Letter to the Editor

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It has recently been suggested that an abnormal anion exchange mechanism operates in the sweat glands of cystic fibrosis (CF) patients (1, 2). According to this suggestion, a defect in the CF sweat gland results in abnormally low permeability of the sweat duct to chloride ion. The normal exchange of chloride for bicarbonate cannot then occur, so that in CF sweat there is an abnormally low level of bicarbonate as well as an abnormally high level of chloride.

There is now well established evidence that pancreatic bicarbonate secretion is abnormal in all CF patients (3, 4, 5, 6) and, therefore, it seemed sensible to look at chloride levels in these secretions. We examined duodenal aspirates obtained during pancreatic function testing previously described (5), and obtained the data shown in Table 1. Bicarbonate values were obtained on the samples at the time of collection. Chloride values were obtained on samples stored at −70°C.

Chloride output from CF patients is lower than that of controls so at first glance Quinton's hypothesis of defective chloride-bicarbonate exchange would not appear to be true for secretin-pancreozymin stimulated pancreatic secretions. Interestingly, however, the ratio of chloride output to bicarbonate output is much higher for CF patients than controls ($P < 0.001$). This is true for all the CF patients regardless of their trypsin output although the patient with highest trypsin output has the lowest chloride/bicarbonate ratio.

It may be, therefore, that both the pancreas and sweat gland in CF exhibit abnormalities in ion exchange involving chloride and bicarbonate. The hypothesis of Johansen *et al.* (8) and Hadorn *et al.* (7), suggesting a generalized disturbance of water and electrolyte movement in exocrine tissue warrants re-examination to take into account this added information. We urge other investigators to collect more data on total electrolyte output of pancreatic secretions to see if our findings can be substantiated and explained.

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Response

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We find the above report and data very encouraging with regard to the possibility of a generalized abnormality in Cl permeability in cystic fibrosis (1, 2). As the authors point out, the production of both Cl^- and HCO_3^- are significantly lower in CF patients than in control subjects. Although this result is probably, at least in part, due to secondary loss of pancreatic parenchyma, the ratio of Cl^- to HCO_3^- production is always >1.0. In control subjects, the same ratio is always <1.0. It is perhaps more than coincidental that these same differences are found with respect to the ratio of Cl to Na production in sweat from CF and control subjects (3).

In the CF sweat gland, we now have evidence that Na is absorbed in excess of Cl^- due to the fact that the duct tissue is abnormally impermeable to Cl. That is, while the mechanism for Na absorption may be normal, net Na uptake is impeded by

Table 1. *Output of bicarbonate, chloride, and trypsin in pancreatic secretions over a time period of 0–15 min after secretin-pancreozymin stimulation*

Patient	Diagnosis	Age (sex)	Bicarbonate mmol/kg ($\times 10^{-2}$)	Chloride mmol/kg ($\times 10^{-2}$)	Trypsin (I.U.)	Chloride to bicarbonate ratio
E.D.	C.F.	8.0 (F)	1.0	3.4	0	3.4
C.B.	C.F.	6.0 (F)	0.5	2.8	0	5.6
L.A.	C.F.	17.0 (M)	0.1	0.8	0	8.0
M.A.	C.F.	14.0 (F)	0.1	0.4	0.54	4.0
S.H.	C.F.	6.0 (F)	0.3	1.2	2.61	4.0
W.H.	C.F.	18.5 (M)	1.6	3.4	12.88	2.1
C.P.	C.F.	11.5 (F)	0.7	4.8	24.70	6.8
T.A.	C.F.	8.5 (F)	6.1	6.3	33.41	1.03
A.H.	Malabsorption	11.5 (M)	21.2	9.2	49.15	0.43
S.H.	Pancreatitis	11.0 (M)	12.6	7.5	18.13	0.6
J.M.	Failure to thrive, diarrhea	8.0 (M)	17.3	17.0	52.37	0.96
R.N.	Hepatitis	7.5 (M)	14.2	10.8	47.27	0.76
K.O.	Pancreatitis	11.0 (F)	9.6	5.2	53.79	0.54
B.P.	Gastrointestinal reflux	6.0 (F)	12.0	7.7	28.77	0.64
			* $P < 0.05$	* $P < 0.05$	* $P < 0.25$	* $P < 0.001$

* P values refer to comparisons of data between the CF patients and controls.

unfavorable electrochemical gradients created by the inability of the principal co-ion, Cl^-, to follow Na in the reabsorptive process (4).

We are greatly handicapped by the lack of a good understanding of how and where the HCO_3^--rich fluid in pancreatic juice is elaborated. Nonetheless, in view of the genetic nature of this disease and the fact that abnormally low Cl permeability has also been demonstrated recently in another target tissue, the respiratory tract (5), it seems reasonable that an abnormality in Cl permeability may also be present in the CF pancreas. Accordingly, the data presented here by Applegarth and coworkers as well as others (6, 7) might be explained as well in similar terms. That is, the inability to absorb Cl in the sweat duct results in the inability to reabsorb Na. Likewise, available data on the pancreas suggests that the inability to absorb Cl in the pancreatic duct may result in the inability to secrete HCO_3^-.

This suggestion would require that Cl^- (and Na^+ and HCO_3^-) move through electroconductive pathways. If this pathway is blocked to Cl^- in the pancreas as it is in the sweat duct and respiratory tissues, we would expect more negative luminal potentials in the CF pancreas. Although such measurements may be technically difficult, they should be extremely informative in testing the hypothesis if they can be obtained.

In response to the authors comment regarding our earlier suggestion that abnormal electrolyte transport in CF may involve a Cl^-/HCO_3^- exchange, we must point out that the more recent electrophysiologic data cited above make it very unlikely that the exchange is closely coupled, at least in the sweat duct. It seems more likely that Cl^- and HCO_3^- may be coupled electrically, but not chemically.

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Letter to the Editor

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The authors of the recent article on increased bone turnover in osteogenesis imperfecta (1) appear to have overlooked a publication of mine (2) in which this question was approached in a different manner. The authors (1) used tetracycline labelling and histomorphometric techniques to show that bone formation rate was increased, as were active osteoclastic and osteoblast surfaces and osteoclast number. My associates and I used a different method to assess bone turnover, namely the rate of release of a "bone-seeker" (in this case, fluoride) in a patient with osteogenesis imperfecta (OI) whose fluoride intake was abruptly diminished.

The patient in question, a 6-yr-old boy with severe OI, was treated with NaF [1 mg F/(kg·d)] for many years in an attempt to halt the progress of his disease. Based on fluoride balance data, and F content of a bone biopsy we concluded that his body burden of F was about 5 g.

It was finally decided that the fluoride treatment was not effective, and so it was discontinued, and for the subsequent 4½ yr a number of 24-h urine samples were obtained for F analysis. Exponential analysis of these data indicated that 10% of his body burden was eliminated with a half-time of 5.4 mo and the remainder with a half-time of 8.9 yr. This latter value is of the same order of magnitude as that observed for F and other "bone-seeking" elements in normal subjects. Our data do not support the conclusions of Baron *et al.* (1); rather, they strongly suggest that bone mineral turnover is normal in this disease.

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Response

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In his letter, Dr. Forbes concludes, on the basis of one case of severe osteogenesis imperfecta, that bone mineral turnover is normal in this disease. Our quantitative data unequivocally demonstrate, in a group of nine children with mild OI, that bone formation rates are increased despite a decreased bone volume; therefore, the rate at which trabecular bone is turned over in these patients, considered as a group, is high. These observations accord with the increased hydroxyprolinuria we observed and which has previously been reported in this disease.

The first possible explanation for the discrepancy between Dr. Forbes' results and ours could relate to the type of disease because they were studying a severe case and our patients had only mild OI (Type IA). The second possibility is that even in our group some individual patients had only a marginally increased turnover rate; Dr. Forbes' case could very well be one of these. Third, the data presented in Dr. Forbes' paper on the elimination half-times for fluoride and other bone seeking agents show normal values varying 10-fold, from 1.3–10 yr in man. This might indicate that either the method lacks precision or that we might not be dealing with only bone mineral turnover but also with some other factors which affect fluoride ion metabolism.

We wonder whether strong conclusions can be drawn from one case, especially because fluoride excretion might reflect other factors as well as resorption or bone turnover. By contrast, our study dealt with a group of nine children and our measurements *directly* dealt with bone turnover. Our results clearly demonstrate that, as a group, children with Type Ia OI remodel their bone at a high rate relative to their otherwise decreased bone mass.