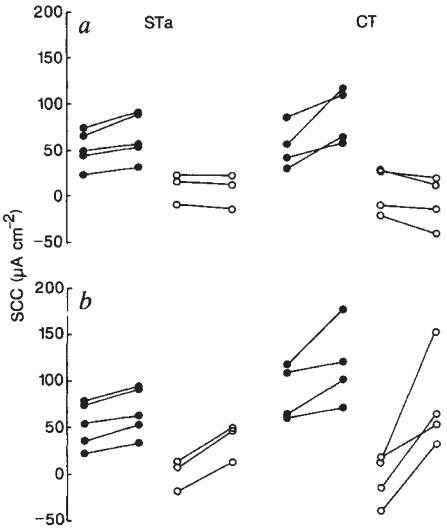
Accounting for cystic fibrosis

SIR—Hansson[1] speculates that if the defect in the control of apical membrane Cl^- channels in cystic fibrosis (CF) extends to the intestine, a resistance to bacterial toxin-mediated diarrhoea may confer a selective advantage to carriers heterozygous for the CF gene.

There is, indeed, direct evidence, both from our group[2,3] and from Powell's group[4], that in CF there is a failure of the Cl^- secretory mechanism of the small intestine. Intestinal tissue from children with CF did not exhibit an increased short-circuit current (SCC), a reflection of net



SCC response of control (•) and CF (o) intestinal biopsy samples to *a* STa (50 U ml^{-1}) or CT (50 μg ml^{-1}). The first value represents the SCC immediately before addition of the toxin. For STa the second value is the peak response, which occurred within 5 min; for CT the second value was obtained at 90 min. *b* the corresponding responses to glucose (10^{-2} M). All agents were added to the mucosal side of the tissue.

Cl^- secretion, when stimulated by secretagogues, although the rise in SCC associated with glucose absorption was unimpaired[2-4]. Intestinal tissue from a control group generated an increased SCC with both secretagogues and glucose.

We have now investigated the actions of two bacterial toxins that induce a secretory response in the normal intestine — *Escherichia coli* heat-stable enterotoxin (STa), which acts via cyclic GMP[5], and cholera toxin (CT), which acts via cyclic AMP[5]. Intestinal biopsy samples were obtained from a control group of nine children undergoing investigation for chronic non-specific diarrhoea or short stature (5 tested with STa, 4 with CT) and a group of seven CF patients, comprising three children undergoing investigation for chronic diarrhoea unresponsive to an increase in pancreatic enzyme supplements (1 STa, 2 CT), two children whose biopsies were taken at operation for meconium ileus (STa) and two adult volunteers (CT). The electrical activity of the biopsy samples was measured using a modified Ussing chamber technique[2,3]. As shown in the figure, five control tissues responded to *E. coli* STa with a rise in SCC of 12.4±3.2 μA cm^{-2}, but no such effect was observed in three CF tissues, whose SCC fell by 2.6±1.5 μA cm^{-2} ($P<0.05$). A similar pattern was obtained with CT: 90 min after addition of the toxin, the SCC of four control tissues had increased by 33.8±9.6 μA cm^{-2}, while that of four CF tissues had fallen by 10.3±3.2 μA cm^{-2} ($P<0.01$). Glucose induced a rise in SCC in all tissues, indicating their viability.

These findings confirm that the intestine in CF homozygotes fails to exhibit a secretory response on exposure to bacterial toxins that would normally induce a secretory diarrhoea. This leads to the speculation that heterozygotes may have a blunted response to such toxins which would confer upon them an evolutionary advantage in the form of resistance to toxin-mediated diarrhoea. This could account for the high frequency of the CF allele. The intestinal secretory responses of heterozygotes is currently under investigation in our laboratory.

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Ice-layer dating of eruption at Santorini

SIR—It appears that the authors of the correspondence on the dating of the Santorini eruption[1] had no knowledge of Baillie and Munro's[2] important new evidence, published one week earlier. Hammer *et al.*[1] state that the main purpose of the paper[3] that stimulated the correspondence was "to show that ice-core dating, radiocarbon dates and a tree-ring (frost-ring) date all point to a seventeenth century BC date for the Santorini eruption". I believe they have succeeded in this general aim, but have reservations about precisely when in that century the eruption occurred. They concluded that the ice-core date was the most reliable, because "the acidity signal in the 1645–44 BC ice layers is clearly related to a major volcanic eruption, whereas the frost damage at 1628–26 BC ... could have been caused by climatic impacts other than volcanism". The one flaw in this otherwise reasonable argument is that the accuracy and precision of ice-layer and tree-ring dates are equated. Whatever the cause of the frost damage in the early 1620s BC, there is no doubt of its precise date (which is in fact 1627 BC, as the time scale used by LaMarche and Hirschboeck[4] included an arbitrarily inserted year '0' at the AD/BC transition). On the other hand Hammer *et al.*[1,3,5] acknowledge the existence of uncertainties in the dates of ice layers (including the Dye 3 core) that are large enough to encompass LaMarche and Hirschboeck's 1627 BC event within the ice-layer date range of 1644 ± 20 BC.

Hence it is surprising that Hammer *et al.*[1] see any basis for differentiating between the timing of the most prominent Dye 3 acidity peak in several centuries (their 1644 BC) and one of only three notable frost-ring events reported[4] for the first three millennia BC. Of the other two such events, one follows the documented eruption of Etna in 44 BC by a year or less and is close to the Camp Century acidity peak reported[5] for 50 ± 30 BC, and the

Greenland ice acidity peaks and Irish oak low-growth (5289–116 BC)

Acidity peaks over 4 microequivalents kg^{-1} ice*	Low-growth events†
210 or 260	207 (1-yr event)
1120	1150s (all)
1644	1620s (all)
–	2340s (4–16)
2690	–
3150	3190s (all)
4400	4370s (all)
–	5060s (4–16)

* Ice-layer dates from Fig. 3 of ref. 5, except for 1644 which is from ref 3. Following ref. 3, 1390 BC has been omitted. Note that these may differ from other dates for the same events given elsewhere in ref. 5. The authors of refs. 3 and 5 give error limits in the range ±20 yr to ±120 yr for these dates.
† Low-growth events from ref. 2. Narrowness indices were calculated for 10-,1-,2-,4-,8- and 16-yr windows. The windows for which an event was notable are given in parentheses after the decade. Other than 207 BC only those events that are strong at several window sizes are listed.