The past few years have seen a considerable increase in research into cystic fibrosis (CF). Although there have been notable contributions to many aspects of this disease, two areas stand out in particular. Genetic studies have closed in on the CF gene, as well as providing opportunities for prenatal diagnosis and heterozygote detection. At the cellular level reduced chloride permeability has now been shown in a number of epithelia, suggesting a focus for investigation of the basic defect.

In late 1985 an important step towards identifying the CF gene was taken by three research groups [1—3]. Using DNA markers, i.e. regions of DNA with a known base-pair sequence, three such areas were shown to be closely related to the CF locus and to reside on chromosome 7. Two of these markers, the met oncogene and the probe J3.11, are particularly tightly linked. An indication of the distance may be obtained from the probability of the marker being separated from the CF locus due to recombination at meiosis – the closer the marker the lower the chance. In this case a study of over 200 CF families has shown a recombination of less than 1 per cent [4]. With the availability of newer and more closely linked probes, geneticists are clearly approaching the CF gene.

These data also indicate that CF is likely to be related to a single gene disorder. However, the demonstration of differing haplotypes for CF chromosomes in patients with or without meconium ileus [5] suggests that various mutations may still exist within the same locus. Finally with regard to the organ-specificity of CF it is likely that the mutant gene is only expressed at a high level within epithelial cells [6].

Practical benefits of this work are already available. Prenatal diagnosis is possible in the majority of families with a previous CF child using restriction fragment length polymorphisms (RFLP). These segments of DNA, cleaved from the complete chromosome at set points, include one or more of the above gene probes. Each of the parents may be either hetero- or homozygous for the RFLP and this determines the degree of certainty or informativeness of the particular case in question. A fully informative family includes both parents as heterozygotes for the RFLP, one previous CF child being available for analysis [7]. Samples may be obtained from chorionic villi as early as the 11th or 12th week of pregnancy. It is estimated that approximately 97.5 per cent of such families are fully informative [8] with at least 98 per cent accuracy [7].

Heterozygote detection using the above techniques is also possible in certain families with a CF sibling. However it has been suggested that such testing should at present be limited to pregnant or would-be-pregnant couples at risk of a further CF child [9].

Progress in defining the underlying pathophysiology of CF has kept pace with attempts to isolate the gene. It is now well established that there is an abnormally reduced movement of chloride ions in both sweat glands and airway epithelia. Within the sweat gland secretory coil,
active movement of chloride drives fluid secretion into the sweat duct. In CF the component of this secretion which is stimulated by β-adrenergic agents is absent [10]. As the fluid passes along the sweat duct active sodium absorption occurs with the passive accompaniment of chloride. Again, in CF the chloride impermeability of the duct epithelia prevents this movement and in turn, that of the accompanying sodium [11].

In normal human airway epithelia the bulk of ion flow is that of absorption of sodium from the luminal surface, probably accompanied by chloride and water moving passively through pathways between cells. These cells can also transport chloride from their submucosal surface towards the airway lumen with sodium and water again the likely accompanying molecules. Both in-vivo [12] and in-vitro [13] studies suggest that in CF the luminal border of these epithelial cells is impermeable to chloride ions. Additionally Knowles et al. [14] have shown that the sodium absorption across these cells in CF is roughly twice normal. Whether this is a secondary response to the chloride impermeability or directly related to the genetic defect remains to be determined. However, both of these electrolyte abnormalities will tend to reduce the degree of hydration of the airways liquid, perhaps contributing to the thick secretions characteristic of CF. Although there have been fewer studies of ion transport in the pancreas, a similar picture of reduced anion secretion has been suggested [15].

The intracellular control of chloride secretion in airway epithelia is now under close scrutiny. Using patch-clamp techniques the activity of individual ion channels within the luminal membrane of these cells can be studied. Agents such as β-agonists which activate the cAMP second messenger system cause the Cl channel to open in normal epithelium [16]. In CF however, despite a normal rise in intracellular cAMP [16], and in turn a normal activation of the cAMP-dependent protein kinase [17, 18], chloride channel opening cannot be elicited. A similar lack of a β-response in CF submandibular acinar cells has also been shown by McPherson et al. [19].

Two practical aspects have emerged from these pathophysiological considerations. Related to the abnormal chloride transport in CF is the finding of a markedly more negative potential difference across the respiratory [20] and sweat duct epithelium [21] in these patients. A technique for the measurement of nasal potential difference is being evaluated as a possible means of diagnosis in CF [22]. Secondly, drugs which alter ion transport processes may be of value in the treatment of CF. Amiloride is a well known inhibitor of sodium transport in many epithelia and would be of theoretical benefit in CF by inhibiting the noted increase in sodium and perhaps water absorption. Clinical trials are presently under way with initial reports suggesting a small improvement in mucociliary clearance [23, 24].

It is to be hoped that the two approaches described above will lead to similar conclusions regarding the basic defect in CF. However, from the patient’s viewpoint such optimism will be tempered by the likely lengthy delay between any such discovery and the availability of specific therapy.

REFERENCES