GASTRIC PROTEOLYSIS IN DISEASE

3. THE PROTEOLYTIC ACTIVITY OF GASTRIC JUICE IN CHRONIC HYPOCHROMIC ANAEMIA AND IN IDIOPATHIC STEATORRHOEA

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In chronic hypochromic anaemia the mean pepsin concentration of the gastric juice is reduced and in some patients the enzyme is totally absent (Davies, 1931; Castle, Heath, and Strauss, 1931; Meulengracht, 1932; Hartfall and Witts, 1933; Griffiths, 1934; Mullins and Flood, 1935; Aitken, Spray, and Walters, 1954). Aitken *et al.* (1954) divide their patients into those with and without achlorhydria. Complete absence of pepsin was found only among the former and the mean pepsin concentration in this group was less than a quarter of that in the patients who secreted free acid.

In idiopathic steatorrhea the pepsin concentration of the gastric juice has been determined by Pollard and Bloomfield (1930) in one case, Castle *et al.* (1931) in one case, and Aitken *et al.* (1954) in 10 cases. In six of these cases the gastric juice had a normal pepsin concentration, in four a subnormal concentration, and in two it was pepsin-free.

Slight proteolytic activity of gastric juice has also been detected at neutral pH in chronic hypochromic anaemia (Griffiths, 1934; Lasch, 1937; Jones and Wilkinson, 1938), and in idiopathic steatorrhea in remission but not in relapse (Fox, 1949).

In both diseases, therefore, a reduced secretion of pepsin confirms the evidence for gastric dysfunction which is derived from gastric mucosal biopsy and from the reduced secretion of gastric hydrochloric acid. There is, however, an underlying assumption that diminished proteolytic activity results from a simple quantitative deficiency of normal pepsin. Estimations of gastric proteolytic activity have been carried out only near pH 2 and 7. The possibility that the gastric secretion in these diseases may contain enzymes different from normal, or differing proportions of normal enzymes, as is the case

in pernicious anaemia (Taylor, 1959d), does not seem to have been considered. An investigation of this possibility is now described.

Materials and Methods

The methods and materials used have been described previously (Taylor, 1956, 1957, 1959a).

Results

Chronic Hypochromic Anaemia.—Curves of pH activity for digestion of plasma protein by gastric juice have been determined in 10 patients (Table I and Fig. 1). Of these, one secreted juice without activity below pH 5. Two gave essentially normal curves with two maxima occurring in the pH ranges 1.8 to 2.4 and 3.5 to 3.7. One patient gave a curve with three maxima, at pH 1.5, 2.9, and 3.9, which resembled curves shown by a minority of normal subjects (Taylor, 1959a). Of

TABLE I
pH MAXIMA FOR DIGESTION OF PROTEINS BELOW pH 5
BY GASTRIC JUICE OF PATIENTS WITH CHRONIC HYPOCHROMIC ANAEMIA

Subject and Substrate	pH 1.5 to 2.4		pH 2.5 to 3.2		pH 3.3 to 5.0	
	Maximum pH	Amino-acid N (mg.)	Maximum pH	Amino-acid N (mg.)	Maximum pH	Amino-acid N (mg.)
Plasma protein						
1. Histamine juice*	Inactive		Inactive		Inactive	
2. " " " "	2.4	0.53	—	—	3.5	0.48
3. " " " "	1.8	0.54	—	—	3.7	0.51
4. " " " "	1.5	0.65	2.9	0.49	3.9	0.50
5. " " " "	1.8	0.32	3.0	0.35	Declining activity	
6. " " " "	1.8	0.67	3.2	0.75	" "	
7. " " " "	1.7	0.64	3.1	0.70	" "	
8. " " " "	2.0	0.92	3.1	0.90	" "	
9. " " " "	2.2	0.56	3.2	0.50	" "	
10. " " " "	Declining activity		2.6	1.25	3.6	1.14
5% Egg albumen						
2. Histamine juice†	1.6	0.42	Declining activity		Declining activity	
6. Resting juice	1.6	0.48	" "		Inactive	

In the tables and figures the amount of liberated amino-acid N is that of the whole digest, which consisted of 5 ml. buffer, 1 or 2 ml. of gastric juice, and 1 ml. of plasma or 5% egg albumen.

* Patients with achlorhydria.

† Patients with chronic blood loss.

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FIG. 1.—Curves of pH activity for the digestion of plasma protein by the gastric juice of two patients with chronic hypochromic anaemia. One (●) had suffered chronic blood loss and one (○) from idiopathic hypochromic anaemia. 37° C., 3 hr.

TABLE II

pH MAXIMA FOR DIGESTION OF PROTEINS AT pH 5 to 8.5 BY GASTRIC JUICE FROM PATIENTS WITH CHRONIC HYPOCHROMIC ANAEMIA AND IDIOPATHIC STEATORRHOEA

Subject	Substrate	pH Maximum	Amino-acid N (mg.)
Chronic hypochromic anaemia	Plasma	7.6	0.12
		6.9	0.14
		Inactive	
		Active, no maximum	
		" Inactive "	
Idiopathic steatorrhoea	Plasma	6.8	0.08
		7.2	0.10
		7.2	0.13
	5% serum albumin	Active, no maximum	

the remaining six patients, five gave curves with two maxima, which fell within the pH ranges 1.5 to 2.2 and 2.9 to 3.2. These ranges are those associated with the proteolytic activity of pyloric mucosal extracts in normal subjects (Taylor, 1959b). The remaining patient gave a pH activity

curve with double maxima at pH 2.6 and 3.6. Such a finding has not been made in normal subjects.

Curves of pH activity for the digestion of egg albumen by gastric juice were determined in two subjects. Both showed only a single maximum at pH 1.6. One of these subjects had shown with plasma a normal digestion curve with two maxima and the other a curve of the "pyloric" type. These curves are similar to those found when normal gastric juice digests egg albumen.

Observations on the proteolytic activity of gastric juice upon plasma protein at pH 5 to 8.5 were made in seven patients of whom three exhibited no activity (Table II). Two showed slight activity at pH 7.4 to 7.7, but no maximum could be ascertained. Two gave curves with single maxima, one at pH 6.9 and the other at pH 7.6. These results do not differ from those obtained in normal subjects (Taylor, 1956, 1959c).

Idiopathic Steatorrhoea.—The gastric juice of four patients digested plasma protein below pH 5 with maxima in the pH ranges 1.5 to 1.9 and 2.8 to 3.0 (Table III, Fig. 2). These maxima are similar to those shown by human pyloric mucosal extracts. The gastric juice of one of these patients

FIG. 2.—Curves of pH activity for the digestion of protein substrates by the gastric juice of four patients with idiopathic steatorrhoea. Plasma protein (●○Δ), serum albumin (▲), 37° C., 3 hr.

TABLE III

pH MAXIMA FOR DIGESTION OF PROTEINS BELOW pH 5 BY GASTRIC JUICE OF PATIENTS WITH IDIOPATHIC STEATORRHOEA

Subject and Substrate	pH 1.5 to 2.4		pH 2.5 to 3.2		pH 3.3 to 4.0	
	Maximum pH	Amino-acid N (mg.)	Maximum pH	Amino-acid N (mg.)	Maximum pH	Amino-acid N (mg.)
<i>Plasma protein</i>						
1. Histamine juice	1.9	0.62	2.8	0.56	Declining activity	
2. " "	1.9	0.64	3.0	0.59		
3. " "	1.5	0.12	3.0	0.07		
4. " "	1.5	0.46	2.8	0.45		
<i>5% Human serum albumin</i>						
5. Histamine juice*	2.2	0.13	Declining activity		"	"
<i>2% Casein</i>						
4. Histamine juice*	1.8	0.14	2.6	0.12	"	"
<i>5% Egg albumen</i>						
4. Histamine juice*	1.6	0.14	Declining activity		"	"

* Patients with achlorhydria.

was also incubated with casein, giving a pH activity curve with maxima at 1.8 and 2.6, and with egg albumen, giving a single maximum at pH 1.6. In a fifth patient human serum albumin was used as substrate and only a single maximum at pH 2.2 was observed.

The juices, which were not bile stained, of three patients also digested plasma protein weakly at pH 6 to 8 with maxima at pH 6.8 to 7.2. In a fourth patient a very slight hydrolysis of human serum albumin at pH 7.1 could be demonstrated. These results are similar to those observed in normal subjects (Taylor, 1959c).

Discussion

Only the two patients whose anaemia resulted from chronic blood loss exhibited normal gastric proteolytic pH activity curves below pH 5, although one patient gave a curve with three maxima, which may perhaps also be considered normal. The principal difference from normal in the other patients was the occurrence of pyloric-type curves. A group of similar pyloric-type curves was found in patients with pernicious anaemia (Taylor, 1959d), a disease in which it is known that the mucosa of the body and fundus is atrophied whereas that of the pylorus may be preserved. Gross atrophy of the fundus and body of the stomach, as severe as that seen in pernicious anaemia, has also been observed in hypochromic anaemia but is relatively rare, occurring only in about 10% of patients (Lees and

Rosenthal, 1958). Severe gastric mucosal atrophy might therefore perhaps account for the inactive juice of one patient but is unlikely to account for the pyloric pattern that has been observed in as many as five of 10 patients, especially as four of them could still secrete gastric acid.

A more likely explanation of the prevalence of the pyloric pattern in hypochromic anaemia is an alteration in the proportions of "pyloric" and "fundic" pepsins (Taylor, 1959b) secreted by the non-pyloric parts of the stomach. There is evidence that the neck chief cells of the fundic glands, which histologically resemble the cells of the pyloric glands, normally secrete a different pepsin from the "true" chief cells (Linderstrøm-Lang, Holter, and Ohlsen, 1935; Linderstrøm-Lang, 1952) and there is circumstantial evidence (Taylor, 1959b) that this enzyme of the neck chief cells resembles pyloric pepsin in activity. In normal gastric juice, however, fundic pepsin from the "true" chief cells preponderates. In hypochromic anaemia there is a tendency for the neck chief cells to proliferate at the expense of the "true" chief cells. Lees and Rosenthal (1958) found that in four of 19 patients there was "marked replacement of normal by pseudo-pyloric glands." Such a replacement of "true" chief cells by cells of the pyloric type might result in "pyloric" pepsin becoming the predominant enzyme, and it would thus be possible to explain the pyloric type of pH activity curve which has been observed.

In idiopathic steatorrhea gastric mucosal atrophy varies from slight to very severe, and it is possible that a similar explanation to that advanced in hypochromic anaemia may account for the predominance of pyloric-type proteolytic pH activity curves.

Only in one patient with hypochromic anaemia (No. 10) and one with idiopathic steatorrhea (No. 5) is it impossible to explain the proteolytic pH activity curves in terms of normally occurring gastric enzymes. In both these patients, and especially in No. 10, whose gastric juice was very active, the deviation from normal is unlikely to be erroneous, and the possibility that abnormal pepsins may have been elaborated arises. In general, however, it is evident that in hypochromic anaemia and idiopathic steatorrhea the abnormal gastric proteolytic pH activity curves are adequately explained by postulating the secretion of abnormal proportions of normal enzymes so that these diseases stand in contrast to pernicious anaemia, in which some abnormal curves can only be explained by postulating the synthesis of abnormal and pathological pepsins.

Summary

The proteolytic activity of the gastric juice from 10 patients with chronic hypochromic anaemia and five patients with idiopathic steatorrhoea has been investigated at pH 1.5 to 8.

The pattern of activity at pH 5 to 8.5 did not differ from that of normal subjects.

Below pH 5 only three patients with hypochromic anaemia exhibited normal pH activity curves. One secreted inactive gastric juice. Five patients with hypochromic anaemia and four with idiopathic steatorrhoea exhibited pH activity curves resembling those of normal pyloric mucosal extracts.

It is suggested that in both diseases these pyloric-type curves result from the secretion of pyloric-type pepsin from the gastric mucosa in relatively increased amounts.

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