Nutrition and the patient with cancer

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Previous papers in this symposium have been concerned largely with nutrition as a factor in the aetiology of cancer. It is right that we should be concerned with these aspects of the problem for a large proportion of oncological disease is environmentally induced and therefore at least potentially preventable. This is the more urgent for our attention because the results of treatment are far from good, at least for the more common kinds. Treatment of breast cancer, for instance, is scarcely more successful now in terms of five year, and certainly in terms of ten year, survival than it was forty years ago. It is equally urgent that we consider the nutrition of the patient with cancer, for the successful treatment of the disease is of little consequence if the patient dies of malnutrition in the process. Moreover, it may be that nutrition, and possibly individual nutrients, may be exploited to increase the effectiveness of treatment and that nutrition can therefore play an adjuvant role in the treatment of the disease.

Effects of cancer on nutrition

Many patients with cancer show evidence of weight loss and reduction of body fat and muscle mass (Soukop & Calman, 1979). Many patients also have low concentrations of plasma albumin and biochemical indicators of vitamin status provide evidence of vitamin depletion. If this condition of malnutrition continues the syndrome known as 'cancer cachexia' develops. This condition is complex and is characterized by anorexia and early satiety, an increase in the basal metabolic rate (BMR) and energy expenditure, the development of anaemia, asthenia and changes in body composition. The increases in BMR, oxidative metabolism and plasma amino acid concentrations that occur in cachexia distinguish the condition from simple starvation and indicate that in cachexia there is a failure of adaptation to a reduced food intake. Cachexia is probably multifactorial in its aetiology and the biochemical changes leading to its development uncertain. There is evidence to suggest that tumours may produce peptides or other small molecules which when taken up by normal cells cause disturbances of the enzymes in those cells resulting in a condition of 'metabolic chaos', increase in energy expenditure and a release into the blood stream of amino acids and peptides which enter the metabolic pool and are taken up by the tumour for the growth of its own tissue (Theologides, 1977).

Malnutrition in the cancer patient results from a poor food intake and this may be caused by a reduction in appetite, changes in taste perception, pain, mechanical obstruction and apathy and depression in the face of an uncertain or poor

0029–6651/81/4013–4505 $01.00

prognosis. The cancer patient may have increased requirements for certain nutrients and in some patients abnormal losses through fistulas, for example, as well as malabsorption contribute to the problem. Factors contributing to anorexia can be divided roughly into three groups (Holland *et al.* 1977). Transient anorexia can be caused by emotional distress during the diagnostic work-up, at the time of diagnosis of recurrence of metastases and during times of pain or discouragement. Anorexia may also be related to treatment, for surgery, chemotherapy and radiation sickness all contribute to the problem. In some patients it is related to the disease and occurs early in patients with gastrointestinal tumours and in the cachexia syndrome of advanced disease.

Taste aberrations are more evident in patients with advanced disease and intensity is related to the tumour burden (De Wys, 1978). It appears that they may be both a cause and a consequence of a reduction in food intake. Hall *et al.* (1980) have reported a lower threshold of recognition of bitter taste in patients with gastrointestinal cancer. Studies of energy balance in patients with cancer (Warnold *et al.* 1978) have confirmed earlier reports of raised energy expenditure and resting metabolism that were not met by higher energy consumption.

Malnutrition has important consequences for it results in general debility, reduction in immunocompetence and in wound healing, an increase in the toxicity of drugs, and changes in psychological state resulting in apathy and depression.

Increased requirements for specific nutrients may result from the presence of a particular kind of tumour in the host or by a tumour that has reached a certain stage of activity. The ascorbic acid status of patients with cancer as determined by the concentration of ascorbic acid in the leucocytes is often low particularly in advanced disease (Basu *et al.* 1974). In our patients there was no evidence of low dietary intake. Leucocyte ascorbic acid levels were lowest in patients with breast cancer and skeletal metastases. In these patients, administration of 1 g of ascorbic acid resulted in a fall in the excretion of hydroxyproline which was elevated as a result of the skeletal involvement. It therefore seems possible that large doses of ascorbic acid may affect the activity of the tumour and its effect on bone, this possibility is being examined more closely in a longitudinal prospective study in collaboration with the breast clinic at St. Luke's Hospital, Guildford. The idea that ascorbic acid may play a role in the management of patients with cancer was suggested by Cameron & Pauling (1978) who have provided information which indicates that the survival time of patients with cancer may be improved by the administration of large amounts, that is up to 10 g/d, of ascorbic acid. These results have as yet not been confirmed and it would seem that a role for ascorbic acid in the management of cancer patients in general is at best unproven.

There are indications that vitamin A may play a key role in relation to certain types of cancer, thus the blood levels of both vitamin A and β-carotene have been shown to be lower in patients with squamous cell carcinoma of the mouth and oropharynx than in age-sex-matched controls (Ibrahim *et al.* 1977). Low plasma levels of vitamin A have also been found in patients with lung cancer and this has been confirmed in a larger series of patients (Atukorala *et al.* 1979). In this latter

study the levels of vitamin A were significantly correlated with the concentration of retinol binding protein (RBP) and it therefore seemed that RBP might have contributed to the low levels of plasma vitamin A. Zinc may play a role in the synthesis of RBP (Ette *et al.* 1979) and the patients with lung cancer were found to have low serum zinc:copper values. It therefore seems possible that the tumour take-up of Zn may have been a factor in contributing to the low plasma concentrations of vitamin A in our patients. However, it is also tempting to suggest that low levels of vitamin A may contribute to the development of lung cancer. Evidence that this may be so has been provided by an epidemiological study (Mettlin *et al.* 1979) in which it was found that individuals who were heavy smokers but who had a high vitamin A intake were less likely to develop lung cancer than heavy smokers who did not consume large amounts of vitamin A. Further support for the involvement of vitamin A in the aetiology of lung cancer is derived from animal experiments in which it has been shown that vitamin A inhibits squamous metaplasia induced by benzo(α)pyrine and 3-methylcholanthrene (see Basu, 1979). These results have stimulated interest in the possibility that the use of synthetic retinoids may offer a practical approach to cancer prevention (Sporn & Newton, 1979).

Nutrition and chemotherapy

Treatment of disseminated cancer with cytotoxic drugs may cause a number of distressing side effects (Dickerson & Tredger, 1978). Almost all drugs cause anorexia, diarrhoea, nausea, stomatitis and vomiting. Oral ulcerations are caused by cyclophosphamide, actinomycin D, 5-fluorouracil, cytarabine, and methotrexate. Nitrogen mustard causes a metallic taste and constipation follows the taking of hydroxyurea, vinblastine, and vincristine. We have been interested in the possibility that some of the side-effects of these drugs may be due to interactions with specific nutrients. Some drugs, e.g. methotrexate, owe their anti-tumour action to such an effect.

Thiamine deficiency is common in both advanced and early malignancy (Basu & Dickerson, 1976). Moreover, thiamine deficiency is induced by the drug 5-fluorouracil (5-FU) and an elevated TPP effect appears within one month of starting drug combinations containing 5-FU (Aksoy *et al.* 1980). 5-FU appears to interfere with the conversion of thiamine to thiamine pyrophosphate (TPP) the active form of the vitamin (Basu & Dickerson, 1976; Soukop & Calman, 1978). This observation is of potential clinical importance because administration of a large dose of thiamine (100 mg/d) subjectively improved the state of well-being of some of the patients being treated with the drug and resulted in an increase in appetite. It was also of interest that in our longitudinal study the administration of thiamine resulted in a fall in plasma alkaline ribonuclease which had been elevated before treatment was commenced. The ribonuclease was of hepatic origin and its release into the blood stream could have been the result of a distant effect of cancer on the liver. It appeared that administration of thiamine improved hepatic function and inhibited the release of the enzyme.

Patients with metastatic testicular teratomas are commonly treated with Samuels regimen (Samuels *et al.* 1976) of vinblastine and bleomycin. A longitudinal study (Dickerson *et al.* 1980) of patients over at least four courses showed that during each course the plasma level of retinol fell and rose again between courses. By the beginning of the fourth course the plasma level was significantly higher than at the beginning of treatment. Similar changes were found in RBP and there was a significant correlation between the rise in plasma retinol and that in RBP. This apparent increase in status with respect to vitamin A may have been due to an improvement in hepatic function and to the increased synthesis or release of RBP or both. Decreased synthesis of RBP could again be a distant effect of the tumour upon the liver. Only one of the seven patients studied had hepatic metastases. The TPP effect, an index of thiamine status, rose during each treatment and fell between treatments but at no stage did the level fall to below the starting level. The lack of improvement in thiamine status could be due to the persistant anorectic effect of the tumour and treatment. Administration of vinblastine to male rats produced similar effects on vitamin A status and body-weight to those found in patients (Atukorala, 1980). The food intake was greatly reduced.

It is clinically of potential interest that administration of vitamin A prior to treatment with vinblastine reduced the anorectic effect of the drug and improved food intake though not to the level found in controls.

A prospective trial of the administration of vitamin A to these patients is in progress. It is of interest in this connexion that Soukop *et al.* (1978) have reported a correlation between the pretreatment plasma vitamin A level (>2μM/l) and improved response rate to anti-tumour chemotherapy. A prospective clinical trial of vitamin A supplementation in patients being treated with chemotherapy is also in progress in Glasgow. It thus seems possible that vitamin A may play a central role both in relation to cancer itself and its treatment (Atukorala, 1980).

Conclusions

It would seem that in considering the relationship of nutrition to cancer in the cancer patient there are four important questions to which we would like to know the answers. (1) Does improving the nutritional status of the patient make the tumour grow more quickly so that the course of the disease is in fact accelerated? This occurs in experimental animals but there is no good evidence that it occurs in man. Nutrition is not, however, a treatment for cancer and improvement of the nutritional status of patients must always be accompanied by treatment of the tumour. (2) Does nutrition have an adjunctive role in relation to treatment? There is evidence, particularly from the United States (Copeland *et al.* 1979) that this may indeed be so. However, more controlled trials need to be carried out before a definite answer can be given to this question. (3) Does nutritional support protect the patient from the undesirable side-effects of treatment particularly radiotherapy and chemotherapy? Again, there are some indications that this may in fact occur, but more work of a carefully controlled nature is needed to produce convincing

evidence. (4) Does nutrition play a role in the psychological support of the cancer patient? Subjective impressions suggest that it does.

Finally, it must be pointed out that nutrition is a life support system and this raises important ethical questions, for the decision as to whether to aggressively nutritionally rehabilitate a patient must be governed to a considerable extent by the nature of the prognosis. As with the treatment of other conditions, particularly in the elderly, medicated survival (Vickery, 1974) is undesirable. Prolongation of life is only part of the goal, improvement of the quality of the life that remains must be the major deciding factor.

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Printed in Great Britain