PROTEOLYTIC ACTIVITY OF THE PANCREAS

TRANSIENT DEPRESSION IN INFANCY

BY

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(RECEIVED FOR PUBLICATION JUNE 4, 1956)

The pioneer work on pancreatic function in infants was carried out by Hess (1912) and since that time many workers employing duodenal intubation have investigated pancreatic enzyme levels in malnutrition, kwashiorkor and acute infections. In recent years interest has been centred on pancreatic insufficiency in fibrocystic disease of the pancreas, in which condition the pancreatic lesion is expected to be progressive and irreversible.

Our interest in pancreatic function was stimulated by following a group of children considered, in the light of both clinical and laboratory evidence, to have fibrocystic disease of the pancreas, but who subsequently had normal levels of trypsin in the duodenal juice.

Present Investigation

Three groups of children with the following conditions were studied: A, Chronic gastro-enteritis; B, acute gastro-enteritis; C, malnutrition.

Methods

Proteolytic Activity of Duodenal Fluid. This was estimated by Andersen and Early's (1942) modification of the method of Fermi (1906).

Amino-acid Absorption Curves. These were carried out according to the procedure devised by West, Wilson and Eyles (1946). Gelatin was chosen as the source of protein, in preference to casein which others have used either wholly (Payne, 1952) or in part (West, Wilson and Eyles), because of their suggestion that with gelatin the elevation of blood amino-nitrogen is greater and more sustained, and that the curves tend to fall into more clear-cut patterns and to show greater differences between normal cases and those with pancreatic deficiency. For every kilogram of actual body weight, 1.75 g. gelatin were dissolved in 30 ml. of water. The resulting syrup, flavoured with sugar and, when necessary, with bottled orange juice, was in every case taken readily when given by bottle or spoon. The feed was given after a fasting period of not less than nine and not more than 10 hours. Blood samples were collected, with care to ensure a free flow, before the feed and at half, one and a quarter,

two and a half, and five hours after. The amino-nitrogen in the samples of whole blood was determined by the method of Frame, Russell and Wilhelmi (1943) as modified by Russell (1944). A preliminary series of control curves obtained from children known to have normal gastro-intestinal function and to be free from infection and from nutritional disturbance showed the normal configuration (Table 1) as originally described

TABLE 1
AMINO-ACID CURVES IN NORMAL INFANTS

Case	Blood Amino-acid Nitrogen (mg. 100 ml.)			
	$\frac{1}{2}$ Hour	1½ Hours	2½ Hours	5 Hours
1	5.0	5.0	4.8	4.4
2	3.1	4.1	5.8	2.8
3	2.0	4.0	2.7	1.6
4	1.1	3.8	2.7	1.6
5	2.8	3.4	4.0	2.1

by West *et al.* (1946) and by Payne (1952); a rise to a point at least 3 mg. per 100 ml. above the fasting level at some point during the first one and a quarter hours after the feed, usually sustained at or near this level until the two and a half-hour point and thereafter declining towards the fasting level. In a number of cases in which an abnormal curve was obtained, the investigation was repeated at the first opportunity, a dose of pancreatin being given before the feed. In all of these a normal curve was obtained by this means, and the probability of proteolytic insufficiency on the part of the pancreas confirmed.

Results

Group A: Chronic Gastro-enteritis. Ten children (Table 2) were studied and after initial investigations were thought to have fibrocystic disease of the pancreas. When first seen these children were between 64 and 80% of their respective expected body weights.

Eight were between 2 and 7 months of age, and two were between 2 and 2½ years old. In the younger group failure to gain weight or slow weight gain was associated with the passage of abnormal,

TABLE 2
AMINO-ACID CURVES IN CHRONIC GASTRO-ENTERITIS

Case No.	Age (mth.)	Expected Weight (%)	Clinical History			Duodenal Trypsin		
			Offensive Stools	Bouts of Acute Diarrhoea	Respiratory Infection	First Examination	Time Interval (mth.)	Second Examination
1	6	65	—	—	—	1 in 40	3	1 in 320
2	3	65	—	—	—	1 in 40	9	1 in 640
3	4	71	—	—	—	Absent	2	1 in 640
4	2	75	—	—	—	Absent	3	1 in 640
5	3	64	—	—	—	Absent	24	1 in 640
6	5	66	—	—	—	Absent	6	1 in 640
7	7	70	—	—	—	Absent	3	1 in 80
8	2	80	—	—	—	1 in 25	3	1 in 1600
9	30	65	—	—	—	Absent	24	1 in 640
10	24	70	—	—	—	1 in 40	3	1 in 640

offensive bulky stools which had been evident since shortly after birth. In five cases there had been exacerbations of a more severe diarrhoea. Repeated respiratory infections and persistent cough were present in five children. Trypsin was absent from an alkaline bile-stained duodenal juice in five, in two it was present in a dilution of 1 in 40, and in one of 1 in 25. The antithrombin titre was estimated in four patients; in two it was normal, and in two it was raised.

When the diagnosis of fibrocystic disease of the pancreas was made substitution therapy with pancreatin was given, together with a high-protein, high-calorie diet, and a satisfactory response occurred in every case.

The seventh child was 2½ years old when he presented with persistent diarrhoea, recurrent respiratory infections and nutritional oedema. Trypsin was absent from the duodenal juice and pancreatin therapy and a high-calorie, high-protein diet resulted in clinical recovery.

The eighth child was 2 years old and had suffered from bouts of diarrhoea since she was 8 months old, but at no time since then had her stools been entirely normal. She had no respiratory infections. Duodenal trypsin was present in a dilution of 1 in 40 and she failed to respond to any treatment until given pancreatin.

Reinvestigation of these children after periods varying from two months to two years, during which time they continued to have pancreatin, revealed normal duodenal trypsin levels, and satisfactory progress was maintained when pancreatin was discontinued.

The diagnosis of fibrocystic disease was discarded in every case.

Amino-acid absorption curves obtained in Cases 7, 8 and 10 during the initial investigations were similar to those found in proved cases of fibrocystic disease of the pancreas. The amino-acid absorption

curves were repeated at the same time as the second examination of the duodenal juice and normal curves were obtained (Fig. 1).

FIG. 1.—Amino-acid absorption curves in patients with chronic gastro-enteritis.

Group B: Acute Gastro-enteritis. Nine infants, aged between 2 months and 1 year, suffering from acute gastro-enteritis were studied (Table 3).

Six of the children were up to their optimum weights before the onset of the illness, one was 76% and two between 65 and 75% of their respective expected weights.

Eight of the children lost 7% or over of their body weights in the course of the illness (minimum 7%, maximum 25%) and in each of these patients a moderately low amino-acid absorption curve was

TABLE 3
AMINO-ACID CURVES IN ACUTE GASTRO-ENTERITIS

Case No.	Age (mth.)	% Expected Body Weight on Admission	Weight Loss (% max. weight)	Duration of Reduced Feeding (days)	Duration of Intravenous Fluid (days)	Relapses	Duodenal Trypsin	Initial Amino-acid Absorption Curves (mg. blood amino-acid N ₂ 100 ml.)			
								½ Hour	1½ Hour	2½ Hour	5 Hour
11	7	100	18	21	3	1	Not estimated	1.1	1.5	1.3	0.8
12	4	100	11	13	0	0	1 in 1,600	1.0	1.2	1.2	1.6
13	3½	95	7	7	0	0	1 in 1,280	0.8	0.3	1.3	1.0
14	12	65	9	10	0	0	1 in 1,280	4.2	4.2	4.6	3
15	5	90	9.5	14	0	0	Not estimated	1.3	0.7	1.8	2.2
16	4	100	25	26	3	3	Not estimated	0.9	1.4	1.4	1.1
17	2	90	20	25	7	2	1 in 320	0.9	1.2	0.9	2.2
18	3	76	2.5	5	0	0	1 in 400	0.5	3.5	3.2	3.5
19	8	72	11	10	0	0	1 in 800	1.2	1.6	2	2

obtained within one week of the cessation of the diarrhoea. The periods of restricted feeding had ranged from seven to 26 days.

One child (Case 18) had mild enteritis, had started treatment within 24 hours of the onset, her feeds were restricted for five days, she lost only 2.5% of her body weight and her amino-acid absorption curve was normal. The three children (Cases 11, 16 and 17) with heavy weight losses (18%, 25% and 20% of their respective body weights) were those who relapsed and were treated with intravenous fluid therapy.

The duodenal trypsin was estimated in six of the patients and was found to be within normal limits. Nevertheless, two children (Cases 17 and 19) who failed to gain weight satisfactorily after full feeding had been resumed for three weeks, were given pancreatin for the subsequent three weeks, during which time the rate of gain improved:

	Weight Gain in Three Weeks, on Full Feeding	Weight Gain in Three Weeks, on Full Feeding — Pancreatin
Case 17	1 lb.	1½ lb.
Case 19	2 oz.	1 lb.

In four patients the gelatin meals were repeated when clinical recovery was complete and weight

gains were satisfactory, and in each case the curve had risen towards normal levels (Fig. 2).

Group C: Malnutrition. Eight malnourished children, aged between 2 and 14 months, were

FIG. 2.—Amino-acid absorption curves in patients with acute gastro-enteritis.

TABLE 4
AMINO-ACID ABSORPTION CURVES IN MALNUTRITION

Case No.	Age (mth.)	% Expected Body Weight	Duodenal Trypsin	Average Daily Weight Gain (oz.) over Period (2-4 wk.)		Initial Amino-acid Absorption Curves (mg. amino-acid N ₂ /100 ml.)			
				High Calorie Feeding	High Calorie Feeding — Pancreatin	½ Hour	1½ Hours	2½ Hours	5 Hours
20	14	66	1 in 320	0.5	1.3	1.7	2.2	1.9	0.6
21	4½	76	Not estimated	0.4	0.8	0.2	2.7	2.4	0.3
22	3½	74	1 in 400	0.5	1.2	2.6	1.1	1.9	3.0
23	8	69	Not estimated	1.2	—	0.2	1.9	2.4	2.3
24	14	70	Not estimated	1.0	—	0.8	1.3	0.8	1.3
25	2	72	Not estimated	1.0	—	1.7	1.2	1.6	1.6
26	3	75	1 in 50	0.8	1.2	0.1	0.3	0.5	0.8
27	4	73	1 in 400	1.2	—	0.8	1.5	2.2	3.8

studied (Table 4). Infections and congenital and endocrine abnormalities were excluded, and the malnutrition was considered due to underfeeding either from mismanagement or neglect. Their weights varied from 69 to 76% of their respective expected body weights, but the duration of underfeeding was difficult to assess. Breast feeding had failed early and it is probable that underfeeding dated from the introduction of artificial feeding. Mixed feeding was minimal in the older children of the group.

Duodenal trypsin was estimated in four children; in three it was well within normal limits, but in the fourth it was present in a dilution of 1 in 50. The amino-acid absorption curves varied considerably and none was normal, but normal curves together with clinical improvement were obtained after the administration of pancreatin in one case reinvestigated after an interval of three weeks, and in a second case after two weeks on full feeding without pancreatin (Fig. 3).

FIG. 3.—Amino-acid curves in two patients with malnutrition.

Discussion

Pancreatic insufficiency associated with definite pancreatic lesions has been found in rats fed on high-fat, low-protein diets (Gilbert and Gillman, 1944). The degree of the degenerative changes in the acinar tissue of the pancreas was in proportion to the duration of the dieting, and after 50 days fatty infiltration and degeneration was also found in the liver (Friedman and Friedman, 1946). Véghelyi (1950) suggested that some conditions diagnosed as fibrocystic disease of the pancreas on

a basis of pancreatic function might be late consequences of a preceding dietary lesion. He found that infants lacking animal protein in their diets suffered more or less complete pancreatic failure; the changes started after seven to fourteen days, and by eight to 12 weeks distinct fibrosis had occurred. In early cases after treatment with milk or a complete protein feed the pancreas started secreting in three to four days.

In our cases of gastro-enteritis the feeding was restricted and it was deficient in the malnutrition group, but milk protein was never completely lacking except for very short periods of starvation during therapy. This may account for the presence of duodenal trypsin in groups B and C although there was evidence of faulty protein digestion in those cases where weight loss exceeded 7% of the body weight and when feeding was restricted for seven days or longer. When weight loss had exceeded 18% of the body weight and where feeding was restricted for 21 days or longer, pancreatin therapy was beneficial despite normal levels of trypsin in the duodenal juice.

The clinical picture of the patients in Group A resembles that of fibrocystic disease of the pancreas, but when satisfactory nutrition was achieved and maintained on high-protein, high-calorie diets, together with the administration of pancreatin, the pancreatic insufficiency was found to be reversible. Thompson and Trowell (1952) reported histological pancreatic lesions in untreated cases of kwashiorkor, but in treated cases when death occurred from an intercurrent infection no pancreatic lesions were found. This suggests that malnutrition may cause degenerative changes in the pancreas, but that these changes may be reversed by adequate feeding. Similar pancreatic lesions in kwashiorkor have been reported by Davies (1948), Dean and Schwartz (1953), and Gómez, Galván, Cravioto and Frenk (1954).

Andersen (1942) stated low values of trypsin are found in marasmus but always above those seen in fibrocystic disease of the pancreas. She described three cases of marasmus with pancreatic depression and a return to normal after clinical improvement. McDougall (1950) reported five children with transient suppression of pancreatic enzyme secretion associated with prolonged diarrhoea. Pancreatic trypsin has been found deficient in scarlet fever (Véghelyi, 1949) and in parotitis (Véghelyi, 1947), and histological lesions of the pancreas, similar but not identical to those found in fibrocystic disease of the pancreas, have been found in fatal cases of uraemia (Baggenstoss, 1948). The diagnosis of deficient proteolytic activity on the part of the

pancreas is usually established by examination of the duodenal secretion, over the normal limits of whose tryptic activity there is some controversy. Activity at dilutions from 1 in 50 up to 1 in 3,200 is usually considered normal (Bodian, 1952), a range whose width blunts the sharpness and precision of the test as a means of detecting any but the grossest departures from full functional activity. As a test of pancreatic function, the amino-acid absorption curve might be expected to reveal both earlier and more accurately the transient and sometimes relatively minor deficiencies in pancreatic function such as are described above.

An attempt has been made by Gómez *et al.* (1954) to correlate duodenal trypsin levels with amino-acid curves after gelatin and casein hydrolysate feeding. They were unable to establish any numerical correlation, but observed as others have done, and as appears in this present study, that where tryptic activity is deficient the amino-acid absorption curve after gelatin is slow to reach a peak, and that a maximum level is often maintained to the end of the test period. There is, in our series, no close numerical relationship to be made out between the proteolytic activity of duodenal fluid and the amino-acid absorption curve, but it may be pointed out that of the 16 curves studied 10 were found to be abnormal according to generally accepted criteria, and that in all but one of these 10 patients proteolytic activity was present in the duodenal fluid at dilutions between 0 and 1 in 400. Of the six normal curves all but one were obtained from infants whose duodenal fluid showed proteolytic activity at dilutions greater than 1 in 400 (Fig. 4). Further investigation into this relationship is continuing; meanwhile it may be said that the amino-

acid absorption curve following the ingestion of gelatin appears to constitute a useful index of the efficiency of protein digestion.

It will be seen from Fig. 5 that the degree of

FIG. 5.—Diagram showing the percentage of expected body weight in the three groups of patients on admission to hospital. Group A, chronic gastro-enteritis, Group B, acute gastro-enteritis, Group C, malnutrition.

FIG. 4.—Diagram showing the relationship between tryptic activity of duodenal juice and the amino-acid absorption curve.

malnutrition (judged by the percentage of expected body weight) is similar in Groups A and C, and yet duodenal trypsin was not depressed in the underfed children, but was absent or greatly diminished in those with prolonged diarrhoea. The amino-acid absorption curves in group A (chronic gastro-enteritis) were uniformly lower than those in the other two groups, and indicate a more constant depression in protein digestion in those children with diarrhoea. In all cases the curves became normal or nearly normal after clinical improvement.

It was hoped that amino-acid tolerance curves following gelatin meals might differentiate fibrocystic disease of the pancreas from other nutritional disorders and be an easier and more accurate investigation than the measurement of duodenal trypsin. Our findings, however, suggest that fibrocystic disease of the pancreas should never be diagnosed on one series of investigations, even when duodenal trypsin is absent and the amino-acid

absorption curve flat. Re-assessment must be made several weeks or months later when nutrition has been improved by dieting and, if necessary, by the administration of pancreatin.

Summary and Conclusions

Attempts have been made by means of amino-acid absorption curves to estimate defects of protein digestion, and to correlate the results with levels of duodenal tryptic activity.

The proteolytic activity of the pancreas is depressed in chronic and acute gastro-enteritis and in malnutrition in infancy. Pancreatic function returns to normal when clinical recovery is reached. Caution must be exercised in diagnosing fibrocystic disease of the pancreas and pancreatic function must be re-assessed when nutrition is satisfactory.

Pancreatic depression may be expected in gastro-enteritis when weight loss exceeds 7% of body weight and when feeding is severely restricted for seven days or longer.

Oral pancreatin is beneficial in speeding up recovery after gastro-enteritis when weight loss has exceeded 18% of body weight and when feeding has been restricted for 21 days or longer. In these

patients amino-acid absorption curves are depressed despite apparently adequate levels of tryptic activity.

The amino-acid absorption curve is a more delicate measurement of depression of proteolytic activity than the estimation of duodenal trypsin.

We are pleased to acknowledge a grant towards expenses from the Research Fund of St. Mary's Hospital, London.

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