e.m.

No significant differences between the groups

TABLE 49 TYPE OF OPERATION PERFORMED IN THE STANOZOLOL AND CONTROL GROUPS OF PATIENTS RECEIVING DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT

	Dextrose-saline		Amino acid		Glucose-amino acid-fat	
Type of operation	stanozolol	control	stanozolol	control	stanozolol	control
Right hemicolectomy	2	3	1	5	2	-
Left hemicolectomy	1	1	1	-	-	1
Sigmoid colectomy	1	3	1	1	2	2
Anterior resection	4	1	1	-	3	2
A-P resection	1	-	4	2	1	3
Transverse loop colostomy	-	1	-	-	-	1
Hartmann's procedure	1	1	1	1	2	2

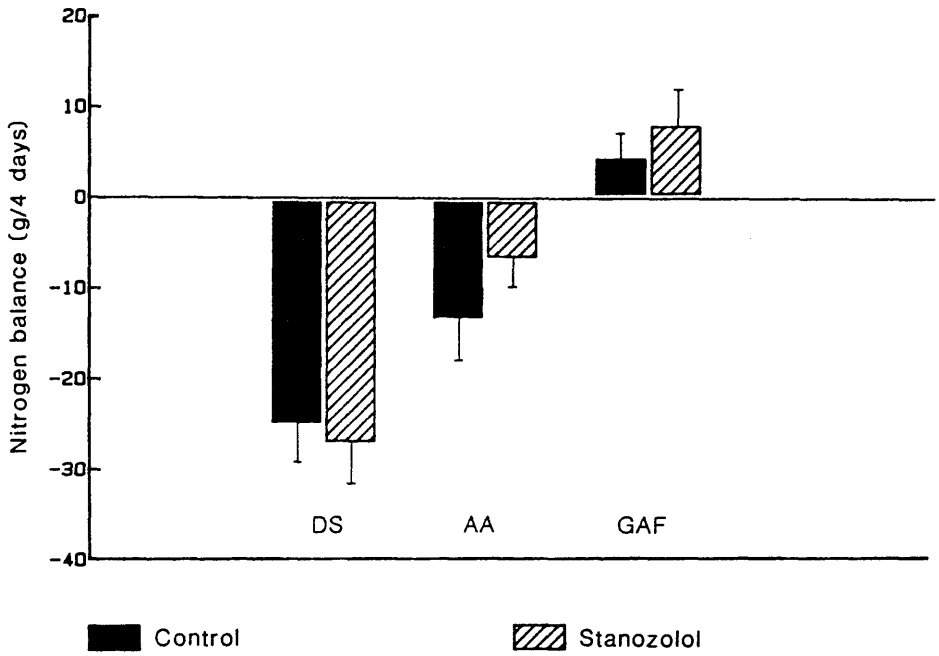


Figure 24

Mean cumulative nitrogen balance (± s.e.m.) in the stanozolol and control groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

for males and females, is shown in Figure 25. Stanozolol significantly improved nitrogen balance in female patients who received amino acids alone ($P<0.01$). Cumulative nitrogen balance in female patients was significantly better than in male patients in both the DS groups ($P<0.01$), and in the stanozolol treated AA group ($P<0.05$).

Nitrogen balance for each of the postoperative days is shown in Figure 26. It was significantly better in the stanozolol treated AA group ($P<0.05$) than in the AA control group on the third postoperative day. There was a significant improvement in nitrogen balance in both the DS groups between the first and fourth postoperative days ($P<0.01$), whereas over the same period nitrogen balance fell significantly ($P<0.05$) in the two AA groups. Nitrogen balance was more positive on each day in the stanozolol treated GAF group compared with the GAF control group, but this did not reach statistical significance. In the two AA groups nitrogen balance was significantly better than in the two DS groups on the first two postoperative days only ($P<0.01$). On the third postoperative day, nitrogen balance in the stanozolol treated AA group was significantly better than in both the DS groups ($P<0.01$). Nitrogen balance in the two GAF groups was significantly better than the two DS groups on each of the postoperative days ($P<0.01$), and significantly

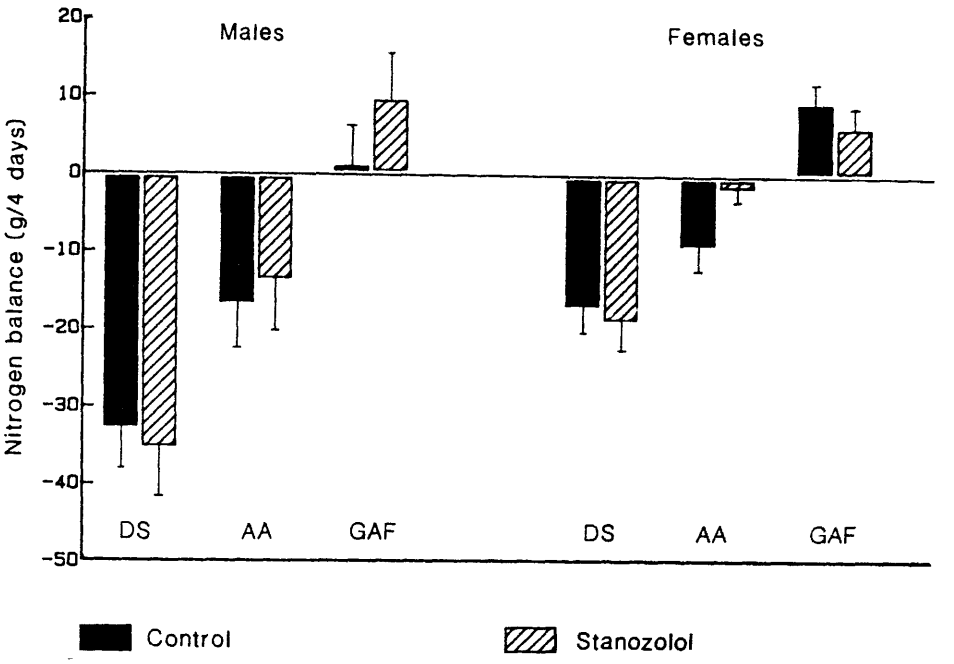


Figure 25

Mean cumulative nitrogen balance (± s.e.m.) in males and females in the stanozolol and control groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

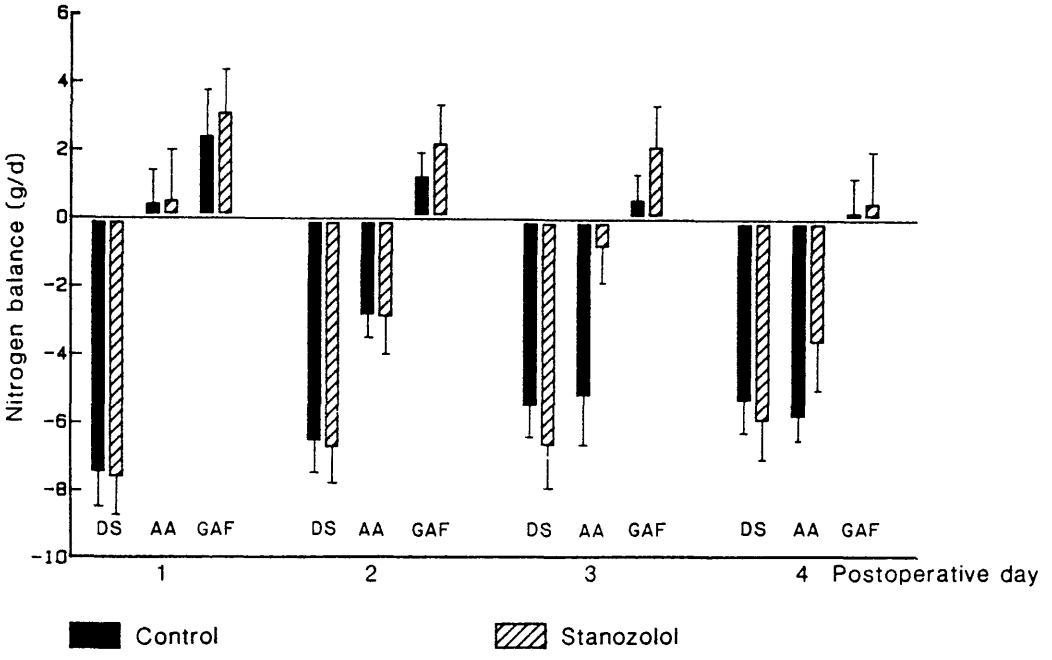


Figure 26

Mean daily nitrogen balance (± s.e.m.) for the first four postoperative days in the stanozolol and control groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

better than the two AA groups on the second and fourth postoperative days ($P<0.01$).

There were no significant differences between the groups in preoperative REE (Figures 27a and 27b) and RQ (Figures 28a and 28b). REE increased significantly ($P<0.05$) in all groups except for the DS control group. Stanozolol had no significant effect on postoperative RQ. RQ fell significantly in both the AA groups postoperatively ($P<0.01$), and was significantly lower than that of the two GAF groups ($P<0.01$).

Stanozolol had no significant effect on postoperative carbohydrate (Figures 29a and 29b) or fat (Figures 30a and 30b) oxidation rates. Carbohydrate oxidation rates fell significantly in both the AA groups ($P<0.01$). Three patients in the AA control group and five in the stanozolol treated AA group had negative values of carbohydrate oxidation on the second and fourth postoperative days. Carbohydrate oxidation rates were significantly lower ($P<0.01$) in both these groups compared with the other groups on the fourth postoperative day. Fat oxidation increased significantly in the AA control group postoperatively ($P<0.05$). On the fourth postoperative day, fat oxidation was significantly lower in both the GAF groups ($P<0.01$) compared with the other groups.

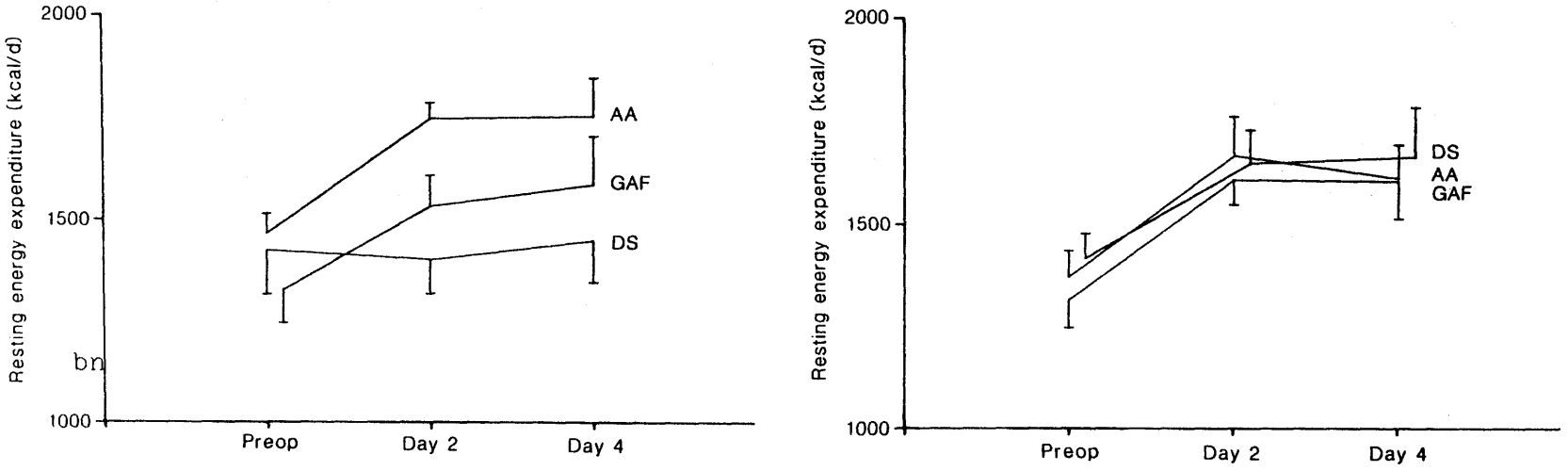


Figure 27

Mean resting energy expenditure (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in (a) control and (b) stanozolol groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

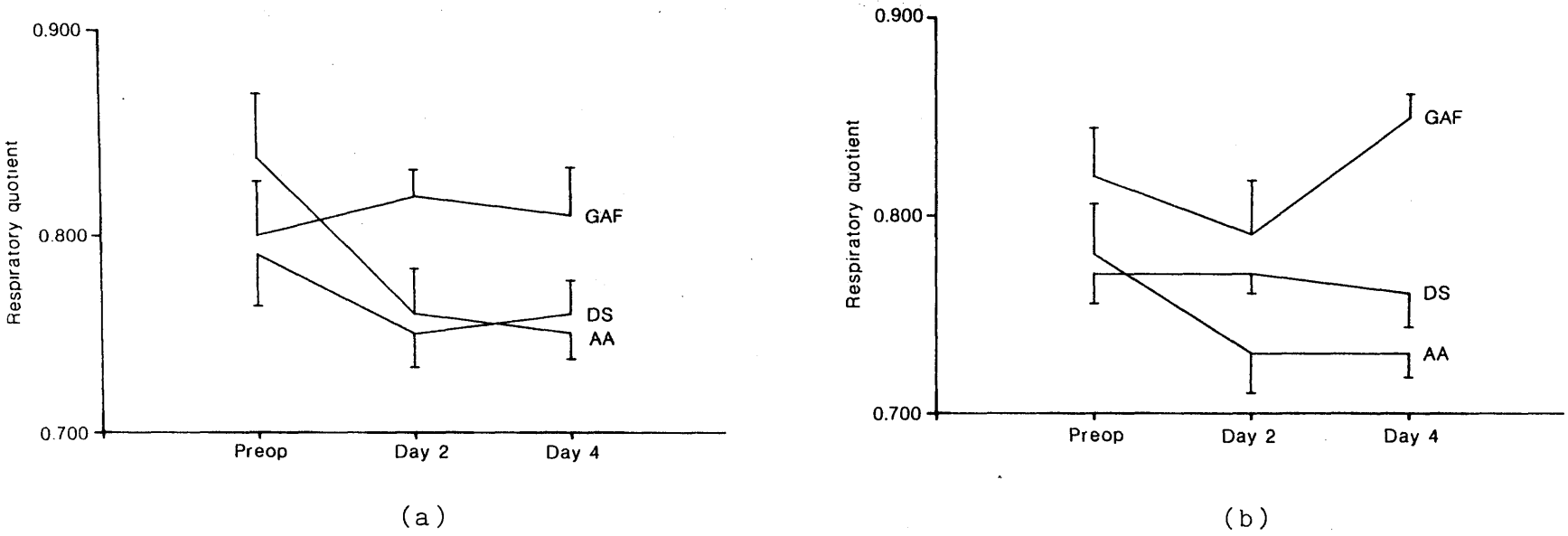


Figure 28

Mean respiratory quotient (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in (a) control and (b) stanozolol groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

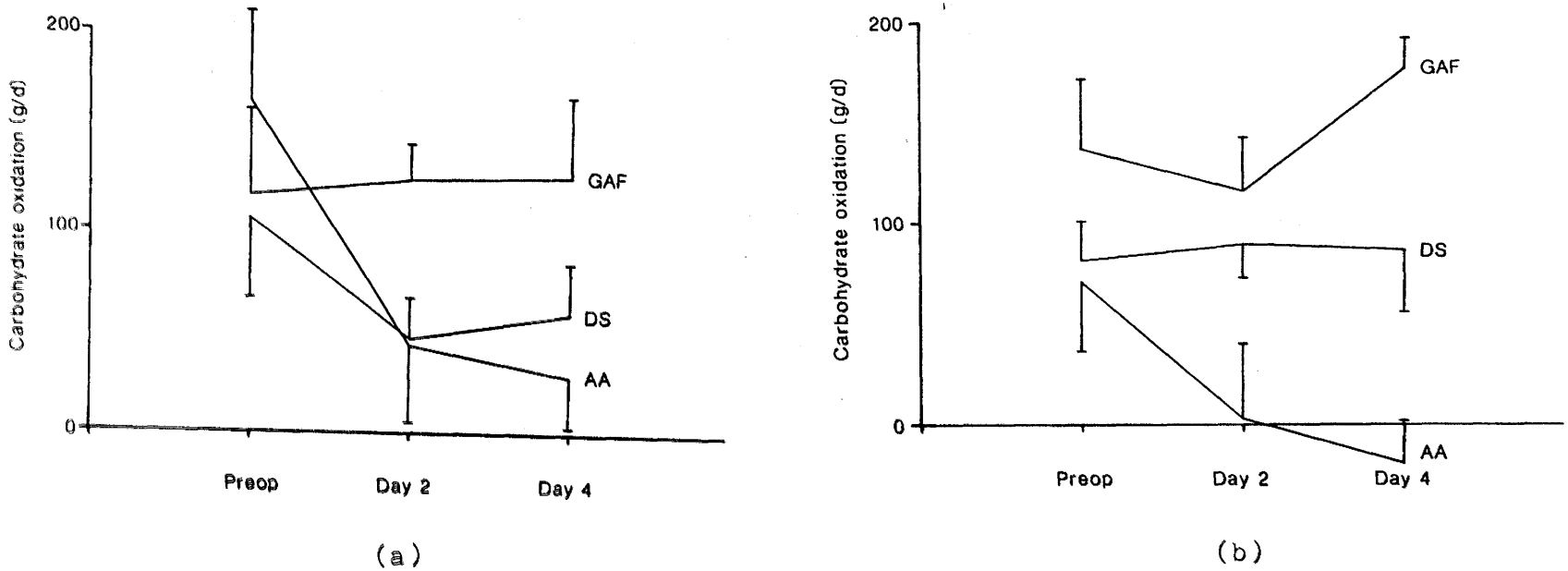
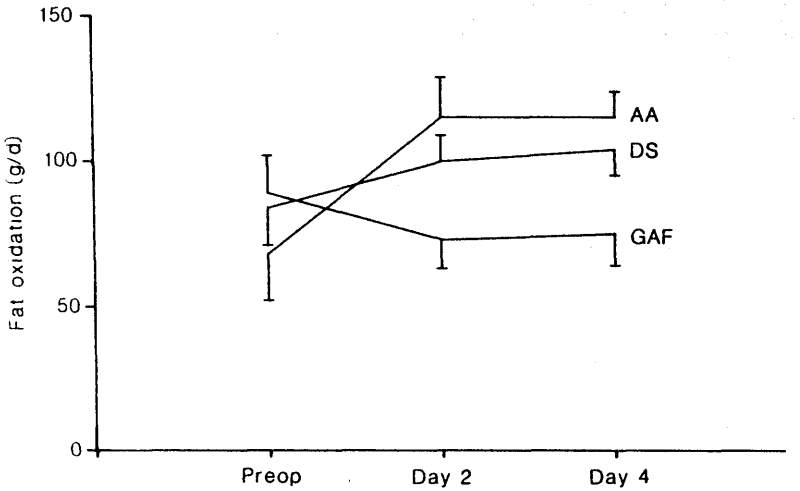
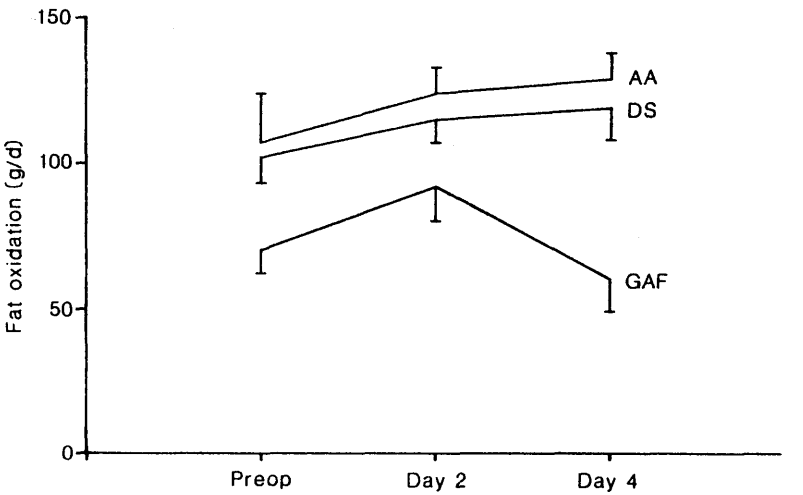


Figure 29

Mean carbohydrate oxidation rates (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in (a) control and (b) stanozolol groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)



(a)



(b)

Figure 30

Mean fat oxidation rates (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in (a) control and (b) stanozolol groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

Stanozolol had no significant effect on measured fluid balance in any of the groups (Figure 31). There was no significant difference between the groups in the number of patients requiring postoperative diuretic therapy. The cumulative fluid balance results (Figure 32) contrast with the total body water measurements which showed a fall between the preoperative and postoperative measurements in the two AA groups (AA/stanozolol = -2.10 ± 0.75 litres; AA/control = -1.61 ± 0.68 litres). These results were significantly different from the two DS groups (DS/stanozolol = +1.65 ± 0.83 litres; DS/control = +1.35 ± 0.73 litres - $P<0.01$) and the two GAF groups (GAF/stanozolol = +1.11 ± 0.85 litres; GAF/control = +1.52 ± 1.12 litres - $P<0.01$).

Preoperatively there were no significant differences between the groups with respect to the urinary excretion of the metabolites shown in Tables 50 and 51. Stanozolol had no significant effect on any of these indices postoperatively. Urinary nitrogen and urea excretion in the two DS groups was significantly lower postoperatively than in the two AA and two GAF groups ($P<0.01$). Urinary nitrogen and urea excretion in both the AA groups was significantly higher than in the two GAF groups ($P<0.01$). There were no significant differences between the groups in the urinary excretion of nitrogen in forms other than that of urea and ammonia, nor in 3-methylhistidine

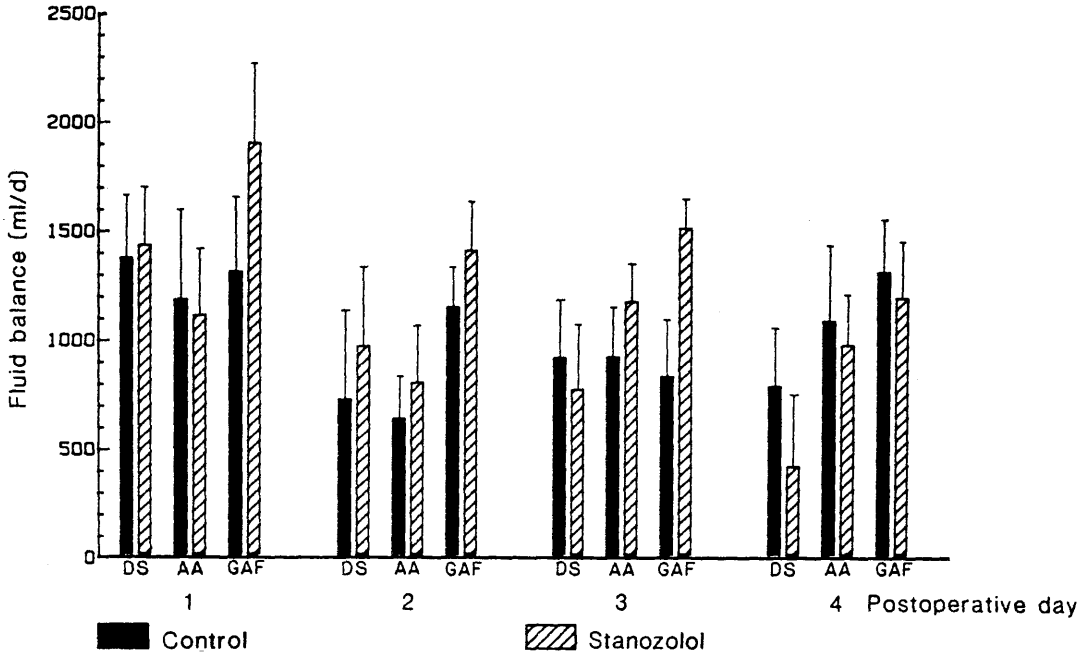


Figure 31

Mean daily fluid balance (± s.e.m.) for the first four postoperative days in the stanozolol and control groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

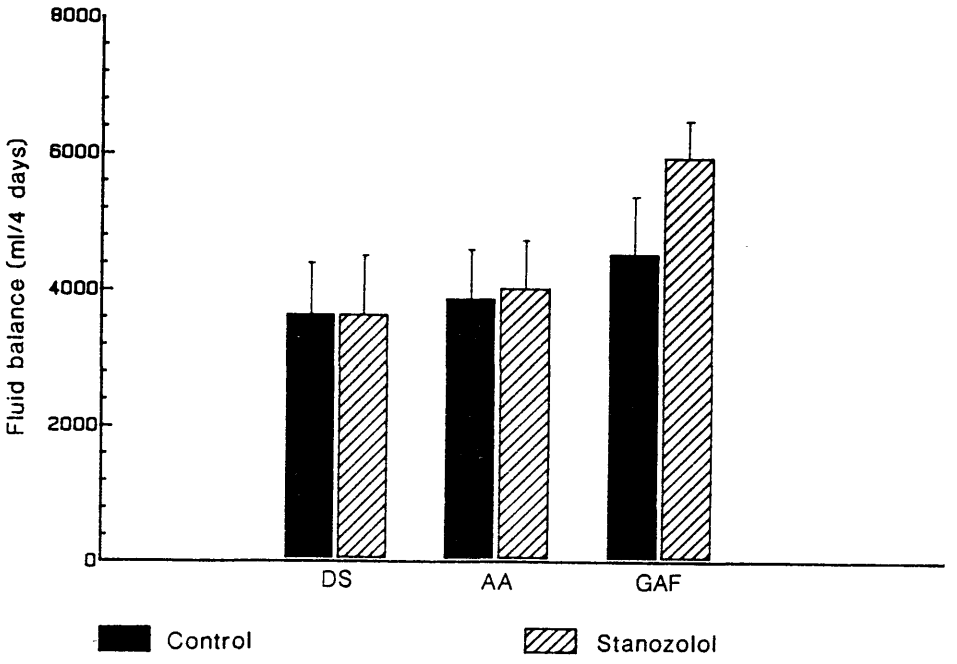


Figure 32

Mean cumulative fluid balance (± s.e.m.) in the stanozolol and control groups of patients receiving dextrose-saline (DS), amino acid (AA) or glucose-amino acid-fat (GAF)

TABLE 50 URINARY EXCRETION OF NITROGEN, UREA AND AMMONIA IN THE STANOZOLOL AND CONTROL GROUPS OF PATIENTS RECEIVING DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT

	Dextrose-saline		Amino acid		Glucose-amino acid-fat	
	stanozolol	control	stanozolol	control	stanozolol	control
Nitrogen:						
Preop (mmol/24hours)	314±32.5	381±57.3	462±110.4	380±64.6	290±45.8	302±24.7
Postop (mmol/96hours)	1969±269	1867±226	4433±290	4724±239	3206±136	3482±153
Urea:						
Preop (mmol/24hours)	126±14.9	160±26.6	197±41.8	159±30.7	122±20.0	120±10.7
Postop (mmol/96hours)	763±149	691±98.4	1856±132	2014±87.6	1284±86.0	1430±80.4
Ammonia:						
Preop (mmol/24hours)	21.6±2.3	21.4±4.5	23.2±8.8	21.3±4.7	16.2±1.7	21.7±3.8
Postop (mmol/96hours)	195±24.5	186±23.9	303±27.8	238±15.8	223±16.1	274±23.1
Non-urea non-ammonia nitrogen:						
Preop (mmol/24hours)	48.2±16.3	57.3±15.3	73.7±27.8	46.2±13.8	34.6±5.3	41.4±8.6
Postop (mmol/96hours)	306±48.3	301±54.7	417±102	468±147	479±117	347±68.7

mean ± s.e.m.

TABLE 51 URINARY EXCRETION OF UREA AND AMMONIA (AS % OF URINARY NITROGEN) AND 3-METHYLHISTIDINE IN THE STANOZOLOL AND CONTROL GROUPS OF PATIENTS RECEIVING DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT

	Dextrose-saline		Amino acid		Glucose-amino acid-fat	
	stanozolol	control	stanozolol	control	stanozolol	control
Urea (as % of nitrogen):						
Preop (%)	81.1±4.2	82.8±4.9	87.4±7.0	82.9±3.5	82.1±3.2	79.0±2.6
Postop (%)	73.7±4.4	73.2±3.4	83.6±2.1	85.7±2.5	79.2±2.7	81.8±2.1
Ammonia (as % of nitrogen):						
Preop (%)	7.0±0.6	6.5±1.6	4.4±0.7	6.0±1.0	6.4±0.7	7.6±1.5
Postop (%)	11.4±2.0	10.1±0.9	7.0±0.7	5.1±0.3	7.0±0.5	8.0±0.7
3-methylhistidine:						
Preop (umol/mmol creatinine/24 hours)	14.0±1.3	14.4±2.1	18.4±1.8	15.4±1.1	15.6±1.1	18.1±1.7
Postop (umol/mmol creatinine/96 hours)	28.7±1.5	29.8±1.3	32.8±1.8	31.4±1.9	31.5±4.9	28.0±2.1

mean ± s.e.m.

excretion.

Stanozolol had no significant effect on postoperative serum urea and serum creatinine levels (Table 52). Serum urea fell significantly in the two DS groups ($P<0.05$) and increased in the two AA groups ($P<0.01$) and the two GAF groups ($P<0.01$).

Preoperatively there were no significant differences between the groups with respect to plasma glucose and insulin (Table 52). The stanozolol treated amino acid group had a significantly lower plasma glucose than the AA control group on the third ($P<0.05$) and fourth ($P<0.05$) postoperative days. Plasma glucose increased significantly in the two DS groups ($P<0.01$) and in the stanozolol treated GAF group ($P<0.01$). On the second and third postoperative days, plasma glucose was significantly lower in the two AA groups ($P<0.01$) compared with the two DS and two GAF groups. Stanozolol had no significant effect on postoperative plasma insulin. Plasma insulin increased significantly in the two DS groups ($P<0.05$) and the two GAF groups ($P<0.01$). There were no significant differences in plasma insulin between the DS and AA groups, whereas plasma insulin levels in the two GAF groups were significantly greater ($P<0.05$) than those of the DS and AA groups postoperatively.

Serum albumin and serum transferrin (Table 53)

TABLE 52 SERUM UREA AND CREATININE, PLASMA GLUCOSE AND INSULIN IN THE STANOZOLOL AND CONTROL GROUPS OF PATIENTS RECEIVING DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT

	Dextrose-saline		Amino acids		Glucose-amino acids-fat	
	stanozolol	control	stanozolol	control	stanozolol	control
Serum urea (mmol/l):						
Preop	3.5±0.3	3.9±0.4	4.6±0.6	4.6±0.7	3.8±0.4	3.9±0.4
Day 2	3.0±0.4	3.2±0.4	6.0±0.5	6.5±0.3	6.4±0.7	6.3±0.7
Day 4	3.0±0.7	2.7±0.4	7.0±0.7	8.7±0.5	7.2±1.3	6.5±0.9
Serum creatinine (umol/l):						
Preop	82±5.7	80±3.4	80±3.7	74±4.0	90±7.5	91±10.8
Day 2	73±5.8	75±5.0	77±5.3	69±2.8	77±8.0	82±10.1
Day 4	72±7.5	71±4.5	69±5.5	65±2.3	65±7.9	68±7.7
Plasma glucose (mmol/l):						
Preop	5.5±0.3	6.2±0.5	5.9±0.9	5.7±0.2	5.6±0.2	5.7±0.4
Day 2	7.0±0.3	7.2±0.5	4.9±0.2	5.3±0.2	6.9±0.3	6.3±0.3
Day 3	7.0±0.5	7.6±0.6	5.0±0.3	6.0±0.4	7.4±0.6	6.4±0.4
Day 4	5.5±0.2	6.8±0.4	5.0±0.4	6.0±0.5	6.7±0.4	6.5±0.5
Plasma insulin (mU/l):						
Preop	12.1±3.0	10.2±1.6	11.9±3.3	11.5±1.4	11.9±2.4	14.3±3.2
Day 2	15.4±2.9	14.2±1.9	13.1±2.1	14.7±1.8	40.7±9.2	46.9±13.1
Day 3	18.0±2.9	12.7±1.2	13.4±2.6	14.1±2.0	45.3±9.5	29.6±7.4
Day 4	12.0±2.7	12.1±1.2	13.0±3.0	10.4±1.0	36.0±8.2	30.1±8.7

mean ± s.e.m.

fell postoperatively in all groups ($P<0.05$), and haematocrit fell in the two DS groups ($P<0.05$) and the GAF control group ($P<0.01$). Stanozolol had no significant effect on serum albumin, serum transferrin or haematocrit.

Four episodes of mild phlebitis occurred in 80 patient days in the DS groups (DS/stanozolol = 4, DS/control = 0), compared with five episodes in the AA groups (AA/stanozolol = 3, AA/control = 2) and 13 episodes in the GAF groups (GAF/stanozolol = 6, GAF/control = 7). These differences were not statistically significant. There were no significant differences between the groups with respect to postoperative complications and hospital stay (Table 54).

TABLE 53 SERUM ALBUMIN, SERUM TRANSFERRIN AND HAEMATOCRIT IN THE STANOZOLOL AND CONTROL GROUPS OF PATIENTS RECEIVING DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT

	Dextrose-saline		Amino acid		Glucose-amino acid-fat	
	stanozolol	control	stanozolol	control	stanozolol	control
Serum albumin (g/l):						
Preop	38.5±1.7	35.6±2.0	37.4±1.4	37.0±1.2	35.0±2.3	35.9±2.0
Day 2	31.9±1.2	29.6±1.2	32.0±0.9	33.0±1.1	31.2±1.5	28.5±1.4
Day 4	29.5±1.0	27.5±1.5	30.1±1.1	33.2±1.1	28.0±1.9	28.1±1.7
Serum transferrin (g/l):						
Preop	2.4±0.2	2.3±0.2	2.6±0.2	2.4±0.1	2.2±0.2	2.5±0.3
Day 2	1.6±0.1	1.6±0.1	1.9±0.1	1.9±0.1	1.7±0.2	1.5±0.1
Day 4	1.5±0.1	1.6±0.1	1.9±0.1	2.0±0.1	1.6±0.2	1.5±0.1
Haematocrit (%):						
Preop	38.9±1.4	39.0±1.6	41.1±1.1	37.7±1.5	39.1±1.2	37.8±1.6
Day 2	33.8±1.3	34.9±1.1	39.6±1.6	34.6±1.0	32.8±1.2	37.5±1.5
Day 4	31.3±1.9	32.9±1.3	36.6±1.8	33.3±2.0	33.4±1.7	34.8±1.0

mean ± s.e.m.

TABLE 54 POSTOPERATIVE COMPLICATIONS IN THE STANOZOLOL AND CONTROL GROUPS OF PATIENTS RECEIVING DEXTROSE-SALINE, AMINO ACID AND GLUCOSE-AMINO ACID-FAT

	Dextrose-saline		Amino acids		Glucose-amino acids-fat	
Complication	stanozolol	control	stanozolol	control	stanozolol	control
Wound infection	3	1	1	2	3	2
Peritonitis	1	-	-	-	-	-
Faecal fistula	1	1	-	-	-	-
Chest infection	2	1	2	4	3	2
Urinary infection	3	3	5	2	2	4
Septicaemia	-	1	-	-	-	1
Deep vein thrombosis	-	-	-	1	-	1
Death	-	-	-	1	-	-
Diuretic therapy	1	1	-	2	3	2
Postoperative stay (days)*	17 ± 2.8	17 ± 3.1	17 ± 3.0	14 ± 1.4	15 ± 1.8	15 ± 2.4

* mean ± s.e.m.

DISCUSSION

The effects of the three nutritional regimens on the metabolic response to surgery were very similar to those reported in the previous chapter, therefore this discussion will be limited to those aspects of the metabolic response which have been influenced by stanozolol.

It appears that preoperative administration of the anabolic steroid stanozolol may improve postoperative nitrogen balance significantly in patients receiving amino acid infusions. This finding is consistent with that of Michelsen and colleagues (193), who reported improved nitrogen balance on each of the first three postoperative days following the administration of nandrolone decanoate and isotonic amino acids to patients undergoing total hip replacement. In the present study, stanozolol did not improve nitrogen balance in patients receiving amino acid infusions until the third postoperative day. In patients receiving the more complete nutritional regimen, glucose-amino acid-fat, nitrogen balance was more positive on each of the postoperative days in the stanozolol treated patients, but these differences did not reach statistical significance.

There have been conflicting results regarding the effect of anabolic steroids in the presence of an adequate nutritional input. Tweedle and coworkers

(192) showed that a combination of nandrolone decanoate and TPN improved nitrogen balance moreso than nandrolone decanoate alone, whereas Yule and colleagues (197) showed that anabolic steroids had no significant effect on nitrogen balance in patients receiving postoperative TPN. In contrast to the findings of the present study, previous work by Blamey and colleagues from this centre (196) showed that stanozolol had a significant effect on postoperative nitrogen balance in patients receiving a dextrose-saline regimen. The patient population in that study, however, consisted mainly of patients with benign disease whereas all patients in the present study had colorectal cancer. Furthermore, mean daily nitrogen balance in Blamey's control group was -10.9gN while in the present study the control patients receiving dextrose-saline had a mean daily nitrogen balance of only -6.3gN. Blamey's stanozolol treated group had a mean daily nitrogen balance of -8.0gN while in the present study the stanozolol treated patients receiving dextrose-saline had a mean daily nitrogen balance of -6.8gN.

The underlying pathology may influence the effect of anabolic steroids on the metabolic response to surgery. Most studies of anabolic steroids have involved either groups of patients with benign diseases only (18,192,194,195,198,199) or groups where the majority of patients had benign disease

(196,200-203), whereas all the patients in the present study had colorectal cancer. The differing patient population, and differences in the type, dose and timing of anabolic steroid administration, make direct comparison of results difficult. The dose of stanozolol used in the present study was identical to that shown to be effective both in Blamey's study (196) and in the prevention of fibrinolytic shutdown in a previous study (265).

The virilising effects of anabolic steroids limit their use in clinical studies, especially in females (18). The high anabolic to androgenic ratio (100:1) of stanozolol has resulted in no evidence of virilisation in the 30 females in the present study. Furthermore, its long duration of action enables stanozolol to be administered as a single intramuscular dose (266). The anabolic to androgenic ratio of many other anabolic steroids such as testosterone (1:1), methandienone (1:1) and nandrolone decanoate (10:1) has prevented their widespread use (18). In the present study, the improved nitrogen balance seen in the stanozolol treated amino acid group was due largely to a significant improvement in nitrogen balance in female patients, all of whom were postmenopausal. In contrast, male patients were found to benefit more in Blamey's study (196) where dextrose-saline was administered rather than amino acids.

The minimal, delayed rise in REE in the dextrose-saline control group cannot readily be explained. A proportion of the postoperative REE in the AA and GAF groups will be due to the specific dynamic action of the infused nutrients (263), but it is unlikely that the significant difference in postoperative REE in the two DS groups is due to stanozolol, since it had no apparent effect on REE in the AA and GAF groups.

Stanozolol did not influence serum protein levels postoperatively, although serum albumin on the fourth postoperative day was lower in the stanozolol treated AA group than in the AA control group. Blamey and colleagues (196), noting a trend towards lower serum transferrin levels in the stanozolol treated group, speculated that improved protein synthesis in skeletal muscle may be at the expense of liver protein synthesis. This is unlikely to be the explanation in the present study since the half life of serum albumin is approximately 16 days. The similar postoperative excretion of 3-methylhistidine in each of the groups suggests that any effect on nitrogen sparing is more likely to be due to improved protein synthesis rather than decreased breakdown. The fall in serum albumin and transferrin in all groups is mirrored in most by a fall in haematocrit. Transfer of proteins and fluid between body compartments, as well as changes in protein synthesis and catabolism, are known to

infuence changes in serum proteins (267).

Fluid retention due to anabolic steroids has been reported previously (196,197,268), but in the present study there was no evidence of fluid retention due to stanozolol. The discrepancy between the fluid balance and total body water measurements has been discussed in the previous chapter. Stanozolol had no significant effect on renal function irrespective of the type of postoperative nutritional regimen infused. The increases in serum and urine urea in the AA and GAF groups indicate metabolism of the infused amino acids. The similar values for the urinary excretion of nitrogen in forms other than that of urea and ammonia indicate that the infused amino acids have been metabolized to a similar extent in both groups.

In conclusion, preoperative administration of the anabolic steroid stanozolol has been shown to improve postoperative nitrogen balance in cancer patients receiving amino acid infusions. This improvement was most marked in female patients. It appears to have little or no effect in postoperative patients receiving either a combination of glucose, amino acids and fat or a simple dextrose-saline regimen. It is possible that alteration in the dose and timing of administration of stanozolol may enhance its effect on nitrogen balance.

CHAPTER 13

THE EFFECTS OF AN ANABOLIC STEROID AND NAFTIDROFURYL ON THE METABOLIC RESPONSE TO TRAUMA IN PATIENTS FOLLOWING SURGERY FOR GASTRIC CANCER

INTRODUCTION

The administration of naftidrofuryl in the postoperative period has yielded conflicting results (21,190,191). Burns and colleagues (21) demonstrated an improvement in postoperative nitrogen balance using this agent, and suggested that its effect may have been due to stimulation of carbohydrate and fat catabolism, thus conserving tissue protein.

In the previous chapter, the administration of stanozolol failed to improve postoperative nitrogen balance in patients with colorectal cancer receiving a standard dextrose-saline regimen. In the present study, the effects of combining naftidrofuryl with stanozolol have been assessed in a randomised study of patients undergoing surgery for gastric cancer. These patients have been compared with similar patients who received either stanozolol alone or no pharmacological agent.

PATIENTS & METHODS

Thirty patients about to undergo elective surgery for gastric cancer were randomised to one of the following treatment groups or to a control group:

(1) Stanozolol group - Patients in this group received a single intramuscular injection of 50mg stanozolol (Stromba - Sterling Research Laboratories) 24 hours prior to surgery.

(2) Stanozolol/naftidrofuryl group - Patients in this group received stanozolol as above plus slow bolus intravenous infusions of naftidrofuryl (Praxilene - Lipha Laboratories) 200mg twice daily commencing on induction of anaesthesia and continuing until the end of the fourth postoperative day.

(3) Control group - Patients in this group received neither stanozolol nor naftidrofuryl.

For the first four postoperative day all patients received a constant infusion of dextrose 5% (2 litres/day) plus one litre normal saline/day administered via a peripheral vein using a peristaltic infusion pump.

Other methods used are as described in Chapters 3 and 11.

RESULTS

Each group consisted of ten patients. There were no significant differences between the groups with respect to mean age, body weight, percentage weight loss and lean body mass (Table 55). The types of operation performed are shown in Table 56.

There were no significant differences in preoperative urinary nitrogen excretion between the groups (control = 6.2 ± 1.3gN/d; stanozolol = 3.9 ± 0.5gN/d; stanozolol/naftidrofuryl = 4.5 ± 0.7gN/d). Postoperatively, there were no significant differences between the groups in the cumulative nitrogen balance for the first four postoperative days (control = -32.7 ± 3.0gN; stanozolol = -23.6 ± 3.1gN; stanozolol/naftidrofuryl = -27.1 ± 3.7gN). Daily nitrogen balance for each of the groups is shown in Figure 33. There were no significant differences between the groups on the first three postoperative days, but on the fourth postoperative day, nitrogen balance in the stanozolol ($P<0.01$) and stanozolol/naftidrofuryl ($P<0.05$) groups was significantly better than in the control group. Nitrogen balance improved significantly between the first and fourth postoperative days in the stanozolol/naftidrofuryl group only ($P<0.05$).

Cumulative nitrogen balance, displayed separately

TABLE 55 CLINICAL DETAILS OF PATIENTS IN THE CONTROL, STANOZOLOL AND STANOZOLOL/NAFTIDROFURYL GROUPS

	Control	Stanozolol	Stanozolol-naftidrofuryl
n	10	10	10
Male : Female	6 : 4	6 : 4	8 : 2
Age (years)	64.5 ± 3.4	70.0 ± 2.7	63.3 ± 3.2
Body weight (kg)	59.9 ± 3.8	54.2 ± 4.8	59.5 ± 4.8
Weight loss (%)	11.8 ± 3.4	9.9 ± 2.1	13.3 ± 4.3
LBM (kg)	45.3 ± 3.2	45.2 ± 3.5	50.7 ± 3.9

mean ± s.e.m.

No significant differences between the groups

TABLE 56 TYPE OF OPERATION PERFORMED ON PATIENTS IN THE CONTROL, STANOZOLOL AND STANOZOLOL/NAFTIDROFURYL GROUPS

Type of operation	Control	Stanozolol	Stanozolol-naftidrofuryl
Proximal gastrectomy	-	1	1
Distal gastrectomy	4	5	2
Total gastrectomy	2	1	5
Oesophago-gastrectomy	1	1	1
Gastroenterostomy	1	1	1
Celestin intubation	1	-	-
Laparotomy + biopsy only	1	1	-

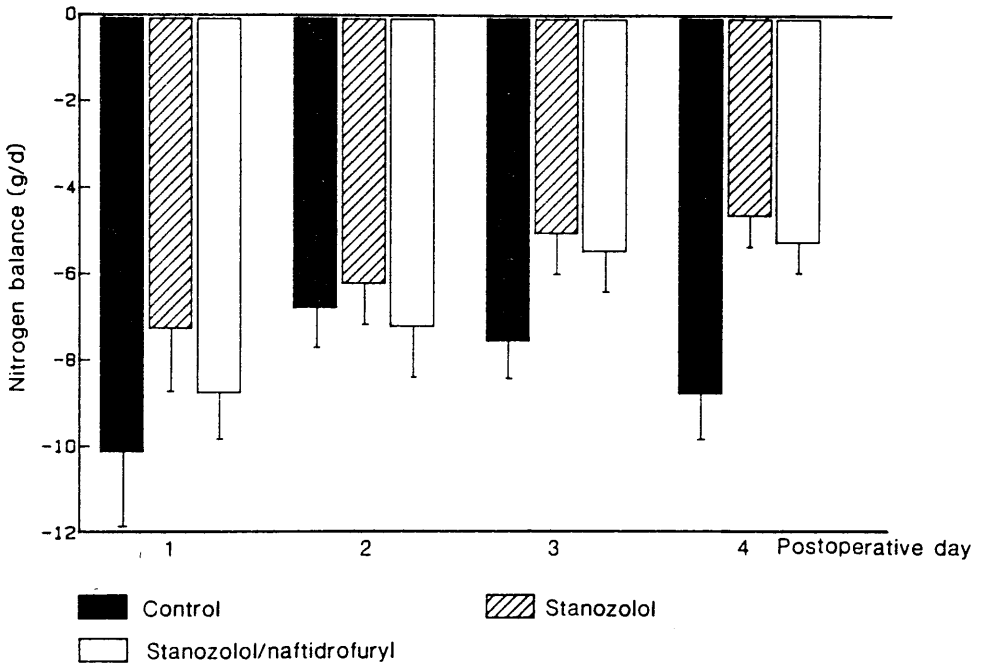


Figure 33

Mean daily nitrogen balance (± s.e.m.) for the first four postoperative days in the control, stanozolol and stanozolol/naftidrofuryl groups of patients

for males and females, is shown in Figure 34. An analysis of variance shows no significant differences within the groups of males or females, but the cumulative nitrogen balance for females was significantly less negative than that for males in the control ($P<0.05$) and stanozolol ($P<0.01$) groups.

There were no significant differences between the groups in pre- and postoperative REE (Figure 35) and RQ (Figure 36). Postoperatively in the stanozolol/naftidrofuryl group, REE increased significantly ($P<0.05$) and RQ fell significantly ($P<0.05$), compared with preoperative values.

There were no significant differences between the groups in pre- and postoperative carbohydrate and fat oxidation rates (Figures 37 and 38). However, postoperative fat oxidation rates were significantly greater than preoperative values in the stanozolol ($P<0.05$) and stanozolol/naftidrofuryl ($P<0.01$) groups.

There were no significant differences between the groups in measured fluid balance on any of the postoperative days (Figure 39), nor in the cumulative fluid balance over the four postoperative days (Control = $+3.7 \pm 0.6$ litres; Stanozolol = $+2.3 \pm 0.5$ litres; Stanozolol/naftidrofuryl = $+3.4 \pm 0.6$ litres). These cumulative fluid balance results

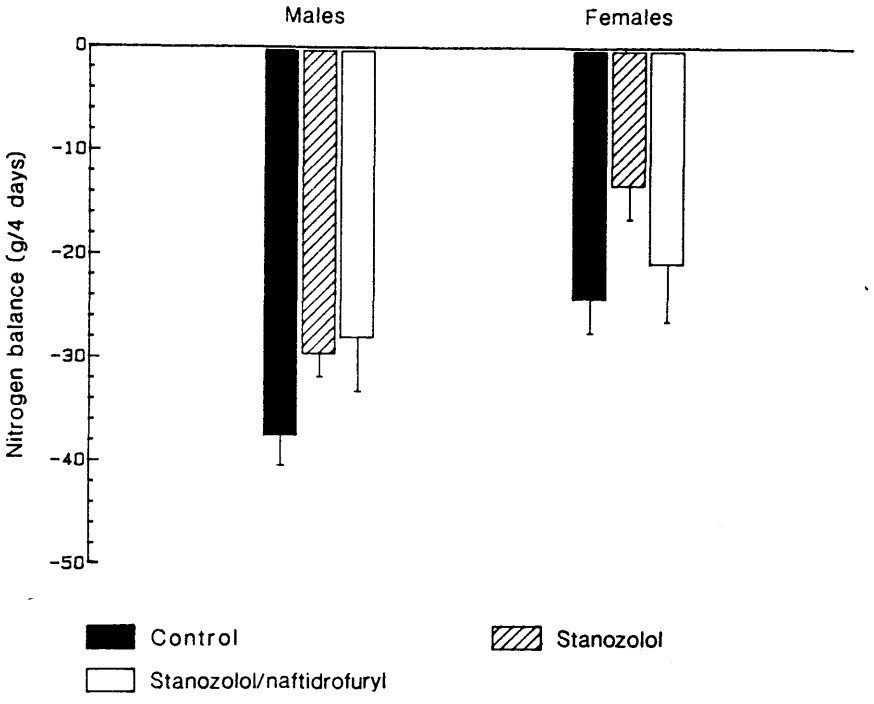


Figure 34

Mean cumulative nitrogen balance (± s.e.m.) in male and female patients in the control, stanozolol and stanozolol/naftidrofuryl groups

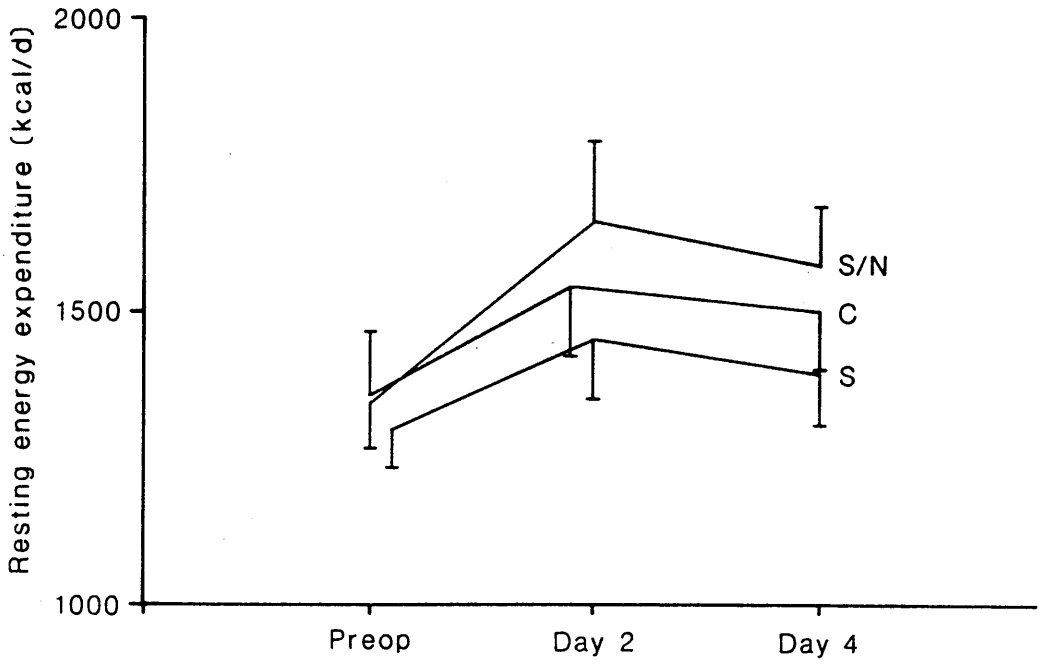


Figure 35

Mean resting energy expenditure (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in the control (C), stanozolol (S) and stanozolol/naftidrofuryl (S/N) groups of patients

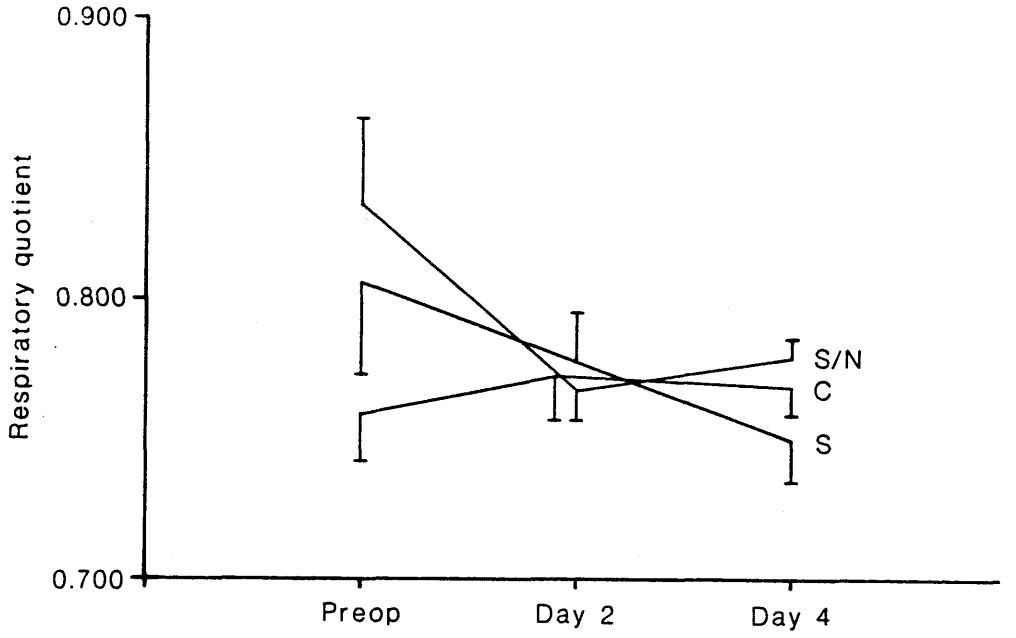


Figure 36

Mean respiratory quotient (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in the control (C), stanozolol (S) and stanozolol/ naftidrofuryl (S/N) groups of patients

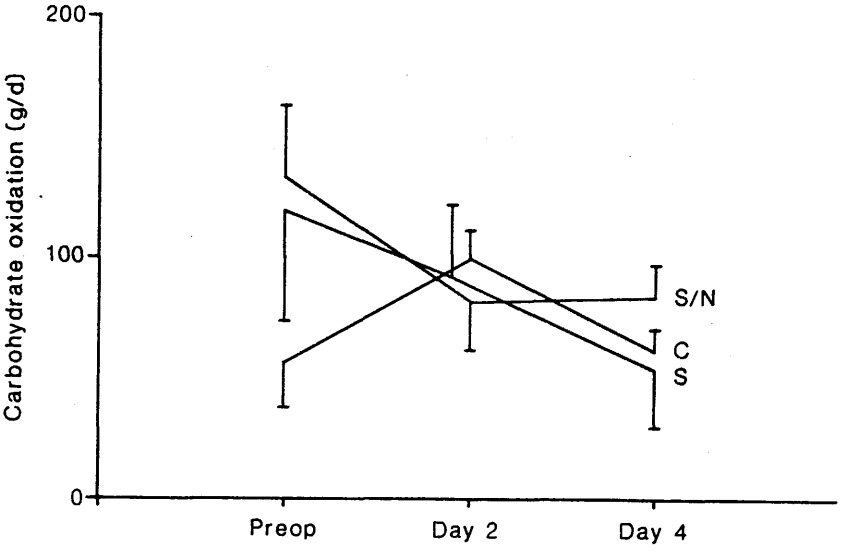


Figure 37

Mean carbohydrate oxidation rates (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in the control (C), stanozolol (S) and stanozolol/naftidrofuryl (S/N) groups of patients

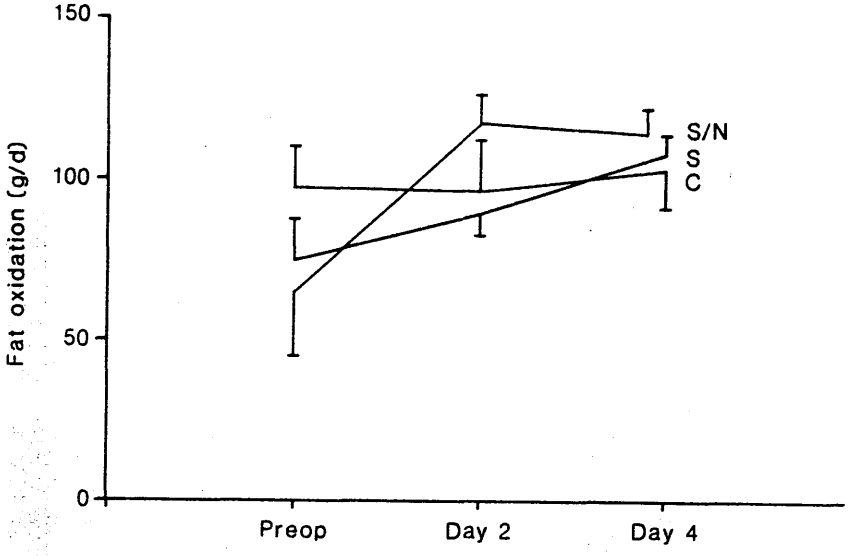


Figure 38

Mean fat oxidation rates (± s.e.m.) preoperatively and on the 2nd and 4th postoperative days in the control (C), stanozolol (S) and stanozolol/naftidrofuryl (S/N) groups of patients

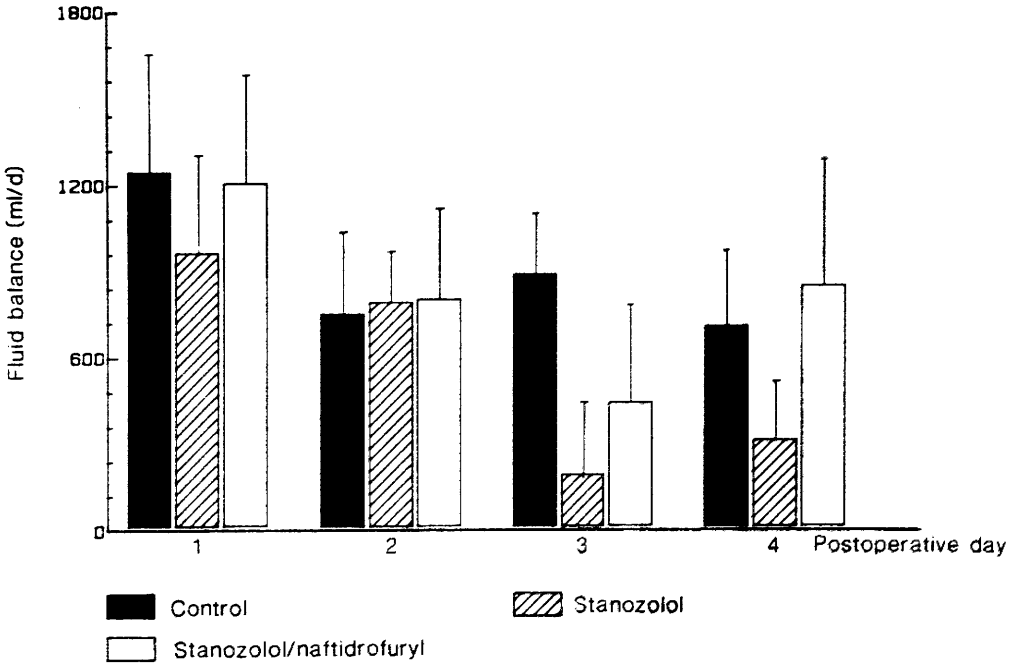


Figure 39

Mean daily fluid balance (± s.e.m.) for the first four postoperative days in the control, stanozolol and stanozolol/naftidrofuryl groups of patients

contrast with the total body water measurements which showed a loss in total body water in the stanozolol/naftidrofuryl group (-0.02 ± 1.1 litres) and a gain in the other two groups (control = +1.1 ± 0.6 litres; stanozolol = +0.07 ± 0.7 litres). The number of patients requiring postoperative diuretic therapy was not significantly different between the groups.

Preoperatively there were no significant differences between the groups with respect to the urinary excretion of the metabolites shown in Tables 57 and 58. Postoperatively, cumulative urinary urea excretion and the percentage of urinary nitrogen excreted in the form of urea were significantly lower in the stanozolol group than in the control group ($P<0.05$). There were no significant differences between the groups in postoperative 3-methylhistidine excretion.

There were no significant differences between the groups with respect to pre- and postoperative serum urea, serum creatinine, plasma glucose and plasma insulin (Table 59). Postoperatively, serum albumin, serum transferrin and haematocrit fell significantly ($P<0.05$), but there were no significant differences between the groups (Table 60).

There were no significant differences between the

TABLE 57 URINARY EXCRETION OF NITROGEN, UREA AND AMMONIA IN THE CONTROL, STANOZOLOL AND STANOZOLOL/NAFTIDROFURYL GROUPS

	Control	Stanozolol	Stanozolol-naftidrofuryl
Nitrogen: Preop (mmol/24hours)	440 ± 91.9	276 ± 37.5	321 ± 47.1
Postop (mmol/96hours)	2475 ± 248	1724 ± 230	2100 ± 249
Urea: Preop (mmol/24hours)	175 ± 34.6	104 ± 15.8	134 ± 19.3
Postop (mmol/96hours)	990 ± 102	615 ± 96.8	798 ± 86.1
Ammonia: Preop (mmol/24hours)	23.6 ± 7.2	17.0 ± 3.2	12.6 ± 2.0
Postop (mmol/96hours)	207 ± 30.7	152 ± 16.2	163 ± 23.1
Non-urea non-ammonia nitrogen:			
Preop (mmol/24hours)	67.1 ± 20.9	50.3 ± 11.9	40.7 ± 15.2
Postop (mmol/96hours)	288 ± 56.8	342 ± 67.2	341 ± 81.1

mean ± s.e.m.

TABLE 58 URINARY EXCRETION OF UREA AND AMMONIA (AS % OF URINARY NITROGEN) AND 3-METHYLHISTIDINE IN THE CONTROL, STANOZOLOL AND STANOZOLOL/NAFTIDROFURYL GROUPS

	Control	Stanozolol	Stanozolol/naftidrofuryl
Urea (as % of nitrogen):			
Preop (%)	80.7 ± 3.3	73.8 ± 4.8	84.8 ± 3.4
Postop (%)	80.0 ± 2.5	69.3 ± 3.7	76.9 ± 1.9
Ammonia (as % of nitrogen):			
Preop (%)	4.9 ± 0.5	8.5 ± 3.2	4.2 ± 0.6
Postop (%)	8.8 ± 1.3	10.4 ± 2.1	8.1 ± 1.0
3-methylhistidine:			
Preop (umol/mmol creatinine/24 hours)	21.1 ± 2.4	20.2 ± 3.4	17.8 ± 1.5
Postop (umol/mmol creatinine/96 hours)	28.6 ± 1.9	30.5 ± 3.1	31.1 ± 2.8

mean ± s.e.m.

TABLE 59 SERUM UREA AND CREATININE, PLASMA GLUCOSE AND INSULIN IN PATIENTS IN THE CONTROL, STANOZOLOL AND STANOZOLOL/NAFTIDROFURYL GROUPS

	Control	Stanozolol	Stanozolol-naftidrofuryl
Serum urea (mmol/l):			
Preop	5.1 ± 0.7	3.7 ± 0.5	5.8 ± 1.3
Day 2	4.3 ± 0.5	4.1 ± 0.8	4.4 ± 0.6
Day 4	3.8 ± 0.5	3.0 ± 0.6	3.3 ± 0.4
Serum creatinine (umol/l):			
Preop	83 ± 4.8	79 ± 5.9	97 ± 10.2
Day 2	79 ± 5.0	89 ± 13.4	95 ± 10.7
Day 4	77 ± 6.6	74 ± 6.1	87 ± 8.0
Plasma glucose (mmol/l):			
Preop	6.8 ± 0.7	5.4 ± 0.3	5.9 ± 0.3
Day 2	7.0 ± 0.4	6.3 ± 0.5	5.9 ± 0.5
Day 3	6.4 ± 0.3	5.6 ± 0.3	5.7 ± 0.3
Day 4	6.4 ± 0.5	5.2 ± 0.3	5.7 ± 0.2
Plasma insulin (mU/l):			
Preop	17.8 ± 4.8	12.6 ± 3.0	8.1 ± 1.7
Day 2	17.5 ± 3.8	14.1 ± 2.6	9.2 ± 1.0
Day 3	13.7 ± 2.4	10.6 ± 1.8	9.3 ± 1.5
Day 4	10.8 ± 1.7	11.7 ± 2.3	8.1 ± 1.2

mean ± s.e.m.

TABLE 60 SERUM ALBUMIN, SERUM TRANSFERRIN AND HAEMATOCRIT IN PATIENTS IN THE CONTROL, STANOZOLOL AND STANOZOLOL/NAFTIDROFURYL GROUPS

	Control	Stanozolol	Stanozolol/naftidrofuryl
Serum albumin (g/l):			
Preop	35.0 ± 1.7	32.1 ± 2.0	32.7 ± 1.3
Day 2	28.5 ± 1.5	28.1 ± 1.3	29.8 ± 0.8
Day 4	27.2 ± 1.7	26.8 ± 1.1	28.8 ± 1.2
Serum transferrin (g/l):			
Preop	2.4 ± 0.2	2.3 ± 0.2	2.0 ± 0.2
Day 2	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1
Day 4	1.5 ± 0.1	1.5 ± 0.1	1.3 ± 0.1
Haematocrit (%):			
Preop	36.7 ± 1.3	38.4 ± 1.8	38.1 ± 1.4
Day 2	33.5 ± 1.8	35.6 ± 1.1	35.1 ± 1.1
Day 4	33.3 ± 1.7	32.3 ± 1.0	32.9 ± 1.5

mean ± s.e.m.

groups with respect to postoperative complications and hospital stay (Table 61).

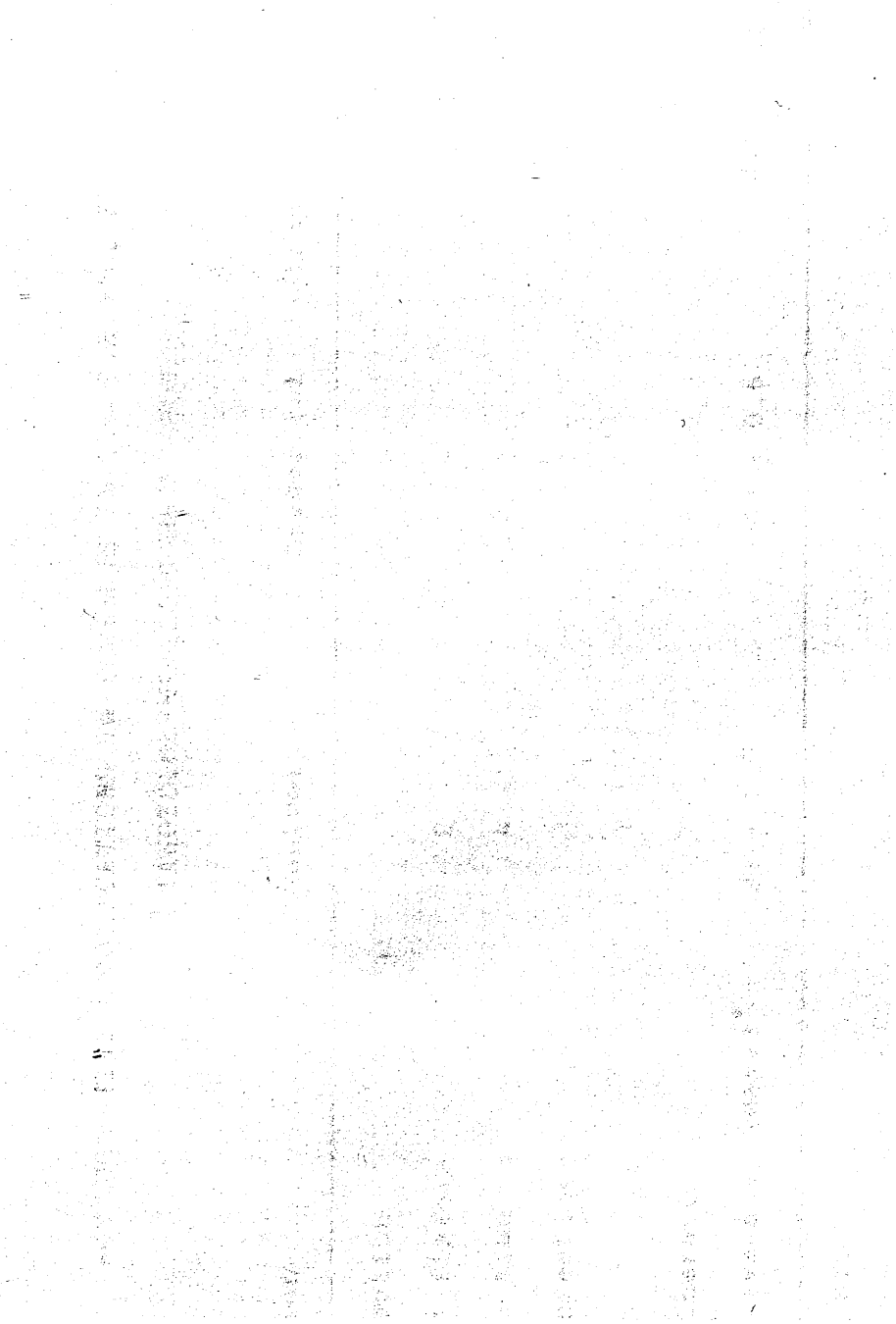


TABLE 61 POSTOPERATIVE COMPLICATIONS IN PATIENTS IN THE CONTROL, STANOZOLOL AND STANOZOLOL/NAFTIDROFURYL GROUPS

Complication	Control	Stanozolol	Stanozolol-naftidrofuryl
Wound infection	1	-	-
Intestinal fistula	2	-	1
Chest infection	4	1	4
Urinary infection	3	1	-
Death	1	-	-
Diuretic therapy	1	1	2
Postoperative stay (days)*	22 ± 6.0	11 ± 0.6	15 ± 2.6

* mean ± s.e.m.

DISCUSSION

This study shows that stanozolol, whether given alone or in combination with naftidrofuryl, has little nitrogen sparing effect in postoperative patients receiving a simple dextrose-saline regimen. However, over the four postoperative days, nitrogen excretion in the stanozolol and stanozolol/naftidrofuryl groups tended to decrease, such that, by the fourth postoperative day, nitrogen excretion in these groups was significantly less than in the control group. This late effect on nitrogen excretion appears to be due solely to the administration of stanozolol, as the addition of naftidrofuryl provided no additional benefit in terms of nitrogen excretion.

This late effect of stanozolol contrasts with the findings of the previous chapter, where stanozolol had no significant effect on nitrogen excretion in colorectal cancer patients receiving the same dextrose-saline regimen. It also contrasts with the study of Blamey and colleagues (196), who demonstrated improved nitrogen balance on the first three postoperative days in patients receiving the same anabolic steroid and postoperative fluid regimen. The differences in the patient populations in the various studies of anabolic steroids have been discussed in the previous chapter. There are also differences in the patient populations used in studies of

naftidrofuryl. Most of these studies have consisted of patients with mainly benign disease (21,190,191). Furthermore, Burns and colleagues (21) excluded patients with weight loss while Jackson and colleagues (191) excluded nearly one third of their patients, including those with considerable weight loss, metastatic disease and postoperative sepsis. In the present study, 12 patients had lost more than 10% of their pre-illness weight, seven had liver metastases and three developed postoperative fistulae. No patient was excluded.

These differences in patient populations and in the dose and method of administration of the pharmacological agents used make comparison of the present results with those of other studies difficult. In the present study, naftidrofuryl was administered by slow bolus, similar to the method used by Burns and colleagues (21) and Jackson and colleagues (191). The latter group of workers were unable to demonstrate any significant effect on nitrogen excretion using this method, while Inglis and colleagues (190), using a continuous infusion of naftidrofuryl, also were unable to demonstrate a significant effect.

The significant increase in postoperative fat oxidation in the stanozolol and stanozolol/naftidrofuryl groups suggests that these agents may influence substrate metabolism. The

greater increase occurred in the stanozolol/naftidrofuryl group, and was associated with a significant fall in RQ. These findings are consistent with the hypothesis of Burns and colleagues (21), who suggested that naftidrofuryl may increase the utilisation of fat and carbohydrate, thus sparing body protein stores. Johnson and colleagues (191) demonstrated changes in lactate and total ketone concentrations in postoperative patients receiving naftidrofuryl which would support this hypothesis, but as in the present study, were unable to demonstrate any significant nitrogen-sparing effect.

In conclusion, there is some evidence to suggest that the preoperative administration of the anabolic steroid stanozolol influences postoperative nitrogen excretion in patients undergoing surgery for gastric cancer. While naftidrofuryl has had no demonstrable effect on nitrogen excretion, both this agent and stanozolol may influence postoperative fat oxidation, which could indirectly affect nitrogen excretion. The effect of these agents on energy substrate metabolism thus appears to warrant further investigation.

CHAPTER 14

CONCLUSIONS

Energy expenditure

Over the past 70 years many authors reported that patients with cancer had a raised resting energy expenditure (REE), and suggested that this could contribute significantly to the development of cancer cachexia. However, many of the early studies were anecdotal and even some recent studies used either inappropriate or no control groups. The first aim of this thesis, therefore, was to assess whether the presence of cancer influenced the REE of the host.

The comparison of weight stable and weight losing patients with cancer and nonmalignant illness (Chapter 4), yields no evidence to suggest that cancer results in a raised REE. The presence of weight loss, irrespective of whether the patient has cancer or not, is related more closely to abnormalities of REE. This suggests that the host response to an illness, benign or malignant, is a major determinant of alteration in REE, rather than any factor associated with the presence of cancer itself.

There are subtle differences in the relationship between REE and indices of body size depending on the type of cancer present (Chapter 7). This finding highlights the disadvantages in using heterogeneous groups of cancer patients in studies of REE.

The importance of expressing REE in terms of the metabolically active portion of body weight has been stressed. The REE studies of this thesis have demonstrated that misleading results are obtained when REE is expressed in terms of body weight, which makes no allowance for the relatively less metabolically active fat mass. The possible disadvantages in using total body water measurements for the estimation of lean body mass in malnourished patients have been discussed, but it should be noted that even total body potassium measurements can be inaccurate in the presence of weight loss.

Many authors have suggested that REE increases with advancing tumour burden, with major increases in REE occurring in patients who have hepatic metastases. In the longitudinal study of patients with colorectal cancer (Chapter 8), no significant differences in REE have been found following either curative resection or progression of metastatic disease. This supports the earlier conclusion that the presence of cancer has no significant effect on host REE.

Prediction of resting energy expenditure

Some authors have claimed that cancer patients have a raised REE, basing their conclusions on a comparison of measured REE with that predicted by

various predictive formulae. In Chapter 5, where four predictive formulae or tables have been compared with measured REE values, significant errors in the predictive ability of these formulae and tables have been found. Of particular importance is the inaccuracy of the widely-used Harris-Benedict formula in predicting REE in male patients, irrespective of disease or weight status. It is concluded that subtle differences in body composition between ill patients and the healthy volunteers used to derive these formulae are responsible for the inaccuracy in prediction of REE.

An alternative method of estimating REE in the absence of indirect calorimeter facilities has been demonstrated (Chapter 6). Close correlations between measured REE and mid-arm muscle circumference (MAMC) measurements have been demonstrated. It is noteworthy that the regression lines relating REE to MAMC are similar to those relating REE to lean body mass (Chapter 4). This suggests that MAMC measurements are representative of the metabolically active portion of the body. A prospective study using the regression equations derived from MAMC measurements would be required to test the accuracy of prediction of REE using this technique.

Substrate metabolism

Patients with cancer have been shown to have decreased rates of endogenous carbohydrate oxidation and increased rates of endogenous fat oxidation compared with patients with nonmalignant illness. These abnormalities are more pronounced in those cancer patients with hepatic metastases. The studies of this thesis can provide no firm explanation for these metabolic abnormalities, but the accelerated rate of body fat oxidation may contribute significantly to the development of cancer cachexia. Furthermore, these abnormalities of fat oxidation are consistent with the recent discovery that tumour necrosis factor, or cachectin, which is produced by the macrophages of some patients with cancer, interferes with fat metabolism.

Some authors have suggested that whole body protein turnover (WBPT) is increased in patients with cancer, and that this may cause an increase in REE. The results of Chapter 10 demonstrate that patients with certain tumour types have increased rates of WBPT. However, abnormalities of WBPT are not related to weight loss and have no demonstrable effect on REE.

The possibility that an acute phase protein response is responsible for some of the metabolic

abnormalities seen in patients with cancer has been discussed. An acute phase protein response can be demonstrated in many patients with progressive cancer, and this phenomenon would be consistent with the observations made in Chapter 4, where it was concluded that the host's response to illness appeared to be a major determinant of abnormalities in REE. Furthermore, the presence of an acute phase protein response would be consistent with the production of cachectin. Studies of the immune response and the production of interleukin-1 in cancer patients are outwith the scope of this thesis, but warrant further investigation.

Peripherally-administered intravenous nutrition

The peripheral administration of glucose, amino acids and fat to patients following surgery for colorectal cancer has been shown to result in a positive nitrogen balance, with minimal phlebitic complications (Chapter 11). In those patients receiving an amino acid solution alone postoperatively, there was a significant fall in carbohydrate oxidation rate and a significant rise in fat oxidation rate. However, the transient improvement in postoperative nitrogen balance in these patients appears to have occurred independently of plasma insulin levels, and it is concluded that this solution

has little to offer compared with a standard dextrose-saline regimen.

This study did not address the question of whether debilitated patients undergoing major surgery should receive intravenous nutritional support. However, it is concluded that where the provision of postoperative peripherally-administered intravenous nutrition is desired, the use of a nutrition mixture containing glucose, amino acids and fat should be used.

Pharmacological manipulation of the metabolic response to surgery

Manipulation of the metabolic response to surgery using anabolic steroids has yielded conflicting results in the literature. The findings of Chapter 12 suggest that the use of the anabolic steroid stanozolol may improve nitrogen balance in patients receiving intravenous amino acid solutions following colorectal cancer surgery. Although stanozolol had no significant effect on postoperative nitrogen balance in those patients receiving glucose, amino acids and fat, the trend towards improved nitrogen balance suggests that alteration in the dose or timing of administration of stanozolol may be worthy of further investigation.

In the study of patients receiving a dextrose-saline regimen following surgery for gastric cancer (Chapter 13), stanozolol appeared to improve nitrogen balance by the fourth postoperative day. This finding contrasts with the results of Chapter 12, where stanozolol had no significant effect on nitrogen balance in patients receiving the same regimen following colorectal cancer surgery. However, it supports the contention that alteration in the dose or timing of administration of this agent may be of value. Naftidrofuryl had no demonstrable effect on postoperative nitrogen balance, but the suggestion that both this agent and stanozolol may have some effect on postoperative fat metabolism warrants further investigation.

Thus, there is some evidence to suggest that postoperative nitrogen excretion and substrate metabolism may be influenced by the pharmacological manipulation of the metabolic response to surgery. It is concluded that further studies of the effects of stanozolol and naftidrofuryl on the metabolic respone should be undertaken.

APPENDIX

The indirect calorimeter was developed in the Department of Surgery largely by Christopher C. Goll. The validation of this equipment, including patient studies, formed a major part of his Ph.D. thesis (269). A schematic representation of the gas circuitry of the indirect calorimeter is shown in Figure 40.

Butane gas calorimetry test

A small gas camping light (Lumogaz Camping Gaz Ltd) which burns commercial butane gas (Camping Gaz Ltd) was burned inside the calorimeter canopy at regular intervals to test the sensitivity and accuracy of the whole system. This test was performed together with regular calibration of the gas analysers (see Chapter 3).

Analysis of the fuel by gas chromatography showed the constituents to be 93.30% butane, 0.34% propane and 6.36% butene. This fuel burns with an RQ of 0.619. Regular test runs revealed the calorimeter to have an error of less than $\pm$5%.

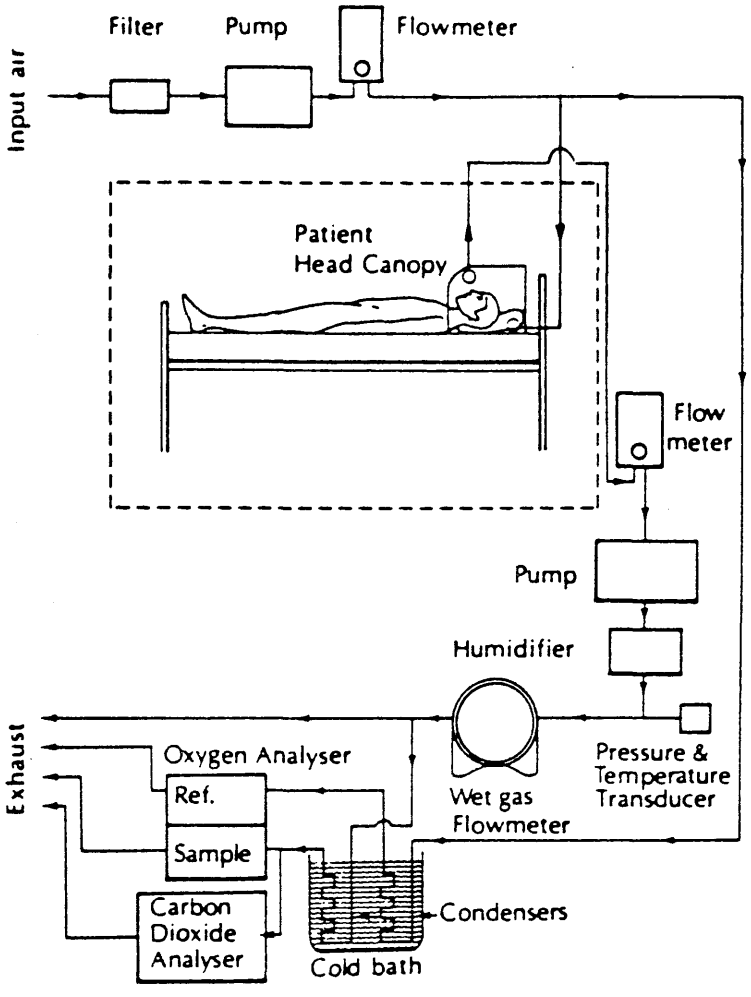


Figure 40

Schematic representation of the gas circuitry of the indirect calorimeter

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