May and June[9], and they disperse widely from the parental habitat to seek empty territories.

The final issue is the overall level of vaccination achieved in the trial. In areas of low to moderate fox density, simple theory suggests that 80 per cent coverage is sufficient. If fox density was of the order of 4 per km^2 (not unusual in some suburban areas in Europe[10]), then a similar calculation produces a figure of 90 per cent to block transmission. It was estimated that the typical density of foxes before the trial was 2 per km^2. But given that some hunting and gassing took place in the preceding years, the habitat might be able to support much higher densities. If vaccination replaces culling, then fox density is likely to rise, as a consequence both of the decreased incidence of rabies (the disease has a considerable effect on fox abundance) and of the cessation of culling. So unless culling is continued, a level of vaccine uptake of over 80 per cent may be required to prevent the re-establishment of the virus.

Nonetheless, the trial results show that mass vaccination may be an alternative (in some countries) to the continual culling of foxes. Aside from long-term control, the availability of a safe and effective vaccine for wildlife raises many other possibilities, such as the control of local outbreaks of rabies in rare mammalian species (one example is the African wild dog, *Lycaon pictus*, in certain East African game reserves, where rabies is threatening the survival of the species). Above all, perhaps, the development of a method of disease control not involving the slaughter of wildlife would be only too welcome in the conservation-conscious social climate of the 1990s. □

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CYSTIC FIBROSIS

The mutant protein responds

Jeffrey J. Wine

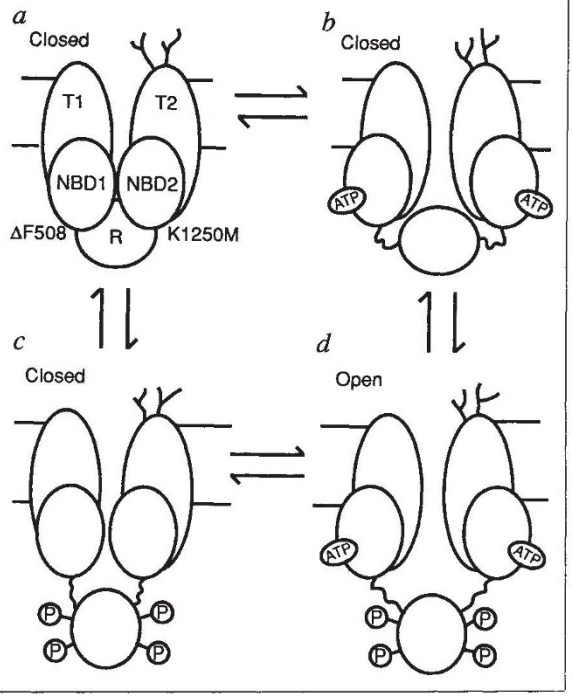
CYSTIC fibrosis results from mutations in a single gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel requiring both cAMP-dependent phosphorylation and ATP hydrolysis to open[1]. At least in some cells, most mutations that give rise to cystic fibrosis cause the CFTR protein to be misprocessed so that little of it reaches the membrane[2,3], providing a direct explanation for the reduced Cl^- conductance in affected tissues[4]. But Dalemans *et al.*, on page 526 of this issue[5], and Drumm *et al.*, in this week's *Science*[6], now report that mutant CFTR *does* reach the membrane when expressed in fibroblasts[5] or oocytes[6], and that, against expectations, cells expressing mutant CFTR become responsive to stimulation. These are exciting results — they offer hope for therapies based on improving the functions of mutant CFTR, which might be important adjuncts to strategies based on replacing the defective gene or protein.

Dalemans *et al.* expressed wild-type or mutant (ΔF508) CFTR in fibroblasts. Consistent with evidence that ΔF508 protein is misprocessed[2,3], ΔF508 CFTR was not detected in the plasma membrane by surface labelling, but low levels of channel proteins can produce significant physiological responses. Drumm *et al.* expressed wild-type and several mutant versions of CFTR in *Xenopus* oocytes. On the main points, both groups agree.

In cells expressing normal or ΔF508 CFTR, but not in mock-transfected fibroblasts or uninjected oocytes, increases in anion conductances were observed following stimulation with a cocktail of forskolin, IBMX and cpt-cAMP, all of which elevate levels of cAMP (but by different means). Iodide efflux, whole-cell Cl^- currents or single-channel activity were measured in fibroblasts, and Cl^- currents were measured in voltage-clamped oocytes. Responses of cells expressing ΔF508-CFTR were 10–25 per cent of the magnitude of wild-type responses, and were qualitatively similar with one exception: the stimulated I^- efflux (fibroblasts) or Cl^- currents (oocytes) had much slower time courses and were more sustained in cells expressing ΔF508. In fibroblasts, single-channel currents attributed to ΔF508 expression appeared to be normal in most respects, but fewer active channels were observed and closed times were at least three times longer than in wild-type CFTR[5].

Drumm *et al.* also varied IBMX levels up to 5 mM, a level required for complete inhibition of phosphodiesterase in oocytes. Although no further increases in Cl^- current were observed in oocytes expressing CFTR, currents in cells expressing ΔF508 CFTR grew in response to increases of IBMX until they were about 60 per cent of the wild-type responses. Similar results were obtained after expressing two other disease-related CFTR mutants.

The new results[5,6] differ from previous ones, in which forskolin and IBMX failed to stimulate anion fluxes in cells expressing recombinant ΔF508 CFTR[3,7].



Conceptual diagram to illustrate experiments on the regulation of the CFTR channel[1]. The transmembrane domains (T1, T2), nucleotide-binding domains (NBD1, NBD2) and the R domain are coded by the cystic fibrosis gene (it is not known that functional CFTR is a monomer). CFTR kis closed when the R domain in unphosphorylated (*a*,*b*) or ATP absent (*a*,*c*). Phosphorylation by cAMP-dependent protein kinase and the presence of ATP opens the channel (*d*). Depiction of the NBD and R domains as blocking particles in conjectural. They could as well be conducting elements. Hydrolysis of ATP by a single NBD may allow the channel to conduct. The ΔF508 mutation is in NBD1 and the K1250M mutation in NBD2.