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NUTRITIONAL FACTORS IN RESPIRATORY DISEASE

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Why should we concern ourselves with associations between nutrition and the respiratory system? During states of starvation, the respiratory system is relatively spared when compared to other major organ systems. The clinical manifestations of the major nutritional deficiency diseases such as protein-energy malnutrition, and the more specific vitamin deficiency syndromes such as scurvy, xerophthalmia, beri-beri and pellagra do not include a primary respiratory disorder. Nevertheless, there are important links between nutrition and respiratory disease which have both clinical and research implications.

In this article, three major areas of association are considered: nutritional factors as a cause of respiratory illness, nutritional consequences of respiratory illness and conditions which include nutritional and respiratory manifestations among their primary manifestations. In addition, the potential respiratory occupational risks to workers in the food industry will be reviewed briefly.

NUTRITIONAL CAUSES OF IMPAIRED LUNG FUNCTION OR RESPIRATORY ILLNESS

A number of mechanisms may be involved. Food allergy or intolerance is widely quoted in both the medical and lay press as a cause of respiratory symptoms. Relative deficiencies or excesses of specific dietary components such as salt, antioxidants, fatty acids and selenium have been implicated in the causation or expression of asthma and wheezing disorders. A complex, as yet incompletely understood, relationship exists between diet and lung cancer.

Food allergy and food intolerance[1]

Food allergy and food intolerance reflect adverse reactions to food constituents which are not the result of food contamination or psychological factors. The published literature on the subject is large, but there is a noticeable paucity of scientifically 'solid' studies and quality data on the role of food allergy and intolerance in respiratory disease are slight. Food allergy has been defined as 'an immunological reaction resulting from the ingestion of a food or food additive' and food intolerance as 'a general term describing an abnormal physiological response to an ingested food or food additive that is not proven to be immunogenic'.[1] At least 30% of individuals experience at least one episode of food intolerance in their lifetime and about 20% of these episodes will represent an allergy.[2]

Food allergy

Approximately 20% of the general population give a history of food allergy, but the prevalence of incontrovertible food allergy is 0.5-3.8% of young children and 0.1-1.0% of adults; it is highest in infants (4-6%); this is believed to be the consequence of immaturity of the alimentary and immune systems.[3,4] Traditionally the term 'food allergy' has been reserved for type I hypersensitivity reactions which are mediated by specific IgE, and the term immune-mediated reactions refers to type II, III and IV hypersensitivity reactions. Research has concentrated on type I reactions, which may

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be the underlying mechanism accounting for up to 72% of food allergies. In children, the most common foods implicated are cow's milk, peanuts, eggs and fish, whilst in adults, nuts and shellfish predominate. The relative incidence of allergy to individual foods is partly determined by the dietary habits of society, so that peanut allergy is rare in countries where peanuts are an uncommon dietary component. Most childhood food allergies are outgrown (90% of cow's milk allergies) but those to peanuts, nuts, shellfish and fish can last a lifetime, and these are the foods that are most frequently implicated in life-threatening anaphylactic reactions.

The diagnosis of food allergy is easy when the reaction is acute and the food suspected is unusual in the individual's diet, but when the reaction is mild and/or delayed, immunological tests are required. Skin prick tests are relatively specific and a negative test excludes an IgE-mediated food allergy; however, the positive predictive value of a positive test is less than 50%, because children who have grown out of a food allergy may continue to have a positive test. Radioallergosorbent (RAST) tests are less sensitive and have similar weaknesses. The 'gold standard' diagnostic test for food allergy is the double-blind, placebo-controlled food challenge. This is a cumbersome, inconvenient, labour-intensive, expensive test which is really a research tool. In the clinical setting an acceptable compromise is elimination and challenge testing.

The most important manifestation of food allergy is acute anaphylaxis, the annual incidence of which has been estimated as 1/234,000, with 30-60% being attributable to peanut allergy. The data suggest acute anaphylaxis is always IgE-mediated and that food allergy should be considered in investigations. If a food allergy is implicated in acute anaphylaxis, obsessive dietary exclusion is essential. Experienced professional dietary advice is vital to ensure a nutritionally balanced diet and for guidance on obscure sources of contamination which may occur during food manufacturing processes. It would appear that the greatest risk to patients occurs when food is prepared by a non-family member outside the home. Patients and their family and friends need to be taught the indications and use of self-administered adrenaline.[5,6,7]

The role of food allergy in asthma is controversial and difficult to quantify because of study deficiencies. Approximately 20-25% of asthmatics perceive themselves to react to food, but detailed provocation studies indicate that food allergies provoke respiratory symptoms in only a small proportion (1-5%) of asthmatics and that most of these symptoms are associated with gastrointestinal disturbance, angio-oedema or urticaria.[4] Asthma as the only manifestation of a food allergy is very rare, occurring in <1% of asthmatics. If a food allergy is identified in an asthma patient, the prophylactic measures required depend on the severity of the response. Dietary restriction is appropriate if consumption of the identified food induces an acute severe asthmatic reaction, especially if associated with urticaria, angio-oedema or laryngeal oedema. In less well-defined food allergies, a recent review concluded that the consideration of food allergy in asthma was inappropriate except in severe cases as outlined above, because of the difficulties of diagnosis, the problems in maintaining a nutritious, attractive food-avoidance diet, and the known safety and efficacy of pharmaco-therapy irrespective of allergic status.

Cow's milk allergy has been implicated in Heiner's syndrome. This is a rare, ill-defined chronic respiratory condition which affects infants who present with anaemia, failure to thrive and chronic lung disease. Chest radiographs demonstrate pulmonary infiltrates, and investigations reveal evidence of pulmonary haemosiderosis. Cow's milk protein precipitating antibodies are present and some improvement with appropriate dietary manipulation may be identified.

Food intolerance

In the general population the prevalence of food intolerance has been estimated as 1.4-1.9% and is greater in adults than in children.[8] In adults, food intolerance is more prevalent than food allergy. The pathophysiology of food intolerance is not fully understood but it would appear that inflammatory mediators are released or mucosal levels are enhanced by food components acting independently of the immune system.

The best documented 'food' intolerance in asthma relates to aspirin (acetylsalicylic acid) sensitivity. The prevalence of aspirin sensitivity in asthma has been estimated as 1.7-5.6% when based on symptoms, but increases to 8-22% when based on challenge studies.[9] Proposed mechanisms include a salicylate-induced change in the balance of bronchoconstricting and dilating prostaglandins and/or a shift in eicosanoid metabolism towards bronchoconstricting leukotrienes. Aspirin-sensitive asthma is not always associated with nasal polyposis, and occurs in atopic and non-atopic asthma. Although commonly associated with sensitivity to other non-steroidal anti-inflammatory drugs (NSAIDs), aspirin sensitivity is occasionally associated with adverse reactions to intravenous hydrocortisone and paracetamol. NSAIDs may induce an acute severe episode of asthma or more commonly a subacute or chronic deterioration. The diagnosis of aspirin sensitivity is based on history and carefully controlled challenge tests. If confirmed, patients should be advised to avoid aspirin and NSAIDs. Unfortunately aspirin is a common component of proprietary preparations and its presence is not always obvious. Naturally occurring salicylates are not known to be a problem.

Aspirin has chemical structural similarities with benzoic acid and the azo dyes which are commonly used as food additives. Although several studies have demonstrated intolerance to the colouring agent tartrazine (E102) in 4-8% of aspirin-sensitive asthmatics, others have been unable to demonstrate an adverse effect. Other dyes which have been reported as having an adverse effect on asthma, are ponceau and erythrosine (E127) but these studies suffer from either loose criteria for positive challenges or regression to the mean. Benzoates (benzoic acid, sodium benzoate, parabens) are used in foods as antimicrobial, bleaching or flavouring agents, and carefully controlled studies suggest that 2% of patients with perennial asthma are intolerant of these agents.[10]

Sulphites (bisulphites, metabisulphites) are commonly used as anti-browning and bleaching agents in food, and when in liquid form may release sulphur dioxide. Both sulphite and sulphur dioxide have been used in laboratory-based bronchial provocation studies. It has been shown that 5% of asthmatics are sensitive to sulphites; occasionally this can be life-threatening and it has led to the banning of their use in the fruit and vegetable industry in the USA.[11] Cases of immune-mediated food allergies to tartrazine, benzoates and sulphites have been described. Guidelines for the management of food additive intolerance in asthma should follow those of food allergy and asthma.

Key points:

- Many patients report food sensitivities, but validated food allergy and intolerance is much less frequent.
- Food allergy is mediated by immune mechanisms and is more prevalent in children (1.4%) than adults (0.3%).
- Common childhood food allergens are cow's milk, peanuts, nuts, eggs and fish.
- Food allergy is a common cause of acute anaphylaxis.
- Food additive intolerance may occur in subjects with aspirin-sensitive asthma.

Diet and susceptibility to wheezing illness

While food allergy and intolerance may be relevant to specific patients with respiratory disease, indirect effects of diet may be more important in the general population. A major increase in prevalence of wheezing illnesses has occurred in developed countries in the last 30 years. Other atopic conditions such as eczema and hay fever have also become more common. A number of possible causes for this increase have been proposed, including exposure to pollution or allergens and a change in the pattern of childhood infections modifying the likelihood of developing atopy. Recently, observation of dietary trends has suggested that nutritional factors may be important, possibly by increasing the susceptibility of the population to the effects of inhaled pollutants and allergens. Excess dietary sodium,[12] relative lack of natural dietary antioxidants[13] and increased consumption of polyunsaturated fatty acid (PUFA) of the ω-6 type[14] have all been suggested as responsible factors.

Sodium

Increased dietary sodium intake is a feature of 'westernised' societies and a plausible hypothesis[12] that this may contribute to the excess prevalence of asthma in these countries has been explored in the past decade. Table salt purchases correlate with asthma mortality but the results of studies linking airway responsiveness (a surrogate for asthma) with 24 hour urinary sodium excretion and dietary interventional studies have been conflicting.[15,16,17] Sodium intake has not been associated with respiratory symptoms or the diagnosis of asthma, and some studies have demonstrated an effect in men only. A recent study has demonstrated that the association between sodium and airway responsiveness (and presumably asthma) is probably the result of population study bias and confounding.[18]

At present the manipulation of sodium intake has no role in the management of asthma, the reported associations between sodium and asthma are probably spurious, and no effect on clinical parameters has been demonstrated. Table salt purchases may be acting as a surrogate marker for other more relevant dietary factors.

Antioxidants

Epidemiological studies have demonstrated that low intake of natural antioxidant vitamins is associated with reduced lung function, chronic respiratory symptoms and increased bronchial responsiveness to methacholine. The importance of vitamin C is suggested by the association of low dietary fruit and fruit juice intake with respiratory symptoms, asthma, chronic bronchitis and impaired lung function. While factors associated with fruit consumption other than vitamin C intake may have contributed to these findings, studies which have specifically quantified vitamin C intake have reported positive associations with lung function in general populations in the UK and the USA. Wheezing in the previous year was inversely associated with serum vitamin C, but not dietary vitamin C, in data from a US general population.[19]

In comparison to vitamin C, fewer studies have evaluated the relationship of vitamin E to pulmonary symptoms. We have recently found[20] low vitamin E intakes and low plasma triglyceride standardised α-tocopherol levels to be a risk factor for adult onset wheeze and other studies have reported an association between low vitamin E intake and lung function in the elderly[21] and a protective effect of vitamin E against asthma in a large cohort of nurses.[22] The biological effects of vitamins C and E are closely interlinked and this may explain why independent effects of each vitamin may not be evident in some studies.

In some areas of the world, such as New Zealand, the soil is deficient in selenium, an essential component of the glutathione peroxidase antioxidant system. Asthma prevalence in these areas is high,[23] suggesting a role for antioxidants in the aetiology of wheezing.

Although evidence of a role for antioxidants is mounting, as with dietary sodium, the results of intervention studies of vitamin administration have been conflicting. Many of these studies have however been of short duration and have focused only on one element of a complex interaction.

Fats

The third 'nutritional hypothesis' relating to the increase in asthma concerns patterns of fat intake. High total fat intake has been associated with bronchial hyperresponsiveness and asthma, and the nature of the fats consumed may be relevant to the development of atopy and wheezing. It has been proposed that an increase in consumption of ω-6 PUFAs, such as linoleic acid, and a reduction in ω-3 PUFAs, such as linolenic acid, promotes allergic sensitisation.[14] There is some evidence that high intake of dietary ω-3 fatty acids, as in fish oils, is protective against chronic obstructive pulmonary disease (COPD) and asthma. The suggested mechanism for these observations is that the ω-6 fatty acids promote prostanoid synthesis whereas this is inhibited by ω-3 fatty acids. However, the effects may be relatively weak and it has been commented that confounding by a higher intake of antioxidant vitamins in association with fish may explain the observed relationships.[24]

The hypotheses relating to antioxidants and fats are not mutually exclusive. The general picture emerging from epidemiological studies is of an increased risk of wheezing illness and poor lung function associated with a diet which is relatively deficient in certain antioxidants and has a high fat content, with possibly a predominance of saturated fats and ω-6 PUFAs. If there is a causal association between these dietary factors and wheezing illness, what might be the mechanism? Allergic conditions, including wheezing illnesses are associated with a T-helper cell population which is biased towards the Th_2 subtype. Vitamin E is known to be immunomodulatory, inhibiting the Th_2 subtype and promoting the Th_1 subtype in some animal model systems.[25] High levels of ω-6 PUFAs may promote the formation of prostaglandin E_2, which then also promotes Th_2 responses and generation of IgE. The importance of vitamin C may reflect its direct activity as an antioxidant or its role in regenerating vitamin E from the vitamin E radical. Some or all of these mechanisms may interact to promote the expression of allergic diseases such as asthma, hay fever and eczema. Research in this area is ongoing.

DIET AND LUNG CANCER RISK

Another area in which the role of antioxidants has been investigated is in relation to lung cancer. A fascinating paradox has emerged.[26] Observational studies of diet and lung cancer have shown that increased fruit and vegetable intake is associated with a reduced risk of lung cancer. The active constituent(s) have not been specifically identified although a role for carotenoids has been suggested with some support from dietary studies. The pattern of effect may differ between races and possibly between sexes, but appears unrelated to histological type of tumour. As with wheezing illness, there has been a suggestion that a high fat diet may also be a risk. Mechanisms which relate to the effects of oxidant free radicals have been proposed. It might therefore be anticipated that supplementation with antioxidants might reduce risk, but in two major clinical trials, the converse has occurred,[27,28] supplementation with beta carotene, alone

or combined with retinol, resulting in an increased risk of lung cancer. The effects were particularly significant in current smokers, and in one study, among subjects who had asbestos exposure.

This apparent paradox is currently unexplained. It may be that beta-carotene impairs the action of other, as yet unidentified, factors by metabolic competition or that, when present in excessive quantities or under specific local environmental conditions, it is itself metabolised to pro-oxidant compounds. This is currently under investigation.

What lessons can we draw from this rather confusing picture in relation to both groups of conditions, and what advice should we give our patients? The primary cause of much wheezing illness and of lung cancer is, of course, smoking and this should be addressed. With regard to diet, there may be an optimum intake of antioxidants and fats to be achieved by dietary manipulation. Intake of dietary fresh fruit and vegetables should be encouraged. High risk groups (e.g. low antioxidant intake, high fat intake, current smokers) should be targeted for advice. However, the routine use of supplements, singly or in combination, should be avoided until our knowledge of the risk/benefit for such preparations is improved.

Key points:
- Dietary factors, particularly antioxidants and fats, may influence lung function, risk of wheezing illness and lung cancer.
- Evidence for an association between sodium consumption and asthma is weak, and clinically relevant associations have not been demonstrated.
- Higher fruit and vegetable, and reduced total fat and ω-6 PUFA, intake may reduce risk of wheezing illness.
- The generalised use of antioxidant supplements may cause adverse effects and is not recommended.

NUTRITIONAL CONSEQUENCES OF RESPIRATORY DISEASE

The occurrence of weight loss and development of cachexia will be familiar to all who deal with patients suffering from severe COPD and those with thoracic malignancy.

In COPD, weight loss is a bad prognostic sign. There is some correlation between the magnitude of weight loss and severity of airflow obstruction, degree of hypoxia and impairment of the transfer factor for carbon monoxide.[29] However, weight loss *per se* in COPD is associated with poor physical performance and impaired survival, independent of the degree of airflow obstruction. The pattern of nutritional depletion in such patients is interesting, affecting somatic stores, as indicated by decrease in arm muscular circumference and triceps skinfold thickness, while visceral stores, as evidenced by serum albumin and retinol-binding protein, are preserved. An important consequence of this is that peripheral skeletal muscle function is impaired.

In recent years, the mechanism of weight loss has become clearer[29] although it remains incompletely understood. The fundamental reason for weight loss is that dietary intake fails to match metabolic demand. Patients with severe dyspnoea may find eating uncomfortable, exacerbated by gastric fullness impairing functional residual capacity and further embarrassing respiratory effort. Their intake may therefore be reduced but this alone does not account for the weight loss observed. Many studies have demonstrated an increased resting energy expenditure in patients with COPD.[30,31] This may be partly related to the increased work of breathing but this is not the sole explanation. Recent work has demonstrated raised circulating levels of inflammatory

cytokines, e.g. tumour necrosis factor alpha (TNF-α) and other acute phase reactants such as C-reactive protein in patients with COPD during periods of weight loss.[32] Exogenous administration of TNF-α in humans increases resting energy expenditure and levels of acute phase proteins, and a cause-and-effect relationship might therefore be postulated. However, if weight stabilises in COPD patients, the rise in TNF-α is not sustained and whether it is causative or simply a further marker of an acute phase response is not clear.

Irrespective of mechanism, can the weight loss of severe COPD be reversed? Nutritional supplementation is difficult due to the aforementioned difficulties for these patients to increase their intake; in research studies, tube feeding has been used.[33] It appears that an increase in energy intake of more than 30% may be necessary to produce benefit[29,34] and that high fat content, rather than carbohydrate loading, may be preferable since the latter may reduce the ability to excrete a CO_2 load.

Key points:
- Weight loss in COPD is a bad prognostic sign.
- Weight loss results from failure to meet increased metabolic demands.
- Inflammatory cytokines such as TNF-α may be important in pathogenesis.
- Achieving the required increase in energy intake to prevent weight loss may be problematic.

Weight loss in lung cancer

One of the characteristics of patients with lung cancer is the development of inexorable weight loss and cachexia. This destructive process is usually referred to as the cancer anorexia and cachexia syndrome (CACS).[35] CACS is characterised by anorexia, decreased food intake and inefficient food metabolism, leading to progressive weight loss, tissue wasting, poor performance status and, finally to death. CACS is known to be a major cause of morbidity and mortality in cancer patients, and ranks alongside tumour stage and performance score as a major prognostic indicator in non-small cell lung carcinoma (NSCLC). Studies of small-cell lung carcinoma (SCLC) and NSCLC suggest that approximately 30% of cases have lost more than 10% of their pre-illness weight at presentation.

The pathogenesis of CACS is complex and incompletely understood, but the fundamental disturbance is an imbalance between an increased metabolic rate and inadequate food intake.[36] Resting energy expenditure (REE) has been shown to be increased in patients with lung cancer and weight loss at presentation. REE is greater in SCLC compared to NSCLC and in central compared to peripheral tumours. Many biochemical abnormalities have been identified in CACS, and these appear to be maladaptive catabolic responses to relative starvation and extremely wasteful in energy terms. In contrast to starvation, CACS is characterised by continuing gluconeogenesis and protein catabolism and, although fat stores are mobilised, there is an impaired ability to use lipids as a primary source of energy. The biochemical changes and the increase in metabolic rate seen in CACS are believed to be the consequence of a generalised inflammatory state. Acute phase proteins and cytokines (released by tumour cells and macrophages) are elevated in CACS. TNF-α (and its circulating receptor complexes), interleukins 1 and 6, and interferon-γ have been shown in animal and preliminary human studies to induce anorexia and the biochemical changes commonly seen in CACS.

The deleterious effects of the increased metabolic rate in CACS are exaggerated by an associated decrease in food intake relative to metabolic needs. Cytokines have been implicated in the anorexia of CACS, however, in the clinical setting, more obvious causes of reduced food intake such as pain, nausea, vomiting, gastroparesis, direct encroachment of the tumour on the gastrointestinal tract, iatrogenic causes such as radiotherapy and cytotoxic therapy, need to be considered. Psychological factors such as learned food aversions may develop due to unpleasant experiences such as chemotherapy, coinciding with exposure to a particular food. It has been suggested that subjects undergoing chemotherapy should eat lightly and avoid protein-rich foods, which are more likely to become targets of a food aversion than carbohydrate-rich foods. Emotional factors such as depression and isolation may also contribute to reduced food intake especially in advanced disease. When anorexia develops early in lung cancer, it is usually tumour-related and the consequence of circulating cytokines. When anorexia develops late, factors such as pain, dysphagia, treatment effects and depression may predominate.

Although research into CACS has concentrated on pharmacological interventions, it should be remembered that before these agents are used, common causes of anorexia such as pain, mucositis, dysphagia, constipation and depression should be sought and controlled. Many drugs have been proposed for the alleviation of CACS but, in general, reports are conflicting, and trials are small, uncontrolled and not specific to lung cancer.[37] Controlled trials have demonstrated a substantial placebo effect, emphasising the psychological aspects of CACS.[38,39] Cyproheptadine is an antihistamine agent with antiserotoninergic properties. It has been shown to mildly stimulate appetite in advanced cancer, but with no effects on weight loss, and is associated with troublesome dizziness and sedation.[38] Hydrazine sulphate is an experimental drug known to block a gluconeogenic pathway implicated in CACS. In the largest study of hydrazine in NSCLC patients undergoing chemotherapy, hydrazine did not influence appetite, weight loss, quality of life or survival.[40] Gastroparesis is often present in advanced cancer and the prokinetic drug metoclopramide has been suggested for the treatment of CACS. In small uncontrolled studies, metoclopramide improved anorexia but with no effect on weight.[41,42] In a small cross-over study, tetrahydrocannabinol at 15mg/day induced a small weight gain but there were problems with associated dizziness, fluid retention, somnolence and dissociation.[43] Anabolic steroids, such as nandrolone decanoate, have theoretical applications to CACS but a small study in NSCLC demonstrated no significant benefits.

Corticosteroids are frequently used empirically in cancer patients for their appetite-stimulating effect. In a double blind placebo controlled trial, prednisolone 15mg/day was associated with increased appetite and feeling of well-being, however, there were no effects on weight, food intake or quality of life.[39] In divided doses of 3mg-6mg/day dexamethasone was associated with increased appetite in a double blind placebo controlled trial, but again there was no effect on weight.[44] Despite early concerns about the side-effects of corticosteroids the available data do not suggest a significant detrimental effect. Recent work has concentrated on high dose progestagens, with large randomised placebo controlled trials of megestrol acetate (MA) and medroxyprogesterone acetate (MPA) demonstrating significant improvements in appetite and weight gain. The weight gain reflects an increase in body mass, especially adipose tissue, rather than fluid retention. MA and MPA do not appear to improve quality of life or survival. A recent dosing study[45] suggested that the majority of patients who are going to respond will do so with 160mg/day of MA, with a few more responding at

320mg/day. The majority of responding patients will have done so after 15 days of treatment and the authors recommended that the dose of MA should either be increased or stopped after 15 days if there is no response. The negative aspects of MA and MPA are cost and side-effects: fluid retention, venous thrombosis, glucose intolerance and hypertension, but these tend to be mild and predictable. Further clarification of cost benefit and quality of life issues is required.

Given that CACS is associated with an increased metabolic rate not matched by an increase in food intake, it would seem logical to increase nutritional intake. Total parenteral nutrition (TPN) is considered to be 'oncologically illogical' because of potential side-effects, cost and increased time in hospital. Indeed, in some studies of TPN and CACS, TPN was associated with reduced survival.[46] A more acceptable form of nutritional support is by the enteral route. The role of nasogastric supplementation is unclear and needs further evaluation. At present it would seem reasonable to provide oral nutritional supplementation, as this is non-invasive and not detrimental to health.

At present there are not enough data to advise the use of TPN, cyproheptadine, hydrazine, tetrahydrocannabinol or nandrolone decanoate. Metoclopramide (10mg b d) is inexpensive, easy to administer and can alleviate gastroparesis. Corticosteroids (prednisolone 15mg/day, dexamethasone 3-6mg/day) are inexpensive, and have documented beneficial effects and a useful co-analgesic effect. Progestagens (MA and MPA) have beneficial effects on weight and appetite. In the UK, however, they are unlicensed for this use and there are unresolved issues of cost and quality of life.

Key points:
- Thirty per cent of lung cancer patients have the cancer anorexia and cachexia syndrome (CACS).
- Causes include reduced food intake and tumour-induced increase in metabolic rate.
- Treatable causes of reduced food intake should be sought and controlled.
- Enteral nutritional supplements may be of value.
- Corticosteroids and metoclopramide may be beneficial.
- High-dose progestagens have promise but their role in CACS needs to be clarified.

CYSTIC FIBROSIS - A CONDITION WITH BOTH NUTRITIONAL AND RESPIRATORY PRIMARY MANIFESTATIONS

The maintenance of optimal nutrition is particularly important in the management of Cystic Fibrosis (CF).[47] Deteriorating pulmonary function in CF is associated with worsening nutritional status; survival is inversely associated with nutritional status and active intervention resulting in improvement in nutritional status has been shown to reduce the rate of decline of pulmonary function.[48] The importance of active nutritional intervention has been emphasised by a study comparing two North American CF clinics differing in their nutritional approach; median survival was greater by nine years in the clinic whose nutritional protocol resulted in superior nutritional status.[49]

Nutritional stresses can occur very early in CF, with important nutritional deficits being documented in screened neonates prior to the development of symptoms; the problems are multifactorial with increased metabolic rate, increased losses, and reduced intake of nutrients. Resting energy expenditure (REE) is increased by 9-30%, and has usually been attributed to the increased work of breathing; however, recent work suggests that circulating cytokines may be implicated, a situation analogous to COPD. A primary

defect influencing cellular metabolism which is associated with the CF gene or a linked locus may also be responsible for the increase in REE, but data on this are conflicting. Gastrointestinal losses of nutrients may account for 10-20% of total energy intake, and are mainly the result of maldigestion secondary to pancreatic insufficiency which can rarely be fully corrected despite improved pancreatic enzyme supplementation. Losses of bile salts, inadequate bile secretion associated with liver disease, and neonatal intestinal resection may contribute to faecal losses. Energy losses occur in poorly-controlled CF-related diabetes because of glycosuria. Sputum production may lose an estimated 1-5% of energy intake. Sodium losses in sweat can be important in hot weather and sub-clinical sodium depletion can result in growth impairment, particularly in infants. Dietary assessments of freely-eating CF patients indicate that the recommended daily intake of energy is rarely exceeded, despite increased energy requirements. Reduced food intake may be the result of the anorexia of chronic respiratory disease (possibly mediated by cytokines), gastro-oesophageal reflux, and coughing spasms which may induce vomiting. Psychosocial influences include behavioural feeding problems (common in young CF patients), inappropriate body image problems, media pressure to eat a healthy low fat, low sugar diet, a cultural aversion to fatty foods, and the financial constraints of chronic disease.[47,50-52]

The specialist care of CF patients tends to be in large centres with trained dieticians being members of a multidisciplinary care team. Key to the dietary management of CF are frequent assessments, and monitoring, which should be conducted at least every three months. Routine dietary assessment usually takes the form of a 24-hour retrospective dietary recall with a three-day prospective recorded diet diary being conducted annually or if nutritional status deteriorates. Routine assessment of malabsorption is carried out commonly to investigate abdominal pain and distension, frequency and changed character of stools; this clinical assessment tends to underestimate malabsorption.

Formal assessment by a three-day faecal fat estimation in conjunction with a dietary diary is usually performed at diagnosis or if there is unexplained deterioration. A coefficient of fat absorption of <93% (85% infants) indicates steatorrhoea. Regular measurements of weight-for-height ratio or body mass index (<20 years), and head circumference (≤2 years) are vital for monitoring nutritional status. Normal nutritional status is 90-110% of ideal weight for height, underweight 85-89%, mild malnutrition 80-84%, moderate malnutrition 75-79% and <75% severe malnutrition. Triceps skinfold thickness may also be used as an indicator of energy status and is probably more suited to CF than mid-arm circumference, the reference ranges of which may be inappropriate for CF because of concomitant disuse atrophy. Annual full blood counts and measurements of serum vitamins A and E, zinc, magnesium, ferritin, albumin, calcium, alkaline phosphatase, glucose, glycosylated haemoglobin and electrolytes are recommended.

The aims of nutritional management in CF are, to achieve optimal weight gain, an appropriate lean body mass-to-fat ratio, and to promote well-being and longevity; the dietary management of CF has changed radically in recent years. The traditional CF diet was low in fat, and resulted in a relentless decline which was considered inevitable. Current dietary management recognises that CF patients have differing energy requirements because of disease heterogeneity and lifestyle, and that dietary management has to be individualised by careful assessment of energy requirements and nutrient losses. Although it is commonly recommended that energy intake should be 120-150% of recommended daily intake, individual requirements differ and need to be

determined by careful assessment and close monitoring. It is convenient to grade nutritional support into three levels.

The basic diet is energy and protein dense, with 35-40% of energy intake being in the form of fat. The diet comprises fatty foods (butter, margarine, chocolate, sausages), sugary foods (sugar, jam, fizzy drinks, cakes, biscuits), dairy products (full cream milk, cheese, yoghurt), starchy foods (cereal, pasta, potatoes, rice, bread), and protein-rich foods (meat, fish, eggs, legumes, nuts). Fruit and vegetables are recommended because of their vitamin and mineral content. Although the principles are simple, the diet should be individualised to take account of clinical condition, nutritional state, dietary preferences, dietary beliefs, appetite and activity levels. Regular monitoring and counselling is essential, and anticipatory guidance is important at times of nutritional stress, e.g. frequent pulmonary infections, rapid growth and adolescence.

Dietary supplementation is the second level of support and is instigated when weight falls below 90% of ideal weight for height. Three main types of supplements are available: nutritionally fortified milk shakes, energy-dense glucose polymer solutions, and nutritionally fortified desserts. Enteral feeding is the third level of support and is instigated when nutritional status deteriorates despite intense oral supplementation. In an adult, nutritional failure is defined as a weight $<85\%$ of ideal weight for height, or weight loss $\geq 5\%$ of usual weight for >2 months.

Methods of enteral feeding include nasogastric, gastrostomy and jejunostomy tubes, the actual method chosen depending on the patient's wishes, nutritional status, motivation and local expertise. Enteral feeding is associated with improved body composition, increased strength, increased sense of well-being, less weight loss during exacerbations and improved nutritional status. To produce lasting benefits, enteral feeding has to be continued long term and this should be outlined to the patient before instigation. With enteral feeding, daytime appetite is invariably reduced and it is common practice to give 40-50% of daily energy requirements for 8-10 hours overnight with occasional 'days off' helping compliance. The enteral feed should be nutritionally balanced with respect to micronutrients, and at present there is no compelling evidence to choose between elemental feeds and energy-dense polymeric feeds. Complications of enteral feeding include tube dislodgement, gastro-oesophageal reflux and vomiting; hyperglycaemia has been reported in up to 64% of enterally-fed patients.

Micronutrient supplementation is essential. Low serum vitamin A levels have been reported in CF. The clinical features of vitamin A deficiency include night blindness, dry thickened skin, conjunctival and corneal xerosis. Although serum vitamin A levels may be low, hepatic levels in supplemented patients are elevated and concerns have been raised about toxicity. Vitamin E deficiency has been commonly reported in CF, and the clinical features of vitamin E deficiency include peripheral neuropathy, dysarthria, tremor, ataxia and decreased visual acuity. Decreased bone mineral density and osteopenia, associated with low 25-hydroxyvitamin D levels have been described in adult CF patients, although rickets is rarely reported in children. Vitamin D supplementation is recommended. Fat-soluble vitamin supplements are absorbed most effectively when taken in the morning with fat-containing meals and pancreatic enzyme supplements.

Sodium depletion is rarely a problem in the UK, and supplementation in adults is usually limited to episodes of foreign travel. Sodium supplementation is recommended for infants on low electrolyte formula (bottle) feeds.

Fundamental to an energy-dense diet with a high fat intake is adequate pancreatic enzyme supplementation. Most CF centres use pH sensitive enteric-coated microsphere

preparations which, if administered in appropriate dosages, should be able to achieve 90% fat absorption. The effectiveness of these preparations can sometimes be improved by the addition of H_2 receptor antagonists or proton pump inhibitors. The dose of pancreatic supplements has to be tailored to nutritional status and dietary constituents, and the enzymes need to be taken throughout the meal with extra enzymes taken with fatty meals. The best way of giving enzyme supplements with enteral feeding is not known; commonly, half the dose is given at the start of the feed and just before the patient goes to sleep. High lipase enzyme preparations initially looked promising because of the reduced dosages; unfortunately these preparations have been linked with colonic strictures and the Committee on the Safety of Medicines has recommended that all CF patients return to ordinary strength enzyme preparations. This has led to suggestions that the upper dose of lipase should be limited to 3000 units/kg/day, and of protease 9000 units/kg/day.

The development of CF-related diabetes is becoming increasingly common as length of survival increases. A conventional diabetic diet will inevitably lead to nutritional failure in a CF patient and, although there are no clear guidelines, it is common practice to continue a normal CF diet with adjustment of insulin dosage to maintain normoglycaemia. If possible CF patients are advised to avoid sugar-rich drinks and to exchange glucose polymer food supplements for fortified milk supplements.

Nutritional support is an integral part of the management of CF patients, and should probably be provided by a qualified dietitian working in conjunction with the CF care team. Individual patients needs should be assessed, regularly reviewed, and interventions should be anticipated and early. Nutritional support should include dietary supplementation and enteral feeding. Meticulous attention to detail is required, with the benefits of improved clinical state and survival being the rewards.

Key points:
- Nutritional support is integral to the management of CF and should be provided by a specialist dietician.
- Nutritional status is precarious in CF because of increased losses, reduced food intake and increased metabolic rate.
- Improved nutritional status is associated with better survival and retards decline in pulmonary function.
- Regular review of nutritional status, with anticipatory and early intervention, is important.
- An energy- and protein-dense diet is recommended with a high fat intake, but this must be individualised and accompanied by supplements of pancreatic enzyme and Vitamin A, D and E.

RESPIRATORY HAZARDS FOR WORKERS IN THE FOOD INDUSTRY

The food industry is a major global employer, incorporating individuals involved in agriculture, fisheries, food processing, distribution and retail. Respiratory hazards which may be encountered in the food industry include occupational asthma, extrinsic allergic alveolitis and respiratory infections.

The broad term ‘occupational asthma’ can include attacks of bronchoconstriction which occur as a reflex in subjects with pre-existing asthma, as an inflammatory response to an acute toxic insult (when it is known as reactive airways dysfunctional syndrome or RADS) or as a response to a pharmacological or allergic insult. The latter syndrome

is important in the food industry; major allergens include wheat and rye flour, grain dust, mites associated with grain stores and poultry, and proteinaceous material aerosolised during prawn and crab processing. Bakers have long been at particular risk. Seven to twenty per cent of bakers may develop asthma or rhinitis during their working lives. Among non-allergic causes of asthma are exposures to antibiotics and chemicals which are administered in the livestock and vegetable industries. The diagnosis of occupational asthma requires a high index of suspicion, an appropriate occupational history, pulmonary function testing, serial peak expiratory flow recording and, in some cases, provocation testing.

In contrast to asthma which is an airway disease, allergic alveolitis is an interstitial lung disease, comprising a complex immunological response to inhalation of spores. Those of particular relevance in the food industry include thermophilic *Actinomyces* which affect farmers and mushroom pickers, *Aspergillus clavatus* which affects maltworkers and *Penicillium casei* which may affect cheese workers. The condition may present acutely with episodes of chest tightness, cough and dyspnea accompanied by mid-late inspiratory crackles on auscultation, or chronically with progressive pulmonary fibrosis. The occupational history is paramount once again, with additional investigations including chest radiography, detection of serum precipitating antibodies, pulmonary function testing and, rarely, challenge testing or lung biopsy.

The final group of conditions to consider is occupationally-acquired infection. Infections, resulting in pneumonia, are principally of concern to those involved in the keeping of livestock. Farmers may be at risk of brucellosis, acquired from exposure to cattle or their milk, Q fever (*Coxiella burnetii*) and hydatid disease (*Echinococcus granulosus*) which are important in sheep farming areas. Poultry breeders may acquire psittacosis infection. The detailed investigation and management of the various occupational risks is beyond the scope of this article. It is however important to remember that for all of these conditions, investigation of the workplace and working practices may be as important as the direct management of the individual patient.

Key points:
- Occupational asthma due to various allergens is important in the food industry.
- Other occupational risks include allergic alveolitis and pulmonary infection.
- Management involves treatment of specific cases and investigation of the workplace.

The potential for nutritional factors to influence the respiratory system, and for the converse to occur, is significant. As the role of dietary factors in the development of respiratory disease is clarified, we may develop population-based strategies to reduce the burden of respiratory illness. These strategies may be generalised or targeted at specific high-risk groups. Improved understanding of the molecular and metabolic consequences of respiratory disease may lead to specific interventions to improve the nutritional condition of our patients. In the increasingly complex business of mass food production, continued and improved vigilance will be necessary to prevent occupationally-acquired respiratory diseases.

REFERENCES

[1] Kitts D, Yuan Y, Joneja J *et al*. Adverse reactions to food constituents: allergy, intolerance and autoimmunity. *Can J Physiol Pharmacol* 1997; 75:241-54.

[2] Chandra RK. Food hypersensitivity and allergic diseases: a selective review. *Am J Clin Nutr* 1997; 66:526S-9S.

[3] Chandra RK, Gill B, Kumari S. Food allergy and atopic disease: pathogenesis, diagnosis, prediction of high risk, and prevention. *Ann Allergy* 1993; 71:495-502.

[4] Monteleone CA, Sherman AR. Nutrition and asthma. *Arch Intern Med* 1997; 157:23-34.

[5] Baker HB, David TJ. Dietetic and nutritional management of food allergy. *J R Soc Med* 1997; 90(Suppl.30):45-50.

[6] Gern JE, Yang E, Evrard HM *et al*. Allergic reactions to milk-contaminated non-dairy products. *N Eng J Med* 1990; 324:976-9.

[7] Sampson HA. Managing peanut allergy. *BMJ* 1996; 312:1050-1.

[8] Warner JO. Food intolerance and asthma. *Clin Exp Allergy* 1995; 25(Suppl.1):29-30.

[9] Dor PJ, Vervloet D, Baldocchi G *et al*. Aspirin intolerance and asthma induction of tolerance and long term monitoring. *Clin Exp Allergy* 1985; 15:37-43.

[10] Weber RW. Food additives and allergy. *Ann Allergy* 1993; 70:183-92.

[11] Lessof MH. Reactions to food additives. *Clin Exp Allergy* 1995; 25(Suppl.1):27-8.

[12] Burney P. A diet rich in sodium may potentiate asthma. Epidemiologic evidence for a new hypothesis. *Chest* 1987; 91:143S-148S.

[13] Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994; 49:171-4.

[14] Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997; 10:6-12.

[15] Burney PGJ. The causes of asthma - does salt potentiate bronchial reactivity? Discussion paper. *J R Soc Med* 1987; 80:364-7.

[16] Burney PGJ, Britton JR, Chinn S *et al*. Response to inhaled histamine and 24 hour sodium excretion. *BMJ* 1986; 292:1483-6.

[17] Lieberman D, Heimer D. Effect of dietary sodium on the severity of bronchial asthma. *Thorax* 1992; 47:360-3.

[18] Devereux G, Beach JR, Bromly C *et al*. Does dietary sodium influence airway responsiveness and is it important in asthma epidemiology? *Thorax* 1995; 50:941-7.

[19] Schwartz J, Weiss ST. Dietary factors and their relation to respiratory symptoms: the second national health and nutrition examination survey. *Am J Epidemiol* 1990; 132: 67-76.

[20] Godden DJ, Bodner C, Seaton A and the WHEASE Study Group. Dietary antioxidants - their importance in adult onset wheezing illness. Lancet Conference Proceedings, Challenge of Asthma, Tours, 1997.

[21] Dow L, Tracey M, Villar A *et al*. Does dietary intake of vitamins C and E influence lung function in older people? *Amer J Respir Crit Care Med* 1996; 154:1401-4.

[22] Troisi RJ, Willett WC, Weiss ST *et al*. A prospective study of diet and adult-onset asthma. *Am J Respir Crit Care Med* 1995; 151:1401-8.

[23] Flatt A, Pearce N, Thomson CD *et al*. Reduced selenium in asthmatic subjects in New Zealand. *Thorax* 1990; 45:95-9.

[24] Britton J. Dietary fish oil and airways obstruction. *Thorax* 1995; 50:S11-S15.

[25] Wang Y, Huang DS, Eskelson CD *et al*. Long term dietary vitamin E retards development of retrovirus induced disregulation in cytokine production. *Clin Immunol Immunopathol* 1994; 72:70-5.

[26] American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. World Cancer Research Fund/American Institute for Cancer Research, Washington D.C. 1997; 130-47.

[27] The effects of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med* 1994; 330:1029-35.

[28] Omenn GS, Goodman GE, Thornquist MD *et al*. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996; 334:1150-5.

[29] Muers MF, Green JH. Weight loss in chronic obstructive pulmonary disease. *Eur Respir J* 1993; 6:729-34.

[30] Schols AM, Fredrix EW, Soeters PB *et al*. Resting energy expenditure in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 1991; 54:983-7.

[31] Wilson DO, Donahoe M, Rogers RM *et al*. Metabolic rate and weight loss in chronic obstructive lung disease. *JPEN* 1990; 14:7-11.

[32] Schols AM, Buurman WA, Staal-van den Brekel, AJ *et al*. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996; 51:819-24.
[33] Whittaker JS, Ryan CF, Buckley PA *et al*. The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. *Am Rev Respir Dis* 1990; 142:283-8.
[34] Efthimiou J, Fleming J, Gomes C *et al*. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988; 137:1075-82.
[35] Nelson KA, Walsh D, Sheehan FA. The Cancer Anorexia-Cachexia Syndrome. *J Clin Oncol* 1994; 12:213-25.
[36] Toomey D, Redmond HP, Bouchier-Hayes D. Mechanisms mediating cancer cachexia. *Cancer* 1995; 76:2418-26.
[37] Vansteenkiste JF, Simons JP, Wouters EF *et al*. Hormonal treatment in advanced non-small cell lung cancer: fact or fiction? *Eur Respir J* 1996; 9:1707-12.
[38] Kardinal CG, Loprinzi CL, Schaid DJ *et al*. A controlled trial of cyproheptadine in cancer patients with anorexia. *Cancer* 1990; 65:2657-62.
[39] Willox J, Corr J, Shaw J *et al*. Prednisolone as an appetite stimulant in patients with cancer. *BMJ* 1984; 288:27.
[40] Kosty MP, Fleishman SB, Herndon JE *et al*. Cisplatin, vinblastine and hydrazine sulfate in advanced non-small cell lung cancer a randomized, placebo-controlled, double-blind, phase III study of the cancer and leukaemia group B. *J Clin Oncol* 1994; 12:1113-20.
[41] Shivshanker K, Bennet RW, Haynie TP. Tumor-associated gastroparesis: correction with metoclopramide. *Am J Surg* 1983; 145:221-5.
[42] Nelson KA, Walsh TD. Metoclopramide in anorexia caused by cancer-associated dyspepsia syndrome. *J Palliat Care* 1993; 9:27-31.
[43] Nelson K, Walsh D, Deeter RP *et al*. A phase II study of delta-9-tetrahydocannabinol for appetite stimulation in cancer-associated anorexia. *J Palliat Care* 1993; 9:14-8.
[44] Moertal CG, Schutt AJ, Reitemeier RJ. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer* 1974; 33:1607-9.
[45] Gebbia V, Testa A, Gebbia N. Prospective randomised trial of two dose levels of megestrol acetate in the management of anorexia-cachexia syndrome in patients with metastatic cancer. *Br J Cancer* 1996; 73:1576-80.
[46] Koretz RL. Parenteral nutrition: is it oncologically logical? *J Clin Oncol* 1984; 2:534-8.
[47] Ramsey BW, Farrell PM, Pencharz P. Nutritional assessment and management in Cystic Fibrosis: a consensus report. *Am J Clin Nutr* 1992; 55:108-16.
[48] Luder E, Kattan M, Thornton JC *et al*. Efficacy of a nonrestricted fat diet in patients with Cystic Fibrosis. *Am J Dis Child* 1989; 143:458-64.
[49] Corey M, McLaughlin FJ, Williams M *et al*. A comparison of survival, growth, and pulmonary function in patients with Cystic Fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988; 41:583-91.
[50] Murphy JL, Wootton SA, Bond SA *et al*. Energy content of stool in normal healthy controls and patients with Cystic Fibrosis. *J Pediatr Child Health* 1987; 111:496-500.
[51] Dodge JA, O'Rawe AM. Nutritional aspects in Cystic Fibrosis. *Eur J Gastroenterol Hepatol* 1996; 8:739-43.
[52] Dodge JA, Morrison G. Diabetes mellitus in Cystic Fibrosis: a review. *J R Soc Med* 1992; 85(Suppl.19):25-8.