(defective secretion in the ducts would give rise to a dehydrated pancreatic fluid that obstructs the ducts, thereby causing pancreatic atrophy). Our understanding of these problems, though, is far from complete.

But what about the pulmonary airways? They are the site of repeated infections in cystic fibrosis and are the main source of morbidity and mortality. Can the pathogenesis and pathophysiology be attributed entirely to a failure of transepithelial Cl^- secretion by airway epithelia? And what about the many different research observations that are not readily accounted for by CFTR being a Cl^- channel (and that have been used to argue that CFTR is not a Cl^- channel)? These questions are not trivial: to understand how mutations in CFTR cause disease, we must first understand how such mutations produce so many different phenotypic manifestations.

That is where the work by Barasch *et al.*[4] fits in. The authors present an intriguing hypothesis by which the loss of Cl^- channel function could produce some of the phenotypic manifestations of cystic fibrosis. They propose that defective acidification of intracellular compartments, caused by defective Cl^- permeability, may be responsible for abnormalities of protein modification.

Certain intracellular vesicles are acidified by a proton pump and a Cl^- channel, located in parallel on the vesicular membrane. The proton pump provides the driving force for acidification and the Cl^- channel provides both a pathway for anion movement (to maintain electroneutrality) and a means to regulate acidification. It has been postulated that the proton pump is constitutively active and that the opening and closing of Cl^- channels regulates acidification. If the Cl^- channel does not open, then acidification becomes impaired. The results of Barasch *et al.* are the first to show that acidification of the *trans*-Golgi, endosomes and prelysosomes is defective in cystic fibrosis airway epithelia. The implication is that a defective vacuolar Cl^- channel is responsible.

The activity of *trans*-Golgi enzymes, such as sialyltransferases, is sensitive to changes in pH. Barasch *et al.* therefore compared sialylation of glycoproteins and glycolipids in transformed cells from either a cystic fibrosis nasal polyp or a normal trachea. They found that sialylation was reduced in the cystic fibrosis polyp cells. This is perhaps the most enticing observation — if defective acidification and sialylation can be demonstrated in several primary cultures and convincingly linked to abnormal Cl^- channel function, then we are well on our way to having established a defect in Cl^- channels that can induce changes in vesicle enzyme activity and thereby alter the properties of proteins and lipids. The mechanism would also provide a way in which a qualitative, all-or-none defect in Cl^- channels can lead to a quantitative defect, such as the increased protein sulphation seen in cystic fibrosis. And could it be that such altered processing of surface proteins contributes to the colonization and adherence of microorganisms to the airway epithelium? In the end, infection of the airways is one of the main causes of morbidity.

Although the hypothesis is intriguing, there are many questions that remain unanswered. Is CFTR directly responsible for normal and abnormal acidification? If the answer is yes, then CFTR should be localized to both the affected intracellular membranes and to the plasma membrane where it causes defective apical Cl^- permeability. And as the Cl^- channel that is defective in cystic fibrosis is regulated by cAMP, does this compound have an effect on vacuolar acidification? A cAMP-regulated Cl^- conductance has been demonstrated in endocytotic vesicles from renal epithelia[9]; is that response due to CFTR or to a different cAMP-regulated Cl^- channel? (The kidney does not have much CFTR.) Is the response in kidney vesicles the same as that studied by Barasch *et al.*, and is it defective in cystic fibrosis? Every cell requires acidification of some intracellular vesicles. If acidification is defective in cystic fibrosis epithelia, one would presume that it is not defective in other organs, because the process is so critical to a variety of cell functions. Perhaps there are different mechanisms of acidification in nonepithelial cells and cells that do not express CFTR.

Another problem is explaining how a defect in CFTR induces an increased rate of Na^+ absorption in cystic fibrosis airway epithelia[10]. Increased Na^+ absorption might alter the respiratory tract fluid; hence therapeutic attempts have been made with inhaled amiloride to inhibit Na^+ absorption in cystic fibrosis patients[11]. The molecular and cellular events that couple Cl^- channel defects to increased activity of Na^+ channels are completely unknown. One wonders whether CFTR, as well as possibly being a cAMP-regulated Cl^- channel, might have an additional, as yet undiscovered function.

There is much to learn about CFTR and how mutations in it cause disease. And cystic fibrosis has never given up its secrets easily. But as the mysteries unfold, we are certain to learn exciting new biology. More importantly, we trust that the new insights will lead to better approaches to therapy. □

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1. Riordan, J. R. *et al. Science* 245, 1066-1073 (1989).
2. Anderson, M. P., Rich, D. R., Gregory, R. J., Smith, A. E. & Welsh, M. J. *Science* 251, 679-682 (1991).
3. Kartner, N. *et al. Cell* 64, 681-691 (1991).
4. Barasch, J. *et al. Nature* **352**, 70-73 (1991).
5. Boat, T. F., Welsh, M. J. & Beaudet, A. L. in *The Metabolic Basis of Inherited Disease* Vol. 6 (eds Scriver, C. R., Beaudet, A. L., Sly, W. S. & Valle, D.) 2649-2680 (McGraw-Hill, New York, 1989).
6. Quinton, P. M. *Nature* **301**, 421-422 (1983).
7. Knowles, M., Gatzy, J. & Boucher, R. *J. clin. Invest.* **71**, 1410-1417 (1983).
8. Quinton, P. M. *FASEB J.* **4**, 2709-2717 (1990).
9. Bae, H-R. & Verkman, A. S. *Nature* **348**, 637-639 (1990).
10. Boucher, R. C., Stutts, M. J., Knowles, M. R., Cantley, L. & Gatzy, J. T. *J clin. Invest.* **78**, 1245-1252 (1986).
11. Knowles, M. R. *et al. New Engl. J. Med.* **322**, 1189-1194 (1990).

DAEDALUS

Flying doctors

Many terrible diseases are transmitted by blood-sucking insects. Some of them, such as yellow fever, dengue, plague and certain forms of encephalitis, are caused by a virus. They cannot be treated, but can be prevented by prior vaccination. Daedalus now wants the insects to transmit, not the disease, but the vaccination.

Vaccination often uses a mutated 'attenuated' virus with mild and transient effects, or the virus of a related and harmless disease (like the cowpox used by Jenner in his pioneering vaccinations against smallpox). These days, genetically engineered viruses are also used. In all cases, the vaccination stimulates the production of antibodies which inactivate the real virus when it comes along.

So DREADCO biologists are loading mosquitoes, fleas and so on with vaccination viruses. Like the fake cows used to attract tsetse flies, their 'vaccination-zombie' looks and smells invitingly human, but has vaccine-loaded fake blood under its skin. The deluded insects bite this, and take up the vaccine.

Much biological cunning will be needed to ensure that the vaccine-virus survives in the insect, and can be transmitted reliably to its subsequent victims. But when the technique has been perfected, vast numbers of vaccination-insects will be released in the disease ridden regions. As in the 'sterile male' technique of combating pests such as the screw-worm fly, the treated insects will briefly overwhelm the local ecology. Since they all carry the vaccine, while relatively few of the wild insects actually carry the disease, vaccination should outpace infection throughout the whole area. The most dispersed, doctor-shy, or needle-averse population will soon be thoroughly bitten and vaccinated. Even animal reservoirs of the disease will be reached and treated. Heroic expeditions through bush and jungle by paramedics and insect-spraying teams will no longer be needed. The insects that previously spread the disease will now spread the treatment.

With luck, the vaccine-virus will become stably established in the human population, or perhaps in some local wild animal. Indigenous bloodsucking insects will then spread booster vaccinations regularly through the population. The disease will be kept permanently in check.

This cunning technique may even work against viral diseases not carried by insects, such as rabies, poliomyelitis and hepatitis B. An insect-compatible virus, genetically engineered to carry some antigen of the chosen disease, should do the trick. Only one problem baffles Daedalus — how to give the patients a bureaucratically valid vaccination certificate? David Jones