

# The pulmonary cachexia syndrome: aspects of energy balance

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The present paper reviews current knowledge of the pulmonary cachexia syndrome with reference to chronic obstructive pulmonary disease (COPD). Aspects of incidence, aetiology and management are discussed. Malnutrition occurs in approximately one-quarter to one-third of patients with moderate to severe COPD. Both fat mass and fat-free mass become depleted. Loss of fat-free mass is the more important and appears to be due to a depression of protein synthesis. Weight loss is an independent prognostic indicator of mortality, and is associated with increased morbidity and decreased health-related quality of life. The aetiology of malnutrition in COPD is not well understood. Reduced food intake does not seem to be the primary cause. Resting energy expenditure (REE) is elevated in a proportion of patients and probably contributes to negative energy balance. Measurement of actual REE is helpful when considering the adequacy of nutritional supplementation. The underlying reason for a hypermetabolic state is not known. Although weight-losing COPD patients are not catabolic, nutritional supplementation alone does not appear to reverse the loss of fat-free mass. Strategies involving nutritional supplementation in combination with a second intervention are being explored, and there are some encouraging results using anabolic hormones.

## **Pulmonary cachexia syndrome: Chronic obstructive pulmonary disease: Energy balance: Body-weight loss: Malnutrition**

Malnutrition is a feature of lung cancer as in many other cancers, but it is also a feature of lung disease of a non-malignant aetiology and then has been termed 'the pulmonary cachexia syndrome'. Weight loss may be very marked and difficult to reverse, in addition the aetiology is not well understood. The following article is a review of current knowledge. The majority of information comes from work with chronic obstructive pulmonary disease (COPD) and the present article will focus on malnutrition in this condition, noting that malnutrition may be seen also in other end-stage lung diseases such as cystic fibrosis and interstitial lung disease.

### **Incidence and pattern of malnutrition**

COPD is characterized by progressive irreversible airflow obstruction, fibrosis and distortion of the small airways, and destruction of the alveolar–pulmonary capillary interface (emphysema). Aetiology is tightly linked to past or present cigarette smoking. The forced expiratory volume in 1 s is the best indicator of the degree of airflow obstruction and is also the best predictor of life expectancy. Typically, symptoms

of exertional breathlessness develop at age 50–60 years and progress with time, sometimes to the point where breathlessness occurs on the most minimal of activities, such as washing. Weight loss has been recognized to be a feature of COPD for many years. Using criteria of loss of 5–10% initial body weight, or weight less than 90% ideal body weight (IBW), the reported incidence of malnutrition is between 24 and 35% of patients with moderate to severe COPD. Early studies tended to report data on either hospital inpatients or other highly-selective patient groups. However, Wilson *et al.* (1989) reported that 24% of 779 men with COPD recruited for a large US national outpatient trial had a body weight less than 90% IBW. More recently, Schols *et al.* (1993) studied 255 consecutive patients of both sexes admitted for intensive pulmonary rehabilitation in The Netherlands. Mean forced expiratory volume in 1 s was approximately 35% predicted value, mean age 64 years, and in this group 35% weighed less than 90% IBW. A similar prevalence was recorded in the UK, in sixty-nine outpatients with moderate to severe COPD (mean forced expiratory volume in 1 s 35% predicted value), 36% weighed less than 90% IBW (Congleton, 1998).

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**Abbreviations:** COPD, chronic obstructive pulmonary disease; DIT, diet-induced thermogenesis; IBW, ideal body weight; REE, resting energy expenditure.  
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Studies of body composition in COPD show that both fat mass and fat-free mass are lost. Although some early studies placed importance on loss of fat mass, more recent work has indicated that depletion of fat-free mass may be more important. Hunter *et al.* (1981) carried out a detailed nutritional assessment of thirty-eight patients with COPD of varying degrees of severity. This group found marked depletion of both subcutaneous fat stores and muscle mass, and that the pattern met the criteria of protein-energy malnutrition. Schols *et al.* (1993) showed that depletion of fat-free mass could occur in patients apparently maintaining weight, and that it was depletion of fat-free mass that was important functionally. The results of studies of leg and whole-body amino acid and protein flux have suggested that the mode of muscle protein depletion in COPD is by a reduction of muscle synthesis rather than an increase in muscle breakdown (Morrison *et al.* 1988). This is a similar mechanism to muscle wasting in cancer cachexia, thyrotoxicosis and muscular dystrophy, but contrasts with cardiac cachexia in which there is increased muscle breakdown in addition to reduced synthesis. There are several possible mechanisms which could lead to depressed muscle protein synthesis. Induced hypoxia depresses protein synthesis in experimental conditions, possibly because cellular hypoxia reduces the ATP production necessary for muscle protein synthesis (Rennie *et al.* 1983). However, the typical clinical picture is of a wasted emphysematous patient with approximately normal arterial blood gases (a 'pink puffer'), and a hypoxaemic overweight 'blue bloater'. A strong correlation between low arterial partial pressure of O<sub>2</sub> and muscle wasting in COPD has not been reported in the literature. Chronic malnutrition itself may contribute to depressed protein synthesis (Holt *et al.* 1963), and immobility leads to both disuse atrophy (Sargeant *et al.* 1977), and depression of muscle protein synthesis (Gibson *et al.* 1987). Corticosteroid therapy is known to depress the rate of protein synthesis and cause a true myopathy, and thus may exacerbate muscle depletion, but severe muscle wasting is seen in patients not taking corticosteroids. Visceral protein appears to be maintained, since circulating levels of serum proteins such as transferrin and albumin are not generally depressed. There is no evidence of vitamin deficiency being important in this group of patients (Driver *et al.* 1982), although interest in the role of vitamins and antioxidant-oxidant balance in respiratory disease is increasing.

### Mortality and morbidity

Weight loss may be only a marker of disease progression in COPD (i.e. a marker of worsening of airflow limitation), but there are several theoretical ways in which malnutrition might independently interact with disease state. Reduced respiratory muscle strength, reduced ventilatory response to hypoxia, poor wound healing and decreased cell-mediated immunity could all compromise a patient with poor respiratory function and increase the risk of deterioration. An acute exacerbation of COPD is itself associated with weight loss, leading to further worsening of nutritional status (Wilson *et al.* 1985). Early work supported the clinical impression that weight loss was associated with a poor prognosis. In the retrospective study of Sukumalchandra &

Williams (1965), mortality was five of twelve in the group with weight loss and five of thirty-two in the group without weight loss ( $P=0.08$ ). Vandenberg *et al.* (1967) found an increased mortality in a group of seventy-one patients with weight loss greater than 10%. The weight-losing group and non-weight-losing groups were selected differently for the follow-up period in this study, and in an attempt to compare prognoses, a subset were chosen who were comparable and were followed-up for a further period. Survival was better in the group without weight loss, 5-year survival being 76% *v.* 49% despite similar mean initial weight. It has been suggested that low body weight is merely a surrogate marker for severely-impaired lung function. Wilson *et al.* (1989) retrospectively examined data from 779 men collected over 3 years and found that weight loss was a prognostic factor independent of forced expiratory volume in 1 s. This finding was particularly marked in the group of patients with better lung function.

Potentially, wasting of the respiratory muscles could be of great importance, as respiratory muscle fatigue and weakness could predispose to respiratory failure and further increase energy requirements. Muscle contains a mixture of type 1 fibres (slow-twitch, O<sub>2</sub>-dependent, fatigue-resistant) and type 2 fibres (fast-twitch, mainly dependent on glycolytic stores). Slow-twitch fibres are recruited during low-intensity contractions. As the intensity of contraction increases, fast-twitch fatigue-resistant, and later fast-twitch fatigable fibres, are recruited. In rats the effect of undernutrition has been shown to be greater on fast-twitch (type 2) fibres than on slow-twitch (type 1) fibres (Lewis *et al.* 1987). Thurlbeck's (1978) study on diaphragm weight implies that respiratory muscle wasting may be an important effect of malnutrition. This post-mortem study of 184 emphysematous patients found that diaphragm weight was lower than expected for body weight, probably because respiratory muscle consists of a higher proportion of type 2 fibres than peripheral muscle and these are relatively more affected by undernutrition than type 1 fibres. Arora & Rochester (1982) showed that severe malnutrition greatly reduced respiratory muscle strength in non-respiratory patients, but in this study thirteen of the sixteen subjects had malignancy and therefore a paraneoplastic process may have been operating. Studies of respiratory muscle strength and malnutrition in COPD have given conflicting results. Some groups have shown reduction in inspiratory and expiratory muscle strength in underweight patients (Donahoe *et al.* 1989; Gray-Donald *et al.* 1989; Schols *et al.* 1991a). However, other groups have shown that body weight makes only a small contribution to respiratory muscle strength, which is more affected by the degree of mechanical disadvantage of the respiratory muscles due to hyperinflation (Lewis *et al.* 1986; Knowles *et al.* 1988). However, peripheral skeletal muscles do seem to be functionally affected. Efthimiou *et al.* (1988) showed a significantly reduced handgrip strength in underweight COPD patients compared with normal-weight COPD patients. Schols *et al.* (1991a) assessed 12 min walking distance in fifty-four patients with severe airflow obstruction, and although there was a strong correlation between % IBW and walking distance ( $r 0.61$ ), there was a better correlation between fat-free mass and walking distance. This latter correlation was particularly

marked in underweight patients, and contrasts with the lack of correlation between airflow obstruction and walking distance in this study.

An increased susceptibility to certain types of infection, probably due to decreased cell-mediated immunity, is a feature of malnutrition in other conditions (Chandra, 1980). This is potentially important in COPD where a relatively minor infection could compromise respiratory function greatly. Cell-mediated immunity can be assessed by skin-prick tests for cutaneous delayed hypersensitivity, which evaluates the T-cell memory response and is usually depressed in protein-energy malnutrition (Chandra, 1980). In addition, there is a reduction in the number of circulating T lymphocytes, and *in vitro* lymphocyte response to mitogens and antigens is also reduced. There have been conflicting results in studies assessing cell-mediated immunity in COPD. Hunter *et al.* (1981) found negative skin-prick tests in approximately one-third of thirty-eight COPD patients with varying disease severity, although the total lymphocyte count was elevated, which is normally associated with a preserved cellular immune function. Similarly, Gray-Donald *et al.* (1989) reported no difference in total lymphocyte count between underweight and normal-weight patients. Driver *et al.* (1982) found a high incidence of skin anergy in a group of malnourished COPD patients with respiratory failure and, in contrast to the previously described studies, that total lymphocyte count was reduced compared with that of the better-nourished non-respiratory-failure group. However, Wilson *et al.* (1986) found intact delayed hypersensitivity in all six severely-malnourished patients in a feeding study (weight 62–81% IBW). An increased incidence of infections in underweight COPD patients has not been shown, and it appears on balance that the integrity of immune function in this group is preserved.

It is possible that low body weight is a factor in the lethargy and exhaustion patients feel. Wilson *et al.* (1989) reported that there was no association between % IBW and the physical score of the sickness-impact profile in 779 male COPD patients. However, our group found a strong relationship between quality of life and malnutrition, with low fat-free mass being particularly associated with a poor 'activity' score in the St George's Hospital respiratory questionnaire (Jones *et al.* 1992), and low fat mass being associated with a poor 'impact' score (Congleton & Muers, 1995).

### Aetiology of malnutrition in COPD

Weight loss occurs when energy expenditure exceeds energy intake, i.e. there is negative energy balance. Negative balance occurs in exacerbations of COPD due to an increased energy requirement and decreased intake. This stepwise fall in weight associated with exacerbations has been proposed to account for weight loss in COPD (Wilson *et al.* 1985). The steady chronic loss which occurs despite a stable clinical state may be at least as, or more, important. Negative energy balance may be caused by reduced intake, reduced absorption, inefficient fuel uptake, and increased energy expenditure. These factors may occur in isolation or in combination, and evidence for each factor is now reviewed.

### Reduced intake?

Reduced energy intake was initially assumed to be an important factor, and there are many reasons why it may occur in these patients. Dyspnoea could increase due to irregular breathing while eating and swallowing, or due to gastric filling reducing functional residual capacity. It has been suggested that patients with COPD may eat sub-optimally because chewing and swallowing alter the breathing pattern and cause arterial O<sub>2</sub> desaturation (Schols *et al.* 1991b). Interpretation of food-intake studies is difficult, since dietary intake is notoriously difficult to assess. Another problem is that intake is often compared with the predicted energy requirement, which may underestimate the true requirement for attaining energy balance. Schols *et al.* (1991b) studied arterial O<sub>2</sub> desaturation during eating in forty-four patients. Overall the O<sub>2</sub> saturation fell by a very small degree within 5 min of commencing eating and rose a few minutes after completion of the meal. Saturation at 30 min was still slightly lower than at baseline (85.3% *v.* 87.5%). There was no difference in desaturation, transcutaneous partial pressure of CO<sub>2</sub> and heart-rate response between the weight losers and non-weight losers. However, when the twenty hypoxaemic patients were subdivided into those for whom desaturation was >4% when eating and those for whom desaturation was <4%, the group with desaturation >4% were found to be more dyspnoeic and weigh significantly less (54.9 kg *v.* 74.7 kg). Any arterial O<sub>2</sub> desaturation that does occur is not metabolic in origin, since the onset after commencing eating is quick and nasogastric administration of food does not cause O<sub>2</sub> desaturation, (Brandstetter *et al.* 1988). In a different study of eighty pulmonary rehabilitation patients, Schols *et al.* (1991c) found a lower dietary intake in the hypoxaemic group compared with a non-hypoxaemic group. Hypoxia-related appetite suppression has been suggested as a cause of under-nutrition in COPD, as it has been noted that appetite suppression, particularly for fatty foods, occurs at extreme altitude (Pugh, 1962), but this hypothesis has not been tested further. Studies of food intake have been informative. Hunter *et al.* (1981) found energy intake in a group of thirty-eight patients with COPD of varying severity was greater than the recommended daily amount at 10.6 MJ (2535 kcal), both in weight losers and non-weight losers. Braun *et al.* (1984) found that energy intake was inversely correlated with % IBW in sixty consecutive outpatients, suggesting that there is an attempt to compensate for weight loss. However, Schols *et al.* (1991c) found that mean dietary intake of energy when expressed as a percentage of actual measured resting energy expenditure (REE) was significantly less in weight losers than in weight-stable patients, although both values were over 100% (119% *v.* 134%, *P*<0.05). Measured REE was greater than theoretical REE in both groups (117% and 108% respectively), and this highlights the importance of measuring REE in this group of patients when assessing whether intake is adequate. The findings of previously mentioned studies suggest that decreased intake is not the primary underlying cause of weight loss, although intake may not match requirements when weight loss is occurring, thus exacerbating the situation. This finding might account for the general failure of

studies of supplemental feeding to show prolonged weight gain in COPD patients.

#### *Reduced absorption?*

Malabsorption does not seem to be an important factor. Semple *et al.* (1979) carried out detailed malabsorption studies on eight severely-underweight COPD patients, including jejunal biopsy, faecal fat estimation, D-xylose excretion, Fe, vitamin B<sub>12</sub> and folate estimation, with normal results for all measurements.

#### *Abnormal handling of nutrients or inefficient fuel uptake?*

The physiological response to semistarvation is for REE to fall and to be associated with a progressive increase in utilization of fat for energy and conservation of N. In conditions such as sepsis or acute injury there is an increase in REE associated with reduced carbohydrate oxidation and increased fat and protein oxidation. It is important to note that unlike other weight-losing patients, e.g. those with severe burns or sepsis, COPD patients are not catabolic (Goldstein *et al.* 1988). This situation has implications when considering intervention as, theoretically, adequate energy intake should lead to an increase in weight at a rate similar to that of other depleted patients. Goldstein *et al.* (1988) reported that malnourished individuals with lung disease have a pattern of energy metabolism that is distinctly different from that of malnourished individuals without lung disease (surgical and anorexic patients), with increased carbohydrate and protein oxidation, and no preferential fat oxidation occurring in the COPD group. However, subsequent studies have reported differing results. Green & Muers (1991) studied ten COPD patients and six controls and found that there was an increase in fasting fat oxidation in the COPD group. Substrate balance calculations showed that the COPD patients stored less protein as a proportion of intake after a meal, and this would exacerbate muscle wasting.

#### *Increased energy expenditure?*

There are three main components to total energy expenditure: diet-induced thermogenesis (DIT), activity-related thermogenesis, and REE. The major component is REE, accounting for between 60 % and 80 % of the total, depending on the level of general activity and the fuel mix. DIT accounts for approximately 10 % of the total and activity-related thermogenesis accounts for little, particularly in a relatively sedentary group.

*Increased diet-induced thermogenesis?* Studies on DIT report differing results and different interpretations of the data. These differences may be due partly to the different test feeds used, different ways of expressing DIT and different types of subjects acting as controls. Goldstein *et al.* (1987) compared DIT in ten malnourished COPD patients with five malnourished non-respiratory patients using both a fat-based and a carbohydrate-based refeeding regimen. The energy intake consisted of 1.7 times the basal REE, which was significantly greater in the COPD group. During the fat-based regimen the average daily energy expenditure rose from 90 % to 98 % of the value predicted by the Harris-

Benedict (Harris & Benedict, 1919) equation in the control group and from 116 % to 130 % of the predicted value in the COPD group (i.e. rose by 9 % and 12 % respectively). With the carbohydrate-based regimen REE rose to 99 % and 136 % of the predicted value respectively (i.e. by 10 % and 17 % respectively). Since (1) these values are given as a percentage of the predicted values, (2) the energy intake of the two groups was different, and (3) the 'control' group were malnourished, it is difficult to decide whether this finding represents a true increase in DIT. In fact, Hugli *et al.* (1993) recalculated the data and reported that on the carbohydrate-based regimen DIT was 15 % of the baseline value in the COPD group v. 18 % in controls and on the fat-based regimen was 11 % v. 13 % respectively, both differences were non-significant. Green & Muers (1991) studied ten emphysematous patients and six healthy controls, and measured DIT following a protein-rich meal standardized to body weight. DIT was expressed as a percentage of energy intake and was found to be increased in patients compared with controls. However, the same group reported different results in a subsequent paper (Green & Muers, 1992), although the study conditions were different. They found that DIT and both pre- and postprandial fuel mix were similar in emphysematous COPD patients, bronchitic COPD patients, chronic asthmatics and healthy controls given a high-carbohydrate meal, standardized to 40 % of measured REE. The explanation for the different results may lie in the composition of the test meal. Hugli *et al.* (1993) carried out a similar study in eleven emphysematous patients and eleven controls given a meal consisting of 8.3 kJ (2 kcal) in the proportions (% energy) 50 carbohydrate, 35 fat, 15 protein, giving an amount equivalent to 30 % of the 24 h energy expenditure, and also reported no increase in DIT in the patients. The discrepancies between the various studies may be due to the way of expressing DIT, either as percentage of the total energy expenditure (which would tend to lower the value in COPD due to the relatively high REE), or as a percentage of the energy intake (which is probably more physiological). Hugli *et al.* (1993) found no increase whichever way DIT was expressed. The problem of interpretation of the results remains unresolved, but it seems likely that any increase in DIT, if present, must be small and cannot account for the degree of weight loss observed.

*Increased activity-related thermogenesis?* As mentioned previously, activity accounts for a small percentage of the total energy expenditure. Although activity is no doubt more costly to this group of patients, this is almost certainly offset by the degree of inactivity (Hugli *et al.* 1996).

*Increased resting energy expenditure?* There has been an interest in this area in recent years, as several groups have reported an increased REE in a proportion of patients with COPD. An increase in BMR of 10–20 % would be enough to account for the order of weight loss seen in COPD patients. This increase in REE in COPD again supports the notion that although a relatively reduced food intake may exacerbate malnutrition, it cannot be the primary cause, since the physiological response to starvation is for REE to fall. It is unclear whether increased REE is the cause of weight loss in COPD. There is some evidence in the literature that an increased REE in COPD is more common



in those patients with a history of weight loss (Schols *et al.* 1991c). However, not all patients who are losing weight are hypermetabolic (Congleton *et al.* 1993) and the relationship between REE and weight loss requires further investigation. Hugli *et al.* (1996) found that although REE was elevated in a group of COPD patients compared with control subjects, total daily energy expenditure was identical in the two groups. This finding was ascribed to spontaneous reduction of activity in the COPD group. Possible causes of the increased REE are now considered, including:

artefact: prediction equations, body composition, measurement;  
increased work of breathing;  
generalized hypermetabolic state.

*Increased resting energy expenditure: artefact.* There are various ways of expressing REE. One of the most usual procedures is for REE to be expressed as a percentage of the expected or predicted value. The most well recognized of these procedures is the Harris-Benedict equation (Harris & Benedict, 1919), which was produced following measurement of BMR in 187 men and 146 women in the age-range 16–74 years. The equation depends on age, height, weight and sex. Other prediction equations have since been developed, the equation of Schofield *et al.* (1985) being one of the more widely used. However, there are various problems with the use of all available equations. Many patients with COPD are in the older age-group and few subjects over 50 years old were studied in the original work. However, control subjects of any age generally give results within  $\pm 5\%$  of the predicted value, implying that the equation remains valid. Second, although weight is included in the prediction formula, a standard body composition is assumed and this may not be valid for COPD patients. An alternative approach is to compare REE with that of age-, sex-, height- and weight-matched controls, but the problem of possible differing body composition remains. It may be more appropriate to base metabolic rate on the amount of metabolically-active tissue, the so-called body cell mass. The best estimate of body cell mass at present is considered to be fat-free mass, and thus REE may be better expressed by adjusting for fat-free mass. There are several different methods of estimating fat-free mass, only some of which have been validated for COPD patients. Schols *et al.* (1991c) found that mean REE, both when expressed as a percentage of the Harris-Benedict equation value and per kg fat-free mass, was elevated in weight losers as compared with weight-stable patients.

It is important that REE is measured under standardized conditions, with the subject rested and in a truly stable state, otherwise erroneously high values may be obtained. Early workers used mouthpiece methods which may lead to an overestimation of REE, but the findings of a raised REE were later confirmed using a canopy and no facial apparatus (Goldstein *et al.* 1987; Fitting *et al.* 1989). The fact that similar results have been obtained by many different groups implies that REE is genuinely raised in a proportion of COPD patients.

*Increased resting energy expenditure: increased work of breathing.* An increase in the energy cost of breathing is often quoted as the cause of increased REE in COPD

(Wouters & Schols, 1993). In normal subjects the contribution to the whole-body metabolic rate by the work of breathing is very small, of the order of 2–3%. In COPD the respiratory muscles have a high load since they need to generate larger forces to expand the thoracic cage. They also work at a mechanical disadvantage with increasing hyperinflation. The two quantities, an increased cost of breathing at rest (which could account for the increase in REE), and an increased cost of elevated ventilation (which would not on its own account for any increase in REE, but might increase total energy expenditure), are distinct entities which are often not distinguished from each other. There is, at present, no reliable method of measuring the energy expenditure of the respiratory muscles at rest. Cherniak (1958) demonstrated that the O<sub>2</sub> cost of breathing at various levels of ventilation could be estimated by increasing dead space. He showed that at equivalent levels of ventilation the O<sub>2</sub> cost of breathing was far greater in an emphysematous patient compared with a normal subject, and that small increases in ventilation are associated with marked increases in O<sub>2</sub> consumption. An important point to note is that differences in the O<sub>2</sub> cost of augmented ventilation need not necessarily be matched by a difference in the O<sub>2</sub> cost of breathing at rest. There is no consensus of opinion as to whether the O<sub>2</sub> cost of breathing at rest is significantly elevated in hypermetabolic patients.

*Increased resting energy expenditure: generalized hypermetabolic state.* There are striking clinical similarities between the malnutrition seen in COPD and that in patients with chronic cardiac failure (cardiac cachexia), chronic liver disease and in carcinoma (cancer cachexia). Hypermetabolism is associated with all these conditions (Green *et al.* 1991; Morrison & Edwards, 1991; Falconer *et al.* 1994). This leads to the hypothesis that there may be a common underlying systemic cause rather than the cause being specific to the respiratory system. Possible mechanisms are via thermogenic hormones (thyroxine, triiodothyronine and cortisol), endogenous catecholamines, cytokines and drug therapy. Semple *et al.* (1979) reported on hormonal status in sixteen males with COPD and found no evidence of thyroid abnormalities or differences between an underweight group and an overweight group. There were also no differences in mid-day cortisol levels between the two groups. Green & Muers (1992) also found no evidence of derangement in thyroid function and found normal circulating cortisol levels in patients who were hypermetabolic. Catecholamines have been shown to increase muscle breakdown in animal studies, but they also cause a reduction in fat content and increase energy expenditure via non-shivering thermogenesis (Yang & McElligott, 1989). There is little published work on catecholamines in COPD. The stress of increasing dyspnoea with worsening status can activate the sympathetic nervous system and release catecholamines which have a role as intermediary molecules in metabolism. Hoffard *et al.* (1990) found raised levels of circulating noradrenaline but not adrenaline in eleven patients with airflow obstruction and emphysema studied when in a stable clinical state. It is not known whether this finding is associated with a reduction in skeletal muscle  $\beta$ -receptor density and development of tolerance. REE was not measured. Hoffard *et al.* (1990) hypothesized that the

raised catecholamine level was a marker of glucose need. Catecholamines reduce insulin secretion and therefore inhibit protein synthesis as amino acids are diverted to gluconeogenesis. In the Hoffard *et al.* (1990) study plasma amino acid levels were maintained. Tumour necrosis factor is a cytokine produced by monocytes and macrophages, it inhibits lipoprotein lipase (EC 3.1.1.34) and is pyrogenic. It triggers the release of other cytokines such as interleukins 1 and 2 which also increase energy expenditure. Tumour necrosis factor is increased in cardiac cachexia (Lavine *et al.* 1990), and there is recent work on tumour necrosis factor in COPD suggesting that it is elevated in a proportion of hypermetabolic patients (Schols *et al.* 1996). This is a difficult area to investigate because of the vast complexity of the cytokine systems and their degree of interaction with each other, the difficulty of knowing whether the measured variables are cause or effect, and also the technical difficulty of and differences in sensitivities of assay techniques. New information in this area is awaited.

The major classes of drugs used in COPD ( $\beta_2$  agonists, methylxanthines, quaternary ammonium compounds and oral corticosteroids) all have an effect on body tissues and metabolism. However, Schols *et al.* (1991c) found no association between REE and either maintenance medication or smoking in a group of eighty patients, and no other evidence has implicated drug therapy as the cause. Certain medications are difficult to assess because of their ubiquity in COPD, e.g.  $\beta_2$  agonists, but studies so far do not implicate them in contributing to a raised REE (Congleton & Muers, 1998).

#### *Attempts to reverse weight loss*

**Refeeding.** As malnourished COPD patients are not catabolic, in theory energy supplementation will lead to weight gain. Disappointingly this has been extremely difficult to achieve in practice. Controlled studies of refeeding underweight COPD patients have generally given poor results, as reviewed by Fitting (1992). A high energy intake is required to show weight gain, e.g. 1.7 times measured REE. This can be achieved in the short term with oral supplementation alone (Wilson *et al.* 1986). Weight gain that has been achieved has been small and not maintained after the study period is over. Any improvement in respiratory muscle strength, walking distance or other functional variables has also been small but has seemed to occur in tandem with weight gain. Once patients are no longer encouraged to continue their diets there is a spontaneous rapid reduction of intake back to pre-intervention levels and a slower fall in weight and physiological measures back to approximately pre-treatment levels (Efthimiou *et al.* 1988; Whittaker *et al.* 1990). In addition, some recent work shows that any increase in weight may be entirely due to an increase of fat mass without an increase in fat-free mass (Donahoe *et al.* 1994). It therefore seems likely that refeeding alone is not an effective treatment in the majority of undernourished COPD patients, and an additional or alternative approach will be necessary to give good results. Current strategies under investigation are the use of growth hormone, anabolic steroids and muscle training, in conjunction with ensuring adequate energy intake. Pape *et al.*

(1991) suggested that growth hormone may lead to an increase in weight and improved N balance in COPD. The findings were based on a pilot study and there was no control group who remained on diet alone. The anabolic effect of growth hormone probably acts via insulin-like growth factor 1. There has been a preliminary report that insulin-like growth factor 1 is a marker of undernutrition in COPD (Sridhar *et al.* 1993). Schols *et al.* (1995) reported a benefit of the anabolic hormone nandrolone in combination with nutritional supplements and an exercise programme, when compared with nutritional supplements and exercise alone.

In summary, the cause of weight loss in COPD is not established. Energy intake obviously does not match requirements, particularly during acute exacerbations of COPD, although a decreased intake does not seem to be the prime cause. REE is increased in a proportion of COPD patients, although the aetiology of this increase and its exact relationship with weight loss is not fully understood. Weight loss in COPD is a major clinical problem which is difficult to reverse, has prognostic value and an associated morbidity. Energy requirements may be greater than predicted and attempts to compensate may be difficult for mechanical reasons. The increased REE in COPD is unique in that the patients are not hypercatabolic. The importance of knowing that a patient has an increased REE has a practical value when advising an energy intake which attempts to achieve weight gain or maintain weight. Understanding the mechanism underlying the increased REE might lead to the development of measures to manipulate it.

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