METABOLIC STUDIES IN A CASE OF FIBROCYSTIC DISEASE OF THE PANCREAS

WITH REFERENCE TO TREATMENT AND TO THE INCIDENCE OF BONE DISEASE

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The treatment of fibrocystic disease of the pancreas has engaged much attention. Both the progress and the fate of the patient depend chiefly on the severity of the chest infection, but nevertheless it is important to discover the best way of achieving and maintaining adequate nutrition. Pancreatin is a logical remedy for a deficiency of external pancreatic secretion and its effects have been studied in many different ways. Pancreatin increases the peak of the vitamin A absorption curve (Gibbs, 1950), and enhances the rise in plasma glycine following oral gelatine (Christensen and Schwachman, 1949), indicating more rapid but not necessarily more complete absorption. By measuring faecal radioactivity after the ingestion of I^{131} labelled protein (Lavik, Matthews, Buckaloo, Lemm, Spector and Friedell, 1952) and I^{131} labelled corn oil (Spector, Matthews, Lemm, Van Erp and Cline, 1958), more complete absorption of these substances with pancreatin has been demonstrated.

The effect of pancreatin on fat balance is not uniform. Ross (1955) found that the mean faecal fat fell from 50% to 27% of the intake in 22 cases, whereas Shohl, May and Schwachman (1943) found little or no change. This discrepancy has been attributed to variation in the lipase activity of different batches of pancreatin (Andersen, 1945a). However, absence of pancreatic lipase may not be the only cause of the steatorrhoea, since a defect in the absorption of free fatty acids has been shown by isotope studies using C^{13} (Blomstrand, Lindquist and Pääbo, 1955) and I^{131} (Reemtsma, di Sant' Agnese, Malm and Barker, 1958). The effect of pancreatin on nitrogen balance seems to be more constant; the most convincing study is that of Harris, Norman and Payne (1955) who, in a study of 12 cases, found a fall in mean faecal nitrogen from 4.62 g. to 2.16 g. daily. Pancreatin also lowers faecal nitrogen and fat in the pancreatic deficiency of chronic pancreatitis (Beazell, Schmidt and Ivy, 1941)

and pancreatic resection (Wollaeger, Comfort, Clagett and Osterberg, 1948).

Despite this impressive body of evidence, many clinicians think it unwise to give pancreatin a prominent place in treatment. In a recent review of all published balance studies, Lowe and Pessin (1959) stated that the effect of pancreatin was small and not statistically significant. Furthermore, pancreatin may depress the voracious appetite by which the patient normally compensates for the absorptive defect (May, 1954), although in spite of the large appetite, the protein content of the diet may not be increased in proportion to its total bulk (Stowens, 1951). It is certainly true that many of the published balance studies are open to methodological criticism because of inadequate equilibration and too short a period of observation.

The state of the bones in fibrocystic disease has received little attention. In a review of 131 cases (Lowe, May and Reed, 1949) bone radiographs were taken in 44 cases. 'Osteoporosis' was found in 18 cases and retarded bone age in 14 cases; apart from an occasional serum calcium of 8.9 mg./100 ml., relevant biochemical tests were normal. In one instance the radiographs showed rickets; unfortunately no biochemical data were recorded in this case. Radiological evidence of osteoporosis has been found in many other cases (Andersen, 1938). Histological evidence of rickets was found in one case who died at 2 years (Oppenheimer, 1956); other post-mortem examinations of the skeleton have revealed no abnormality (Zuelzer and Newton, 1949; Bodian, 1952). Only one other case of infantile rickets in fibrocystic disease could be found in the literature, but at a time when nutritional rickets was common (Siwe, 1932). Late rickets has never been described. In keeping with the rarity of rickets is the fact that tetany has never been reported. The absence of rickets has usually been attributed to failure of longitudinal growth (Andersen, 1938), but

this explanation is unlikely because growth is often not severely retarded and may improve with treatment. For example, four out of 16 surviving treated cases of Andersen (1945b) were on or above the 50th percentile for height, and none of the autopsy cases of Bodian (1952) were more than one standard deviation below average height.

It is the purpose of this paper to report the results of a prolonged metabolic study in a case of fibrocystic disease, to consider the implications of the results for treatment and to put forward an alternative explanation for the rarity of rickets in this disease.

Case Report

D.R. was born on June 4, 1954, delivered at full term by caesarean section because of foetal distress. His birth weight was 8½ lb. (3.9 kg.) and this was not regained for 17 days. From birth his stools were loose, bulky, greasy and offensive, and despite a large appetite he gained weight slowly and irregularly. He received the usual cod liver oil and orange juice supplements and later was given 'adexolin' capsules (each containing vitamin A 6,000 units and vitamin D 1,000 units) regularly. At 6 months he developed a persistent dry cough, but he never had bronchitis or pneumonia. At 1 year he developed a rectal prolapse. He walked at 18 months and thereafter was normally active. His legs were always bowed but never painful. At 4 years he saw an orthopaedic surgeon because of difficulty in walking. Radiographs showed irregularity of the proximal metaphyses of both femora with some slipping of both epiphyses. He was thought to have rickets and was admitted to Chase Farm Hospital under Dr. C. A. Birch on September 1, 1958. His stools contained visible fat, and tryptic activity was not detected at a dilution of 1:10. A finger print test (Schwachman and Gahm, 1956) was positive. A diagnosis of fibrocystic disease of the pancreas was made and the patient was given pancreatin triple strength 16.5 g. daily, increasing to 21 g. daily, with vitamin A 100,000 units and vitamin D 18,000 units daily.

On November 14, 1958, the patient (now aged 4 years 5 months) was admitted to the metabolic ward of the Royal National Orthopaedic Hospital. On examination he was a thin, pale, underdeveloped child with a pot belly (girth 23 in. (58.4 cm.)) and clammy extremities. His weight was 35½ lb. (16.1 kg.) and height 39 in. (99.1 cm.). The skull circumference was 21 in. (53.3 cm.) and there was slight frontal bossing. The tibiae were bowed laterally with genu varum (gap between knees 1½ in. (3.2 cm.)). The sternum was slightly depressed and there were shallow Harrison's grooves. None of the epiphyses were tender. His appetite was voracious, and his stools were loose and bulky. Examination of the blood showed: Haemoglobin 11.7 g./100 ml.; white blood cell count 17,000/c.mm. with 69% neutrophils; calcium 9.1 mg./100 ml., phosphorus 5.3 mg./100 ml., alkaline phosphatase 9.5 King-Armstrong units; urea 27 mg./100 ml., cholesterol 110 mg./100 ml., albumin 3.5 g./100 ml., globulin 2.8 g./100 ml.,

sodium 137 mEq/litre, potassium 4.5 mEq/litre, chloride 109 mEq/litre, bicarbonate 26 mEq/litre and bilirubin 0.73 mg./100 ml. Glucose tolerance test: fasting level 68 mg./100 ml. rising to 126 mg./100 ml. at one hour. The urine specific gravity range was 1,000-1,024, and 96% of a water load (20 ml. per kg. body weight) was excreted in four hours. Analysis of sweat obtained by the method of Finch (1957): total sweat 3.8 g., sodium concentration 88 mEq/litre, chloride concentration 94 mEq/litre. Radiographs of skull, feet, hands and chest were normal. Radiographs of knees showed sclerosis of upper tibial metaphyses. The bone age was 3 years 6 months.

Plan of Metabolic Study

This was conducted in accordance with methods previously described (Nassim, Saville, Cook and Mulligan, 1959). Urine and stools were collected in six-day periods, the stools being demarcated with carmine. Vagaries of appetite necessitated changes in the diet at the beginning of periods 5 and 12. The diet contained approximately 1,750 calories and 75 g. fat daily. The patient was not confined to bed except during episodes of chest infection which were treated with appropriate antibiotics and 'tryptar' inhalations (as shown in Fig. 1) without interrupting the balance. The pancreatin used was in the form of triple-strength enteric-coated granules;* each 100 g. contains 4.5 g. nitrogen, 550 mg. phosphorus and 70 mg. calcium.

Periods 1-4. Normal diet, no special treatment. (This was followed by a short break for Christmas, during which the first episode of chest infection occurred. The rest of the periods were consecutive.)

Periods 5-8. Gluten-free diet (G.F.D.) and calciferol 0.05 mg. daily by mouth.

Periods 9-11. G.F.D. and calciferol 2.5 mg. daily by mouth.

Periods 12-14. As for periods 9-11, and calciferol 2.5 mg. every three days by injection.

Periods 15-21. As for periods 9-11, + nor-testosterone phenyl propionate ('durabolin') 25 mg. i.m. every six days.

Periods 22-26. As for periods 15-21, + pancreatin 10 g. daily.

Periods 27-31. As for periods 15-21, + pancreatin 20 g. daily.

Period 32. As for periods 27-31, but gluten reintroduced into diet.

Periods 33-36. As for period 32, + thyroid gr. 1 daily.

Results

The amounts of calcium phosphorus and nitrogen in diet, urine and stools, and fat in stools, for each six-day period, together with successive and cumulative balances, are given in Table 1. Average values for each group of periods corresponding to a different therapeutic regime are given in Table 2,

* From Messrs. Clay and Abraham.

FIG. 1.—Metabolic data in relation to treatment.

together with mean values for absorption (diet—faecal excretion), balance (diet—faecal and urinary excretion) and utilization (balance/absorption $\times$ 100). For comparison, mean values for normal children of the same age are included (Macy, 1951). The average values are charted according to the method of Reifenstein, Albright and Wells (1945), together with serial observations of height and weight (Fig. 1). Cumulative balances, constructed from individual data, are charted in Fig. 2.

Consistency and Reliability of Data. In periods 1-14 the observed total phosphorus balance was -164×6 mg. and the theoretical balance expected from the nitrogen and calcium balances (Reifenstein *et al.*, 1945) $+815 \times 6$ mg., an average discrepancy of -70 mg. daily. In periods 15-36 when growth was occurring, the observed total balance was $+2,319 \times 6$ mg. and theoretical balance $+2,912 \times 6$ mg., an average discrepancy of -27 mg. daily.

The total nitrogen retention was 244.5 g. (40.75

FIG. 2.—Accumulative balance data.

× 6); and the corresponding gain in weight 3,405 g. (7½ lb.). Even if this gain was all due to protoplasm, the expected nitrogen retention would only be 110 g. Unmeasured nitrogen loss occurred from the skin and in blood taken for analysis, but this was estimated to be less than 30 g. Both of these discrepancies could be accounted for by an error in the nitrogen intake of 0.6 g. daily. However, similar discrepancies were noted by Macy (1942), and it is possible that the conversion factor of 1 g.

of nitrogen to 32 g. of protoplasm (Reifenstein *et al.*, 1945) does not apply to growing children, particularly if they are initially depleted of nitrogen.

Comments on and Conclusions from Metabolic Data. A gluten-free diet was without effect. There was no deterioration when gluten was reintroduced into the diet in period 32, in contrast to the findings in coeliac disease (Nassim *et al.*, 1959).

In control periods 1-4 the faecal calcium was high

TABLE 1
METABOLIC DATA: INDIVIDUAL RESULTS

Period	Ca (mg./day)					P (mg./day)					N (g./day)					Fat (g./day)
	Intake	Faecal Excretion	Urinary Excretion	Individual Balance	Cumulative Balance*	Intake	Faecal Excretion	Urinary Excretion	Individual Balance	Cumulative Balance*	Intake	Faecal Excretion	Urinary Excretion	Individual Balance	Cumulative Balance*	
1	885	629	37	+219	+219	1,036	218	775	+43	+43	10.80	3.91	5.61	+1.28	+1.28	34.0
2	"	755	31	+99	+318	"	248	800	-12	+31	"	4.30	6.15	+0.35	+1.63	39.0
3	"	867	29	-11	+307	"	293	796	-53	-22	"	4.66	6.02	+0.12	+1.75	42.4
4	"	733	40	+112	+419	"	279	820	-63	-85	"	4.33	6.27	+0.20	+1.95	39.6
5	1,185	1,100	25	+60	+479	1,283	342	943	-2	-87	10.00	3.77	5.78	+0.45	+2.40	43.4
6	"	1,080	25	+80	+559	"	319	833	+131	+44	"	3.62	5.02	+1.36	+3.76	40.4
7	"	1,250	36	-101	+458	"	367	906	+10	+54	"	4.20	5.28	+0.52	+4.28	56.0
8	"	1,189	32	-36	+422	"	314	998	-29	+25	"	3.52	5.73	+0.75	+5.03	44.0
9	"	1,255	37	-107	+315	"	315	956	+12	+37	"	3.80	5.82	+0.38	+5.41	50.0
10	"	785	39	+361	+676	"	243	922	+118	+155	"	3.00	5.48	+1.52	+6.93	40.0
11	"	1,150	68	-33	+643	"	360	989	-66	+89	"	4.26	5.96	-0.22	+6.71	62.0
12	1,180	944	52	+184	+827	1,244	309	924	+11	+100	8.50	3.09	5.03	+0.38	+7.09	40.0
13	"	1,000	60	+120	+947	"	436	876	-68	+32	"	3.51	4.57	+0.42	+7.51	43.6
14	"	1,226	80	-126	+821	"	341	1,099	-196	-164	"	3.82	5.64	-0.96	+6.55	40.6
15	"	1,000	63	+117	+938	"	320	778	+146	-18	"	3.50	4.32	+0.68	+7.23	46.0
16	"	894	39	+247	+1,185	"	270	763	+211	+193	"	2.28	3.90	+2.32	+9.55	34.8
17	"	1,050	42	+88	+1,273	"	238	837	+169	+362	"	3.15	3.43	+1.92	+11.47	42.4
18	"	1,110	43	+27	+1,300	"	300	841	+103	+465	"	3.72	3.39	+1.39	+12.86	45.0
19	"	1,155	53	-28	+1,276	"	236	945	+63	+528	"	3.22	4.05	+1.23	+14.09	43.0
20	"	1,025	60	+95	+1,367	"	240	921	+83	+611	"	3.30	4.05	+1.15	+15.24	36.6
21	"	1,110	55	+15	+1,382	"	230	973	+41	+652	"	3.65	4.11	+0.74	+15.98	43.7
22	1,200	1,240	75	-115	+1,267	1,325	221	960	+144	+796	8.92	3.00	4.57	+1.35	+17.33	50.0
23	"	936	75	+189	+1,456	"	174	980	+171	+967	"	2.00	5.17	+1.75	+19.08	31.6
24	"	1,090	75	+35	+1,491	"	223	1,010	+92	+1,059	"	2.40	5.13	+1.39	+20.47	36.0
25	"	952	60	+188	+1,679	"	198	1,125	+2	+1,061	"	2.22	5.78	+0.92	+21.39	35.5
26	"	1,115	74	+11	+1,690	"	242	1,138	-55	+1,006	"	2.74	4.52	+1.66	+23.05	38.8
27	1,210	867	74	+269	+1,959	1,380	167	1,128	+85	+1,091	9.35	1.97	5.66	+1.72	+24.77	27.7
28	"	1,035	85	+90	+2,049	"	196	1,107	+77	+1,168	"	2.50	5.48	+1.37	+26.14	37.0
29	"	1,073	86	+51	+2,100	"	230	1,026	+124	+1,292	"	2.33	5.34	+1.68	+27.82	34.5
30	"	1,035	77	+98	+2,198	"	198	1,134	+48	+1,340	"	2.14	5.76	+1.45	+29.27	34.8
31	"	1,430	83	-303	+1,895	"	258	1,140	-18	+1,322	"	2.87	5.93	+0.55	+29.82	41.6
32	1,300	1,088	83	+129	+2,024	1,408	222	1,140	+46	+1,368	10.60	2.46	5.93	+2.21	+32.03	34.7
33	"	1,290	82	-72	+1,952	"	211	986	+211	+1,579	"	2.75	5.72	+2.13	+34.16	42.2
34	"	1,115	82	+103	+2,055	"	188	1,039	+181	+1,760	"	2.67	6.26	+1.67	+35.83	36.0
35	"	1,035	87	+178	+2,233	"	198	903	+307	+2,067	"	2.27	5.16	+3.17	+39.00	30.6
36	"	1,320	88	-108	+2,125	"	230	1,090	+88	+2,155	"	2.88	5.97	+1.75	+40.75	38.0

* Cumulative balance ($\times \frac{1}{2}$).

and urine calcium low. In contrast the faecal phosphorus was normal and urine phosphorus high. This was on no treatment, but followed two months' treatment with oral vitamin D 0.45 mg. daily. There was a progressive rise in urine calcium while large doses of calciferol were given, temporarily interrupted by nor-testosterone. The changes in faecal calcium with oral and intramuscular calciferol in periods 5-14 are not statistically significant. In periods 1-16 there was a net calcium retention of 7,934 mg. despite no increase in height; in periods 17-36 there was a net retention of 5,640 mg. with an increase in height of 1.75 in. (4.45 cm.). The positive calcium balance despite absence of growth suggests that the patient had been in negative balance at some time in the past.

Calciferol did not significantly alter the blood levels of calcium, or alkaline phosphatase, but produced a slight rise in serum phosphorus (Table 3).

In periods 15-21, nor-testosterone lowered urine nitrogen, phosphorus and calcium, with increased retention of these substances and a corresponding gain in height and weight; the upward trend in urine calcium due to calciferol was temporarily interrupted. The beginning of this treatment coincided with the most severe episode of chest infection. When pancreatin was added there was a rise in urinary nitrogen and phosphorus, but utilization remained higher than before nor-testosterone was given. There was a significant fall in serum calcium and phosphorus (see Table 3), comparable to that observed in adult patients with osteoporosis treated with stilboestrol and methyl testosterone (unpublished data).

Pancreatin produced a fall in faecal nitrogen and phosphorus sustained throughout periods 22-36. Since in experimental pancreatic deficiency the percentage absorption does not vary with intake

TABLE 2
METABOLIC DATA: AVERAGES FOR EACH GROUP OF PERIODS

Periods	1-4	5-8	9-11	12-14	15-21	22-26	27-31	32-36	Normal*
Ca (mg./day)									
I: Intake	885	1,185	1,185	1,180	1,180	1,200	1,210	1,300	832 ± 117
F: Faecal excretion	746	1,155	1,063	1,057	1,049	1,067	1,088	1,170	501 ± 75
U: Urinary excretion	34	29	48	64	51	72	81	84	103 ± 31
A: Absorption (I-F)	139	30	122	123	131	133	122	130	331 ± 159
B: Balance (I-F-U)	+105	+1	+74	+59	+80	+61	+41	+46	+228 ± 182
Utilization (B/A100)	75%	3%	60%	47%	61%	46%	34%	35%	69%
P (mg./day)									
I: Intake	1,036	1,283	1,283	1,244	1,244	1,325	1,380	1,408	1,137 ± 160
F: Faecal excretion	259	335	306	362	262	212	210	210	309 ± 48
U: Urinary excretion	798	920	956	966	865	1,043	1,107	1,032	619 ± 73
A: Absorption (I-F)	777	948	977	882	982	1,113	1,170	1,198	828 ± 149
B: Balance (I-F-U)	-21	+28	+21	-84	+117	+70	+63	+166	+209 ± 186
Utilization (B/A100)	—	3%	2%	—	12%	6%	5%	14%	25%
N (mg./day)									
I: Intake	10.80	10.00	10.00	8.50	8.50	8.92	9.35	10.60	9.32 ± 0.71
F: Faecal excretion	4.30	3.78	3.69	3.47	3.26	2.47	2.36	2.61	1.04 ± 0.15
U: Urinary excretion	6.01	5.45	5.75	5.08	3.89	5.03	5.63	5.81	7.67 ± 0.98
A: Absorption (I-F)	6.50	6.22	6.31	5.03	5.14	6.45	6.99	7.99	8.28 ± 0.68
(60%)	(62%)	(63%)	(59%)	(60%)	(72%)	(75%)	(75%)	(75%)	
B: Balance (I-F-U)	+0.49	+0.77	+0.56	-0.05	+1.35	+1.42	+1.36	+2.18	+0.61 ± 0.49
Utilization (B/A100)	7%	12%	9%	—	26%	22%	19%	27%	7.4%
Fat (g./day)									
	39	46	51	41	42	38	33	38	1.4 ± 0.3

* Data from Macy (1951).

TABLE 3
SERIAL ESTIMATIONS OF SERUM CALCIUM, PHOSPHORUS AND ALKALINE PHOSPHATASE

Periods	1-4	5-8	9-14	15-21	22-26	27-31	32-36
Calcium (mg./100 ml.)	9.55 (4)	9.77 (3)	9.53 (3)	9.10 (4)	8.83 (3)	8.95 (4)	9.02 (5)
Phosphorus (mg./100 ml.)	6.15 (4)	6.33 (3)	6.40 (4)	5.68 (6)	6.41 (4)	6.35 (4)	5.98 (5)
Alkaline phosphatase (units)	11.75 (4)	13.13 (3)	12.46 (5)	12.00 (6)	13.12 (4)	14.47 (4)	15.90 (5)

Figures in parentheses refer to numbers of observations.

(Handelsman, Golden and Pratt, 1934), this parameter affords a satisfactory basis for comparison. In periods 1-21, the faecal nitrogen fell in proportion to the intake, the percentage absorption remaining fairly constant at about 60%. On pancreatin, absorption improved to 75%, so the fall in absolute faecal nitrogen was not due to changes in diet. There was a smaller but still statistically significant fall in faecal fat. There was no significant difference between 10 g. and 20 g. daily of pancreatin, either for faecal nitrogen or fat. The patient's appetite was depressed at first, but improved after a few weeks. The gain in height and weight initiated during nor-testosterone therapy continued while on pancreatin, and at the end of the study the patient was above the mean normal weight for his age. There was a slight progressive rise in alkaline phosphatase from period 22 onwards.

Thyroid in periods 33-36 produced a fall in urinary and serum phosphorus and increased retention and utilization of phosphorus and nitrogen.

Further Course and Treatment. During the last four months of his stay in hospital, the patient's general health improved considerably, he became more active and walked much better. He gained 7½ lb. (3.4 kg.) in weight and 1½ in. (4.45 cm.) in height, and his bone age increased to 4½ years by June 1959, representing a gain of three months (Table 4). At the end of the metabolic study pancreatin was temporarily stopped; this was followed by a relapse in his diarrhoea and some loss

TABLE 4
PATIENT'S BONE AGE AT DIFFERENT CHRONOLOGICAL AGES

Date	Chronological Age	Bone Age*
12.8.58	4 yrs 2 mths	3½ yrs
12.6.59	5 yrs	4½ yrs
3.5.60	5 yrs 11 mths	6 yrs

* Bone age determined by comparison of radiograph of hand with standards compiled by Greulich and Pyle (1959).

of weight. He remained well until October 1959 when he developed a severe chest infection and was admitted once more to Chase Farm Hospital. He was discharged in December, still on pancreatin, with inhalations of neomycin and polymyxin two or three times daily, but no extra vitamins. He was seen again at the Royal National Orthopaedic Hospital on May 3, 1960. His legs were now straight with no gap between the knees; his height was 3 ft. 6½ in. (107·9 cm.), his weight was 3 stone (19·05 kg.) and his bone age was 6 years. Results of biochemical tests on the blood were calcium 8·8 mg./100 ml., phosphorus 5·6 mg./100 ml., alkaline phosphatase 15·5 units, bicarbonate 25·7 mEq/litre and urea 30 mg./100 ml. Radiographs of pelvis, hands and wrists were normal.

Discussion

Our data show that pancreatin improves nitrogen (and to a lesser extent fat) absorption in fibrocystic disease. It has been argued that pancreatin cannot overcome the nitrogen wasting of infection (May and Lowe, 1948), and it could be objected that the observed improvement in retention was due to the relative freedom from infection in the latter part of the study. However, the adverse effects of infection were slight. The inadequate nitrogen balance is due to a combination of impaired absorption, for which increased protein intake and pancreatin are complementary measures, and poor utilization due to infection which can be overcome by treating the infection (Schwachman, Silverman, Patterson and Zheutlin, 1952) and by providing abundant calories (Lowe and Pessin, 1959). Our data suggest that anabolic hormones may be a useful addition to this aspect of treatment; probably intermittent short courses would be most effective.

The calcium balance data imply that calcium deficiency on a normal intake would commonly occur in fibrocystic disease, because of increased faecal excretion. This is unlikely to be due to lack of or resistance to vitamin D because of the poor response to parenteral calciferol, and because of the low faecal phosphorus (most marked in periods 22-36), in contrast to the normal or high faecal phosphorus which usually accompanies the high faecal calcium of idiopathic steatorrhoea (Nassim *et al.*, 1959), renal osteodystrophy (Liu and Chu, 1943) and resistant rickets (Saville, Nassim, Stevenson, Mulligan and Carey, 1955). The most obvious explanation for the calcium loss is the formation of insoluble calcium soaps with the excess fat in the stools. This also accounts for the lack of effect of a large dose of vitamin D. Calcium absorption was not improved by the increase in dietary calcium

from 880 mg. daily in periods 1-4 to 1,300 mg. daily in periods 32-36, or by the fall in faecal fat produced by pancreatin; presumably these changes were too small to affect the availability of soluble calcium. The data of Chung, Morales, Snyderman, Lewis and Holt (1951) suggest that with a high calcium intake (2·3 g. daily) adequate absorption is possible and, moreover, the adverse effects of extra dietary fat are mitigated.

The liability to calcium deficiency correlates with the occurrence of osteoporosis as the principal bone lesion in fibrocystic disease. Calcium deficiency produces osteoporosis in experimental animals (Harrison and Fraser, 1960), and there is much evidence, reviewed by Nordin (1960), that the result in man of prolonged calcium deficiency in the presence of adequate amounts of vitamin D is osteoporosis, not rickets or osteomalacia. In fibrocystic disease, protein deficiency may also contribute to the development of osteoporosis.

The question arises as to why vitamin D deficiency is rare in fibrocystic disease, in contrast to coeliac disease, in which rickets is commonly attributed to failure to absorb vitamin D. However, studies from this unit (Nassim *et al.*, 1959), confirmed by C. E. Dent (personal communication), have shown that the state of untreated gluten sensitivity is characterized by a resistance to the action of vitamin D, whether given by mouth or by injection. This explains why rickets may occur with mild steatorrhoea, despite the rarity of clinical deficiency of other fat soluble vitamins in coeliac disease even if severe. In contrast, in fibrocystic disease, steatorrhoea is usually much worse, and laboratory evidence of vitamin A deficiency is common. However, clinical evidence of this is rare, provided that the diet contains adequate fat and vitamin supplements (May, 1954). We suggest that clinical vitamin D deficiency is rare in fibrocystic disease for the same reason that clinical vitamin A deficiency is rare, because adequate absorption is possible with a normal fat intake and vitamin supplements, and the metabolic abnormality of coeliac disease is absent.

These considerations make it unnecessary to invoke growth failure to explain the rarity of rickets. The relation of rickets to growth is complex; although rickets is a disease of growing bones, almost complete cessation of growth is needed to prevent its occurrence. Moreover, active rickets invariably leads to slowing of the growth rate (without inducing a spontaneous cure) and, if prolonged, to permanent loss of stature. Delayed epiphyseal development without rickets may not impair ultimate height, because of prolongation of the growth period. An analysis of the data for

TABLE 5
RELATIVE IMPAIRMENT OF HEIGHT AND WEIGHT IN
FIBROCYSTIC DISEASE AND COELIAC DISEASE

	No. of Cases	Weight	Height
Fibrocystic disease* ..	17	-1.13	-1.25
Coeliac disease† (Group A) ..	16	-1.15	-1.33
Coeliac disease (Group B) ..	12	-0.70	-2.27

Expressed as standard deviations from age and sex expected means.

* Data from Andersen (1945b).

† Data from Hardwick (1939).

height and weight in fibrocystic disease (Andersen, 1945b) and coeliac disease (Hardwick, 1939) is shown in Table 5. In fibrocystic disease, both height and weight were depressed to approximately the same extent; the cases of coeliac disease could be divided into two groups: (a) in which height and weight were equally affected, resembling fibrocystic disease, and (b) in which height was much more severely retarded, although weight less severely affected. Unfortunately, it was not possible to determine the incidence of rickets in these two groups, but even so the data lend no support to the theory that retarded growth prevents rickets.

Although our patient was at one time thought on clinical grounds to have rickets, no conclusive evidence of this was obtained. The initial radiographic appearances of the bones resembled those of cretinism, but there was no other evidence of this, and the skeletal abnormality reverted to normal without thyroid (except for a short time at the end of the metabolic study). When last seen, the patient had been growing more rapidly than normal, with rapidly advancing epiphyseal development; he had not received any vitamin supplements for over a year; but, nevertheless, there was no clinical, radiological or biochemical evidence of rickets.

Summary and Conclusion

Detailed metabolic balance data in a case of fibrocystic disease of the pancreas are presented. The results confirmed that pancreatin decreased faecal nitrogen and, to a lesser extent, fat excretion; these results were independent of dietary intake or the presence of infection. 19 nor-testosterone phenyl propionate ('durabolin') decreased urine nitrogen excretion, both in the presence and absence of infection. The calcium balance data showed a high faecal calcium excretion, only very slightly improved by large doses of oral and intramuscular vitamin D; these results are considered to indicate a liability to deficiency of calcium but not of vitamin D, and this correlates with the frequency of osteoporosis and the rarity of rickets.

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