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Nutrition and immunity in cystic fibrosis

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'Of all man's miseries the bitterest is this, to know so much and to have control over nothing'. HERODOTUS.

The precise defect in cystic fibrosis is still unknown despite vast amounts of basic research over the past twenty years (Bearn, 1973*a*). It is common in white European and North American populations with a birth incidence of around 1 in 2000 (Bearn, 1973*b*), and where intensive birth screening has been undertaken, the incidence may be as high as 1 in 1200 (Stephan, 1973). It is a multisystem disorder with its main impact on the respiratory tract, leading to repeated chest infections, and on the gut where the main problem is exocrine pancreatic insufficiency. In the neonate this latter defect leads to acute intestinal obstruction due to meconium ileus, a complication which was encountered in 5% of a large series of cystic fibrosis (CF) patients studied in France (Chazalette, Dutau, Chevalier, Filliat & Galabert, 1977). Other clinical problems in the disease include rectal prolapse and ileal atresia, and in older patients nasal polyposis, diabetes and hepatic cirrhosis. Abnormalities in vitro are also diverse and include abnormal serum factor(s) as well as histochemical changes in cultured fibroblasts and various leucocytes (see Raeburn, 1975*a*). Amidst so many definable abnormalities both clinical and in the laboratory the problem is to distinguish primary from secondary defects.

In most CF patients the hallmark of the disease is the chronic cough and other respiratory symptoms associated with repeated infections. At first sight the cause of such infection seems obvious for the sputum is excessively viscid (Sturgess & Reid, 1969) and the pathological changes, including emphysema and bronchiectasis, would lead to inadequate bronchial clearance. However, none of these findings is specific for cystic fibrosis (Reid & Ryland, 1973); in addition, the glycoprotein constituents of bronchial mucus from CF patients are qualitatively (but not quantitatively) similar to those of other patients with chronic lung disease. Nevertheless, since severe respiratory infection and respiratory failure are the major causes of death the main focus in management has been upon attempts to minimize respiratory damage. This has led to a variety of studies of antibiotic therapy (e.g. Lawson & Porter, 1976; Raeburn & McCrae, 1974; Raeburn, 1976) or of other treatments such as mist-tent therapy or even repeated bronchial lavage. There is still no consensus as to the most effective respiratory management, but

most authors would agree that the prognosis in cystic fibrosis has improved considerably in the past twenty years (Mearns, 1972; *British Medical Journal*, 1973).

Has too much attention been focused on antibiotic therapy in cystic fibrosis, thereby overshadowing other measures which have led to the improved prognosis? This may well be true and there is no doubt that regular intensive physiotherapy, performed daily by the patients' relatives, plays the major part in improving airway obstruction (McCrae, 1974). More skilful nutritional management including adequate pancreatic replacement therapy and high-energy, high-protein diets will also have had indirect beneficial effects on the respiratory defects. An increasing interest in many CF treatment centres has been the measurement of different aspects of the human response to infection. Changes in immune function occur in the underweight CF patient with repeated chest infection (Raeburn & McCrae, 1977) very similar to those that have been described in children with kwashiorkor (Douglas & Schopfer, 1976). In the following sections the immunological findings in cystic fibrosis are reviewed and compared with those found in malnutrition.

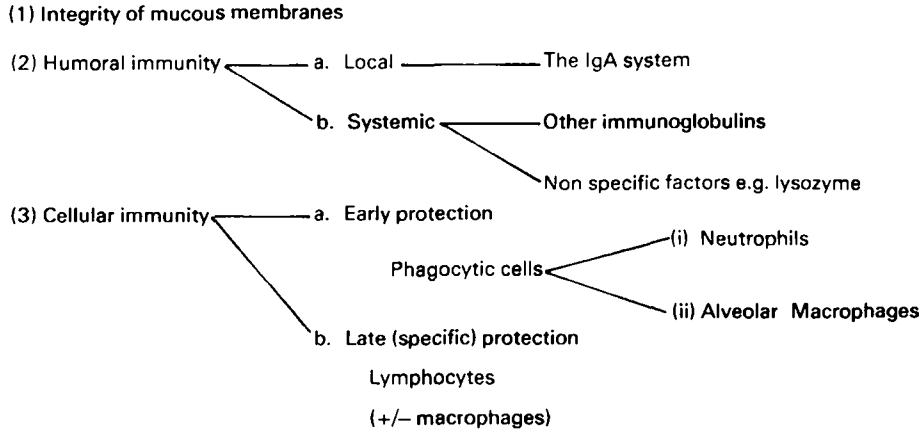

Fig. 1. Host resistance of the respiratory tract.

Host resistance to infection in cystic fibrosis

There are many factors which combine to produce normal protection from infecting bacteria and those applicable in the respiratory tract are summarized in Fig. 1 (based on van Furth, 1972; Raeburn, 1974). Since these patients often receive antibiotic therapy, sometimes on a very long-term basis, it is legitimate to argue that antibiotics should be included in a discussion on host resistance. Certainly all the endogenous host factors are well co-ordinated one with another, but antibiotics are prescribed with little thought as to their effects on the immune system (see below).

(1) *Integrity of the mucous membranes*

There is surprisingly little information about the mucous membranes in CF, but studies of mucociliary clearance in thirteen CF children showed that it was comparable to that in a group of healthy adults (Newhouse, Sanchis, Dolovich, Rossmann & Wilson, 1973). There is some indirect evidence that CF patients initially are to some extent protected by the excessive mucus. Thus, in CF children without an excess of chest infections, immunoglobulin G (IgG) levels were significantly lower than in normal children matched for age (McCrae & Raeburn, 1974; Wright, Dooley, Levy & Stiehm, 1973). Gastro-intestinal protein loss is unlikely to account for the lower IgG levels in these CF patients and it seems that the CF mucus may have provided an extra barrier between the bacteria and the child's immune system.

(2) *Humoral immunity*

(*a*) *The secretory IgA system*

Biggar, Holmes & Good (1971) found that 70% of CF sera failed to enhance the phagocytosis of *Pseudomonas aeruginosa* by rabbit alveolar macrophages. Since the phagocytic system used was, in part, dependent on functional IgA they suggested that the IgA system may be defective in CF. Wallwork, Brenchley, McCarthy, Allan, Moss, Ward, Holzel, Williams & McFarlane (1974) found low serum IgA levels in two CF children out of fifty-nine studied and, in addition, noted precipitins to many antigens, including food proteins, in the sputum. More recently these authors have presented evidence that some CF patients may have a defect of assembly of secretory IgA (Wallwork & McFarlane, 1976).

A probable clinical correlate of these laboratory findings is that CF patients suffer from atopic symptoms more often than controls; see Table 1 (Allan, Moss, Wallwork & McFarlane, 1975; Warner, Norman & Soothill, 1976). Since there is evidence that infants who have an initial low serum IgA (between 3 and 9 months of age), may later develop various types of allergy (Taylor, Norman, Orgel, Stokes, Turner & Soothill, 1973), it is reasonable to consider other IgA defects in the pathogenesis of atopy as it occurs in CF. However, it is likely that the IgA defects (not in any case present in all CF subjects) occur secondarily and all workers agree that more data about these phenomena in suitable control subjects (e.g. children with bronchiectasis) are urgently required.

Table 1. *Atopic manifestations in cystic fibrosis*

	Subjects (% +ve)		
Atopic features	Cystic fibrosis	Controls	References
Asthma	23	12	Warner, Norman & Soothill (1976)
Eczema	11	6	
Hay fever	16	8	
+ve skin tests	59	20	
+ve skin tests	77	Not stated	Allan, Moss, Wallwork & McFarlane (1975)
Raised IgE level (500 ng/ml)	53	Not stated	

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Severe protein malnutrition and also marasmus has been shown to reduce the concentration of IgA in both gut fluids (Heyworth, 1974) and upper respiratory secretions (Faulk & Chandra, 1974; Reddy, Raghuramulu & Bhaskaram, 1976). However, there is little information about atopy in subjects with kwashiorkor, furthermore interpretation of laboratory tests would be hampered by the effects of concomitant parasite infestation.

(*b*) *Serum immunoglobulins*

Elevated levels of IgG, IgA and IgM have been described in CF patients (Schwartz, 1966) as well as increased γ-globulins (Green, Kulczycki & Schwachman, 1960). However, McCrae & Raeburn (1974) pointed out that the degree of pulmonary infection determined whether immunoglobulin levels were raised. Grossly elevated levels in patients with considerable pulmonary damage would be sufficient to make the mean levels of a CF group significantly higher (although the variance, greater in the CF group than in controls, emphasizes the heterogeneity).

Similarly in malnourished children serum immunoglobulins G, A and M vary and elevations can be attributed to concomitant infection. Serum antibody responses are usually normal but there may be a diminished response to *Salmonella typhi* (Faulk & Chandra, 1974). Table 2 compares the changes in humoral factors in CF and malnourished children.

Table 2. *Humoral factors in cystic fibrosis or malnourished children*

Measurement	Cystic fibrosis	Kwashiorkor
Complement	Normal	Reduced
IgG	Depends on stage	Normal to Tetanus and Pneumococci
IgA	Normal or increased	Reduced to *Salmonella typhi* or
IgM	Normal	Influenza vaccine
Opsonins	Decreased	Normal

(3) *Cellular immunity*

(*a*) *Phagocytic cell functions*

Phagocytic cells, initially granulocytes and later macrophages, play the major part in the first 24 h of the acute inflammation which follows bacterial invasion (Raeburn, 1974). Deficiencies in their function can therefore be crucial in determining the outcome of each infective episode. Table 3 summarizes the available information about phagocytic (usually granulocyte) function (based on Douglas & Schopfer, 1976; Raeburn & McCrae, 1977; Hill, Warwick, Dettloff & Quie, 1974). There is a striking similarity between the CF and the kwashiorkor patient as regards several phagocytic cell functions.

There is a consensus that such defects are secondary in both disease situations, but the findings may be of considerable practical importance. Thus in some instances iron therapy has reversed the intracellular killing defect in malnourished

Table 3. *Phagocytic function in cystic fibrosis or malnourished children*

Measurement	Cystic fibrosis	Kwashiorkor
Neutrophil and monocyte counts	Usually increased	Minimal increase
Phagocytosis	Normal	Normal
Intracellular killing	Reduced	Reduced
Chemotaxis	Increased (during infection)	Reduced
N.B.T.—Resting	Usually increased	Variable
N.B.T.—Stimulated	Decreased	Decreased

subjects (Faulk & Chandra, 1974). Furthermore, there are now several non-antibiotic agents available which can also enhance phagocytic cell function (Raeburn, 1975*b*). More important still is that certain antibiotics may interfere with important metabolic pathways of the granulocyte and may thereby reduce still further the intracellular killing capacity (Raeburn, Watson, Hanson & Johnston, 1976). Studies of this aspect of immunity in the CF and kwashiorkor patients may clarify the best therapeutic regimen.

(*b*) *Lymphocyte functions*

The major function of B lymphocytes is to produce specific antibody following antigenic stimulation. As Table 2 indicated, this is probably normal in CF, but may have localized defects in kwashiorkor. T lymphocyte function, the hallmark of cell-mediated immunity, is currently under further study and the results are not yet conclusive. Thus Wallwork *et al.* (1974) found normal phytohaemagglutinin (PHA) transformation in fourteen CF patients while Boskova (1976) found this lymphocyte function decreased. It is known that PHA transformation is reduced in infected patients (Forbes, 1971). In addition, Gibbons, Allan, Holzel & McFarlane (1976) have shown that CF leucocytes, incubated in the presence of lung, pancreatic or certain fungal and bacterial antigens, showed a reduction of migration compared with controls; i.e., there may have been some sensitization of T lymphocytes in CF possibly in keeping with the excess of allergy. Further studies are needed, particularly to understand the opposing effects of co-existing infection (suppressive) and atopy (? stimulatory).

For some time it has been known that malnourished children have reduced tuberculin skin reactions even in the absence of frank kwashiorkor (Harland, 1965). Smythe, Schonland, Brereton-Stiles, Coovadia, Grace, Loening, Mafoyane, Parent & Vos (1971) extended this finding by demonstrating marked reduction of the delayed hypersensitivity skin response to 2,4-dinitrochlorobenzene, and of the

Table 4. *Lymphocyte function in cystic fibrosis or malnourished children*

Measurement	Cystic fibrosis	Kwashiorkor
B lymphocytes	Normal	Normal
T lymphocytes	Normal or reduced	Normal or reduced
PHA response	Normal	Decreased
Delayed hypersensitivity	Normal or reduced	Decreased

lymphocyte transformation response to PHA, in protein-energy malnutrition. Chandra (1974) found, in addition, that the proportion of T lymphocytes was decreased in such patients. Table 4 summarizes these findings and contrasts the CF with the malnourished patient.

Discussion and conclusions

Malnutrition is a major health problem in many areas of the world and it will unfortunately continue so, unless there are rapid economic, educational and political measures. In the meantime an improved outlook for affected children could result from greater understanding of the pathogenesis of infection, the major complication of the malnourished state. Cystic fibrosis is an increasing problem in many wealthy nations and, as with malnutrition, its major complication is infection. Although the survival rate has improved (e.g. 60% of CF children without meconium ileus now survive to the age of 16; George & Norman, 1971) there is still a great need for improvement. Furthermore, the morbidity of young adults with CF is very high and a recent study showed that 71% had severe lung disease, particularly infection (Mitchell-Heggs, Mearns & Batten, 1976). In both malnutrition and cystic fibrosis, therefore, the primary defect is not amenable to therapy. After thirty years of antibiotic therapy, the infections in both diseases continue to be refractory and the major cause of death.

Present-day immunological methods have been criticized for their irrelevance in clinical medicine (Bryceson, 1976), but in the area of host resistance to infection they can point to many practical measures. Thus the infected, malnourished child may benefit as much from modest iron supplements to his diet as from expensive intravenous alimentation. The infected CF patient may not require high doses of antibiotics; he too might benefit more from simple nutritional alterations.

A study of similarities and contrasts between diseases with such different primary causes is valuable because it crosses the boundaries between different areas of medicine. It is not new to suggest that nutritional factors are important influences on the resistance to infection of the CF patient. What we can now do is measure the different aspects of the immune response in such patients and those with malnutrition, so that the simplest and most direct therapy can be chosen. This will lead to 'individual therapy' for each patient and consequently to control of the basic disease in a larger proportion of the population. Management of two conditions, one genetic, one environmental, depends less on the primary pathology than on the secondary invasion by microorganisms which ultimately are the final determinants of the prognosis.

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