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QUANTITATIVE MEASUREMENTS OF PEPSIN IN GASTRIC JUICE BEFORE AND AFTER HISTAMINE STIMULATION

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While the chloride and other inorganic constituents of the gastric juice have been thoroughly studied by many workers, few observations on pepsin are on record. The inadequacy of knowledge about this substance is doubtless due to lack of suitable methods inasmuch as accurate pepsin determinations, as a rule, have not been available in the clinic. In another paper (1) we have described a quantitative method for the estimation of pepsin which has been found to be serviceable and fairly accurate and the present report deals with the application of this procedure to the study of gastric secretion in patients.

During the course of analyses of pure gastric juice, obtained both with the stomach at rest and after histamine stimulation, it was found (2) that the secretion of various constituents did not run parallel with one another. Concentration of chloride and total output of chloride rose after stimulation but concentration of nitrogen and of fixed base fell although the total output was somewhat increased at the height of secretion. With regard to pepsin, then, we desired to determine: (a) the actual amounts put out by normal people and those with gastric disease, and (b) whether there was a quantitative relation between the curve of pepsin secretion and that of other elements such as nitrogen. No data bearing on either of these points were found in the literature since such pepsin estimations as are recorded have usually been made on mixtures of gastric juice and test meal and not on pure gastric juice. The true relations are therefore obscured. Lim, Matheson and Schlapp (3) report some observations on pepsin before and after histamine stimulation by estimating the time necessary to digest an egg white suspension. They state that the concen-

tration is usually little altered after stimulation although it is sometimes greatly increased and that no definite relationship has been found with the other constituents of the gastric juice. This is at variance with our findings.

PROCEDURE

The subjects were all in bed in the hospital. After an over-night fast, a duodenal tube was inserted into the stomach and the fasting contents were withdrawn. The total secretion over ten-minute periods before and after an injection of histamine (0.1 mgm. per 10

TABLE 1
Data from Case 1

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|-------------------------------------|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| <i>cc.</i> | | | | <i>mgm. per 100 cc.</i> | | |
| 35 | Clear—some mucus (fasting contents) | | | | | |
| 13 | Clear, limpid, some mucus | 25 | 35 | 90.8 | 735 | 9,490 |
| Histamine 0.6 mgm. | | | | | | |
| 10 | Clear, thin, some mucus | 85 | 98 | 106 | 1,540 | 15,300 |
| 39 | Clear, thin, some mucus | 114 | 120 | 59.8 | 1,240 | 48,750 |
| 32 | Clear, thin, some mucus | 126 | 132 | 42.2 | 790 | 25,600 |
| | Part of specimen bile stained | 128 | 132 | | 710 | |
| 24 | Clear | 128 | 132 | 42.2 | 690 | 16,500 |

kilos body weight) was then collected exactly as previously described (2). The following determinations were made: (a) titratable acidity, (b) pepsin, and (c) total nitrogen. Titratable acidity was determined with di-methyl in the usual way, total nitrogen (Kjeldahl) is expressed in milligrams per 100 cc., and pepsin in terms of the number of milligrams of edestin digested by one cubic centimeter of gastric juice in 30 minutes.

RESULTS

Case 1. A man, age 27, was convalescent from a mild acute enteritis. He was to all intents and purposes well and had never had

any symptoms of gastric disease. The results of the examination are shown in table 1 and chart 1. The volume of secretion, the acid

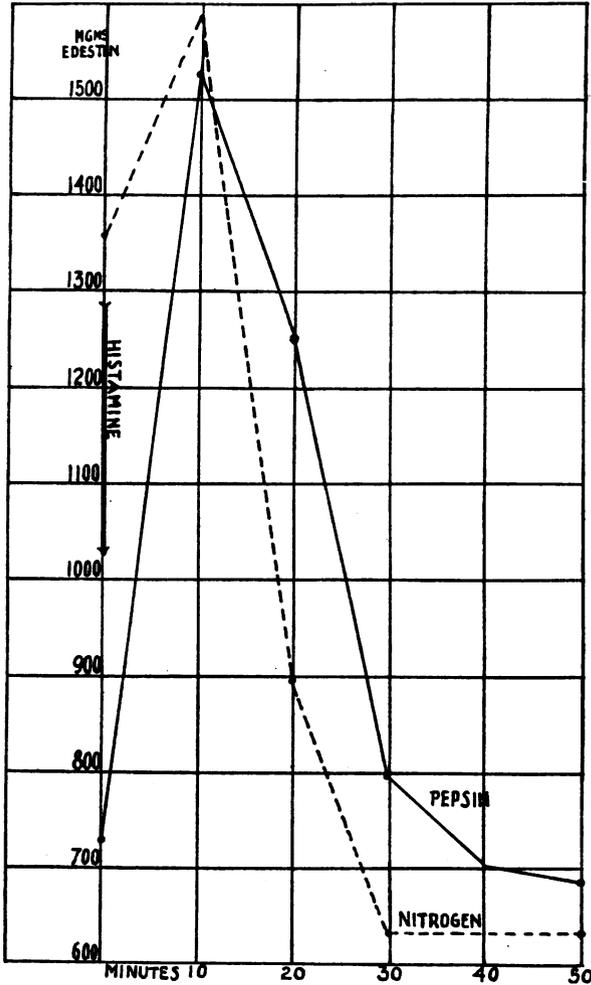


CHART 1. CURVES OF NITROGEN AND PEPSIN CONCENTRATIONS FROM CASE 1 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

values, and the nitrogen values which show the typical fall in concentration after stimulation were all normal. The degree of peptic

activity is measured in terms of milligrams of edestin digested by 1 cc. of juice. It is seen that the concentration of pepsin not only falls after stimulation in spite of increased volume of secretion, but that the curve of pepsin concentration at various intervals almost parallels that of nitrogen when both are reduced to a corresponding scale by multiplying the nitrogen values (milligrams per 100 cc.) by 15. Unless otherwise indicated, nitrogen values are expressed in this way in all the charts.

TABLE 2
Data from case 2

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|-----------------------------|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| <i>cc.</i> | | | | <i>mgm. per 100 cc.</i> | | |
| 20 | Colorless, mucoid | | | | | |
| 18 | Colorless, mucoid | 45 | 69 | 102.0 | 1,730 | 31,140 |
| Histamine 0.5 mgm. | | | | | | |
| 15 | Thin, colorless, some mucus | 86 | 107 | 81.0 | 1,610 | 24,150 |
| 18 | Thin, colorless, some mucus | 115 | 128 | 58.5 | 1,030 | 18,540 |
| 19 | Thin, colorless, some mucus | 120 | 131 | 49.5 | 860 | 16,340 |
| 15 | Thin, colorless, some mucus | 126 | 138 | 61.5 | 977 | 14,620 |
| 11 | Thin, colorless, some mucus | 118 | 130 | 63.0 | 1,010 | 11,110 |

Case 2. A man, age 24, East Indian, entered the hospital for nervousness. No evidences of organic disease of any sort were found. The results of the examination are shown in table 2 and chart 2. The volume of secretion, the acidity and the nitrogen output were all normal. As in case 1, the concentration of pepsin fell markedly after stimulation and paralleled the fall in nitrogen concentration very closely.

Case 3. A man of 23 years, entered the Hospital for minor complaints and showed no evidence of organic disease. The volume of gastric secretion was rather high but not abnormal; acidity and nitrogen were within the usual range. Here again, after stimulation,

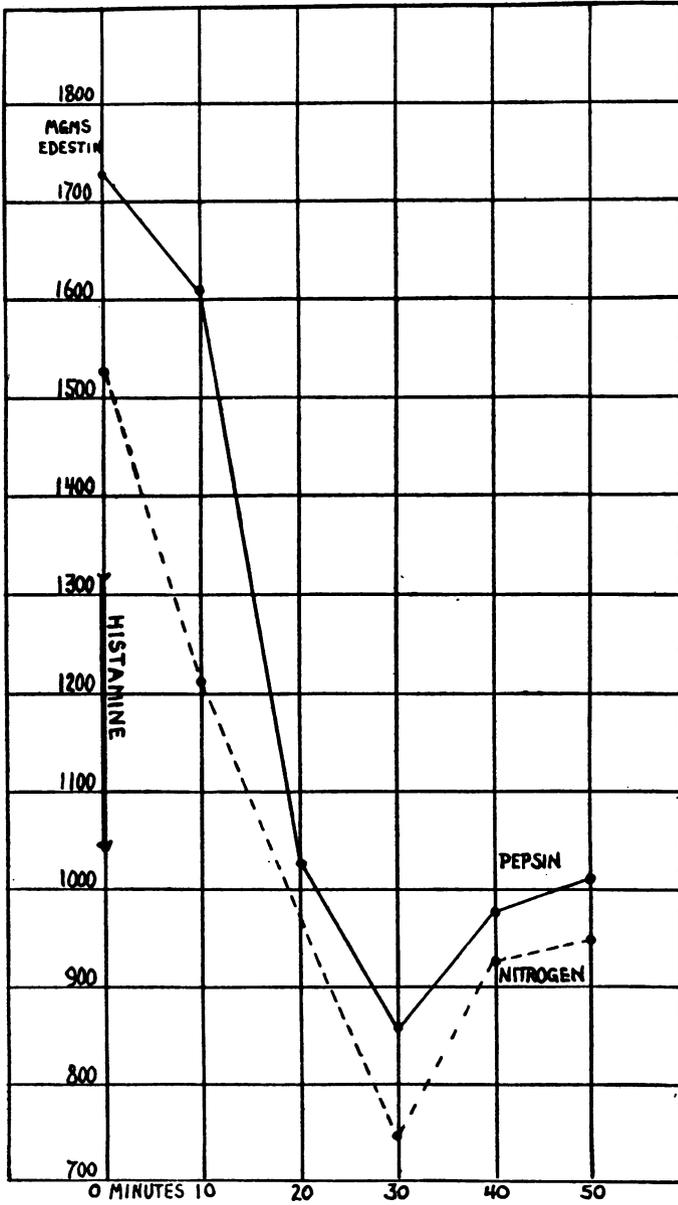


CHART 2. CURVES OF NITROGEN AND PEPSIN CONCENTRATION FROM CASE 2 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

there was a striking fall in concentration of pepsin which ran parallel to the fall in nitrogen (table 3, chart 3).

Case 4. A man, age 19, had disseminated lupus erythematosus. There were no gastric symptoms nor evidences of disease of the stomach. The volume of secretion, acidity and concentration of nitrogen were within normal limits. In this case again the concentration of pepsin fell after stimulation and paralleled the nitrogen concentration although the curves do not correspond as closely as in

TABLE 3
Data from case 3

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|---------------------------------------|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| <i>cc.</i> | | | | <i>mgm. per 100 cc.</i> | | |
| 23 | Slightly bile tinged fluid some mucus | | | | | |
| 8 | Colorless—some mucus | 35 | 52 | 112.5 | 1,495 | 11,960 |
| Histamine 0.6 mgm. | | | | | | |
| 12 | Colorless—considerable mucus | 75 | 90 | 127.5 | 2,075 | 24,900 |
| 23 | Water clear fluid | 110 | 116 | 58.5 | 1,220 | 28,060 |
| 42 | Water clear fluid | 121 | 126 | 46.5 | 720 | 30,240 |
| 32 | Water clear fluid | 118 | 122 | 36.0 | 605 | 19,200 |
| 31 | Water clear fluid | 103 | 112 | 46.5 | 660 | 20,460 |

the three previous cases. The maximum concentration of pepsin, furthermore, is considerably lower than in cases 1, 2 and 3.

Case 5. A man of 32 had a penetrating ulcer of the lesser curvature of the stomach. The acidity was within normal limits but the volume of gastric secretion was distinctly high. The pepsin concentration again runs parallel to the nitrogen concentration but is lower than in the normal cases 1, 2 and 3. The low concentration of pepsin is largely explained by the high volume of secretion; the total output of pepsin is not low (see chart 9).

Case 6. A man, age 32, was convalescent from a mild attack of influenza. There were no digestive symptoms and the temperature

had been normal for several days at the time of the test. The findings on gastric analysis were of interest since the acid values were distinctly low, while the volume of secretion was well above the average. Fur-

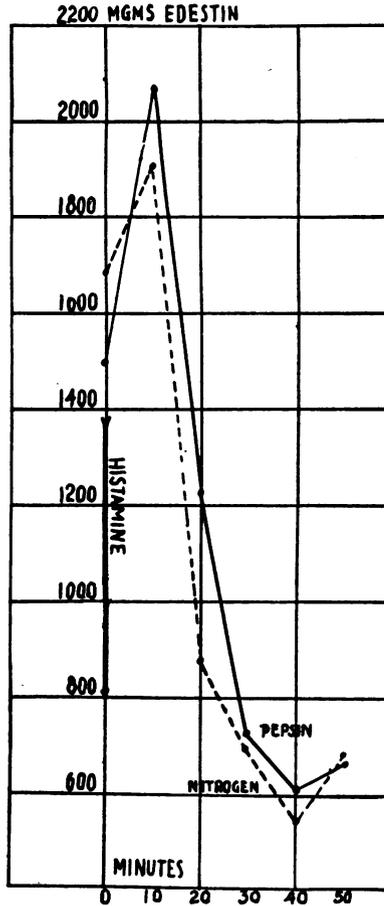


CHART 3. CURVES OF NITROGEN AND PEPSIN CONCENTRATION FROM CASE 3 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

thermore, the gastric juice was unusually viscid and it was suspected that the nitrogen values would be high. The concentration of pepsin was distinctly lower than in cases 1, 2 and 3, but showed the usual drop

TABLE 4
Data from case 4

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|--|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| cc. | | | | <i>mgm. per 100 cc.</i> | | |
| 50 | Bile stained, mucoid | | | | | |
| 22 | Thin fluid, slightly bile tinged, mucoid | 35 | 50 | 75.0 | 680 | 14,960 |

Histamine 0.6 mgm.

| | | | | | | |
|----|--|-----|-----|------|-----|--------|
| 16 | Thin fluid, faint brownish (blood) tinge | 35 | 50 | 84.0 | 950 | 15,200 |
| 20 | Thin fluid, faint brownish (blood) tinge | 110 | 110 | 53.4 | 870 | 17,400 |
| 26 | Thin fluid, faint brownish (blood) tinge | 135 | 145 | 42.6 | 750 | 19,500 |
| 16 | Thin fluid, faint brownish (blood) tinge | 130 | 140 | 43.5 | 530 | 8,480 |
| 10 | Thin fluid, faint brownish (blood) tinge | 118 | 125 | 55.0 | 810 | 8,100 |

TABLE 5
Data from case 5

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|---|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| cc. | | | | <i>mgm. per 100 cc.</i> | | |
| 30 | Thin fluid, very slight bile tinge—some mucus | | | | | |
| 22 | Colorless fluid, some mucus | 94 | 100 | 52.5 | 365 | 8,030 |

Histamine 0.6 mgm.

| | | | | | | |
|----|-------------------|-----|-----|------|-----|--------|
| 26 | Water clear fluid | 86 | 93 | 29.4 | 405 | 10,530 |
| 38 | Water clear fluid | 119 | 124 | 43.5 | 595 | 22,610 |
| 55 | Water clear fluid | 126 | 130 | 35.1 | 350 | 19,250 |
| 45 | Water clear fluid | 128 | 133 | 28.5 | 345 | 15,525 |
| 35 | Water clear fluid | 118 | 125 | 27.9 | 290 | 10,150 |

after stimulation. The curve also ran parallel with nitrogen concentration but when the nitrogen values were charted as in the previous

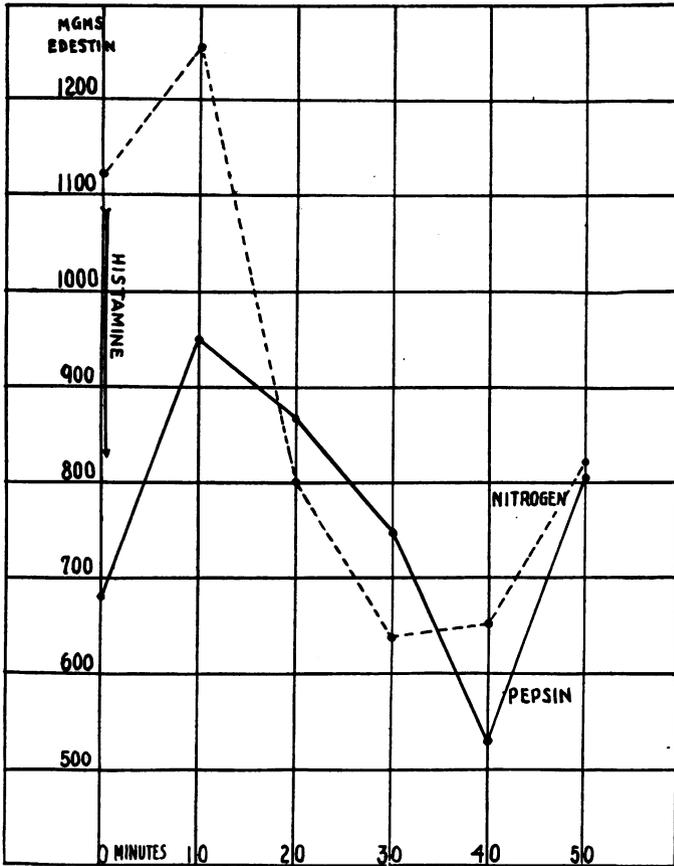


CHART 4. CURVES OF NITROGEN AND PEPSIN CONCENTRATION FROM CASE 4 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

cases (N mgm. per 100 cc. $\times 15$) a wide gap between the two curves is seen. In other words, while a relation between nitrogen and pepsin seems likely there is relatively much more nitrogen present than usual.

DISCUSSION OF CASES 1-6

The first point which becomes evident from the preceding charts is the necessity of interpreting the concentration of pepsin in relation to the secretory activity of the stomach. Clearly, a determination of pepsin on a single specimen aspirated after a test meal gives only the most rudimentary sort of information. In case 3, for example, the digestive power of a cubic centimeter of juice was nearly 2100 mgm.

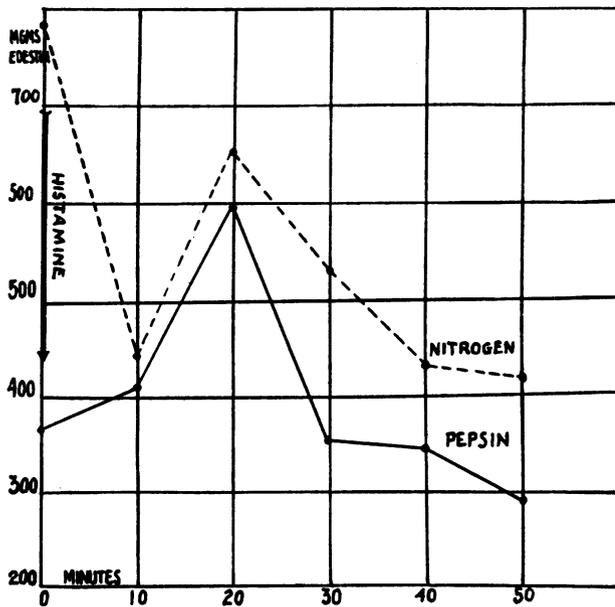


CHART 5. CURVES OF NITROGEN AND PEPSIN CONCENTRATION FROM CASE 5 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

of edestin 10 minutes after stimulation; 30 minutes later it was only 600 mgm. The most striking point in all the curves is the fall in concentration of pepsin at the height of secretion. This is to some extent explained by dilution from increased output of water at this time but as appears from chart 9 the total amount of pepsin secreted is actually increased. The actual values both for concentration and total output of pepsin vary considerably in the six cases. Many

more examinations would be necessary to define accurately normal standards but the limits are indicated.

The parallelism between the curves of pepsin and nitrogen concentration suggests strongly that pepsin is secreted in combination or

TABLE 6
Data from case 6

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|-----------------------------|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| <i>cc.</i> | | | | <i>mgm. per 100 cc.</i> | | |
| 70 | Colorless fluid—very mucoïd | | | | | |
| 21 | Colorless fluid—very mucoïd | 8 | 24 | 109 | 685 | 14,385 |
| Histamine 0.5 mgm. | | | | | | |
| 28 | Colorless fluid—very mucoïd | 22 | 35 | 100 | 690 | 19,320 |
| 40 | Colorless fluid—very mucoïd | 56 | 68 | 116 | 860 | 34,400 |
| 47 | Colorless fluid—very mucoïd | 63 | 75 | 81.4 | 610 | 28,670 |
| 50 | Colorless fluid—very mucoïd | 52 | 63 | 86.0 | 520 | 26,000 |
| 36 | Colorless fluid—very mucoïd | 64 | 75 | 69.5 | 450 | 16,200 |

TABLE 7
Relation of acidity to pepsin concentration of gastric juice

| Case | Highest acidity | Highest concentration pepsin |
|------|-----------------|------------------------------|
| 4 | 135 | 870 |
| 1 | 128 | 1,540 |
| 5 | 128 | 595 |
| 2 | 126 | 1,730 |
| 3 | 121 | 2,075 |
| 6 | 63 | 860 |

in association with some nitrogenous body. It is equally clear that there is no close correlation between the acidity of the gastric juice and its peptic activity (see table 7).

PEPSIN BEFORE AND AFTER HISTAMINE

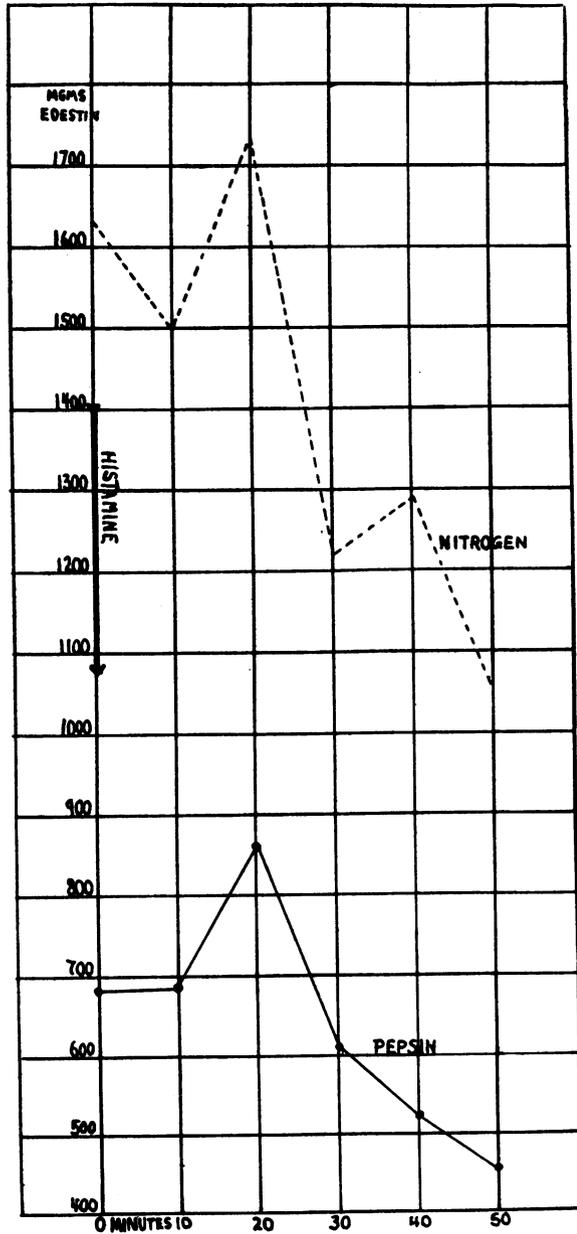


CHART 6. CURVES OF NITROGEN AND PEPSIN CONCENTRATION FROM CASE 6 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

TABLE 8
Data from case 7

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|-----------------------------|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| cc. | | | | <i>mgm. per 100 cc.</i> | | |
| 40 | Turbid colorless fluid | | | | | |
| 29 | Colorless thin mucoid fluid | 12 | 25 | 45.3 | 380 | 11,020 |

Histamine 0.6 mgm.

| | | | | | | |
|----|-------------------|----|----|------|-----|-------|
| 13 | Water clear fluid | 27 | 37 | 32.1 | 318 | 4,111 |
| 17 | Water clear fluid | 43 | 53 | 43.5 | 270 | 4,624 |
| 16 | Water clear fluid | 60 | 70 | 50.1 | 320 | 4,960 |
| 15 | Water clear fluid | 27 | 40 | 54.9 | 170 | 2,580 |
| 7 | Water clear fluid | 23 | 41 | 47.3 | 265 | 1,955 |

TABLE 9
Data from case 8

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|------------------------------|--------------------|-------|-------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| cc. | | | | <i>mgm. per 100 cc.</i> | | |
| 30 | Clear colorless mucoid fluid | | | | | |
| 7 | Clear colorless mucoid fluid | 0 | | 104.6 | 17 | 112 |

Histamine 0.6 mgm.

| | | | | | | |
|-----|------------------------------|---|--|-------|----|-----|
| 4 | Clear colorless mucoid fluid | 0 | | 105.6 | 60 | 240 |
| 3.5 | Clear colorless mucoid fluid | 0 | | 126.6 | 50 | 175 |
| 3 | Clear colorless mucoid fluid | 0 | | 142.0 | 85 | 240 |
| 3 | Clear colorless mucoid fluid | 0 | | 137.3 | 50 | 150 |

OBSERVATIONS IN GASTRIC DISORDERS

The following observations, made in patients with evidence of deficient gastric secretion, bring out certain points of importance in contrast to the preceding group.

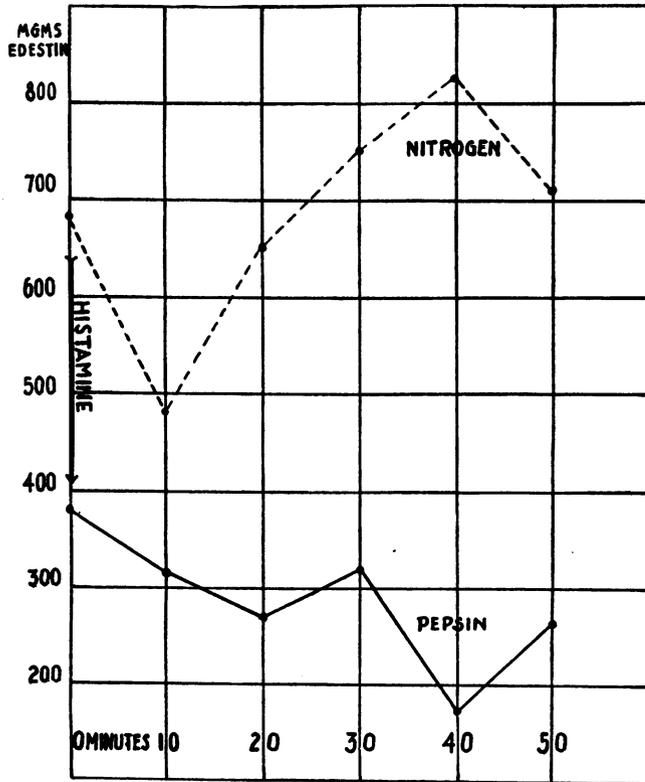


CHART 7. CURVES OF NITROGEN AND PEPSIN CONCENTRATION FROM CASE 7 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

Case 7. A man, age 57, was under treatment in the Hospital for sprue. Routine fractional gastric analyses showed the presence of HCl in the stomach contents but only in small amount. The observations are summarized in table 8 and chart 7. The gastric acidity even after histamine stimulation is low but the volume of secretion is

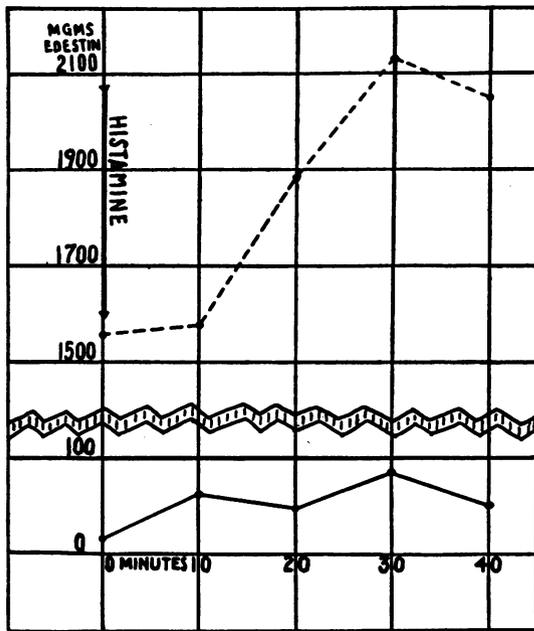


CHART 8. CURVES OF NITROGEN AND PEPSIN CONCENTRATION FROM CASE 8 AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

TABLE 10
Data from case 9

| Volume of specimen | Appearance | Titratable acidity | | Nitrogen concentration | Pepsin | |
|--------------------|---|--------------------|-------|------------------------|---|--|
| | | Free | Total | | Mgm. edestin digested by 1 cc. of juice | Total mgm. digested per 10 minute period |
| cc. | | | | mgm. per 100 cc. | | |
| 30 | Fasting contents: foul mucus, pus and blood | 0 | | | | |
| 5 | Pale brown foul thin fluid | 0 | | | 58+ | 290+ |
| Histamine 0.5 mgm. | | | | | | |
| 5.5 | Pale brown foul thin fluid | 0 | | | 57 | 313 |
| 0.5 | Pale brown foul thin fluid | 0 | | | 20 | |
| 3.5 | Pale grey-brown mucoid, foul | 0 | | | | |
| 0 | | | | | | |

not remarkable. The concentration of pepsin is much lower than in the normal cases and it neither shows the typical drop after stimulation

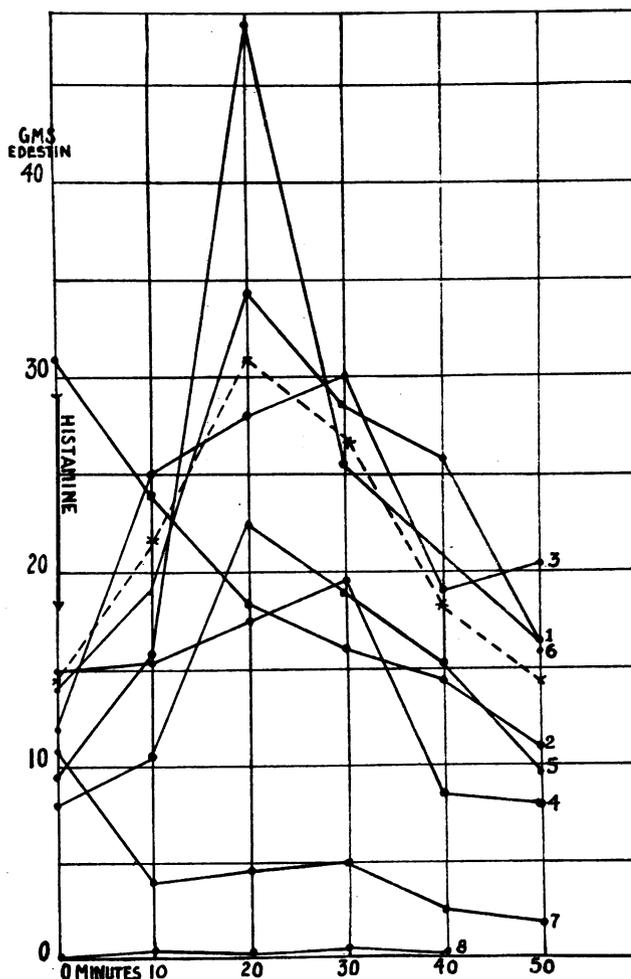


CHART 9. TOTAL OUTPUT OF PEPSIN PER TEN-MINUTE PERIOD BEFORE AND AFTER HISTAMINE

nor does it follow the nitrogen curve. The total output of pepsin is also low.

Case 8. A woman, age 57, had been under observation for four years with pernicious anemia. The findings were typical and recently there had been a good response to liver feeding although at the time of the present test there was an anacidity even after histamine stimulation. The results are shown in table 9 and chart 8. The usual almost complete absence of secretion is evident. However, in spite of the anacidity the small amount of juice obtained showed definite though diminished peptic activity, the concentration of pepsin being roughly one-tenth to one-twenty-fifth normal. There was no relation between the nitrogen and pepsin curves and the total output of pepsin (chart 9) was, of course, small—approximately one-hundredth normal.

Case 9. A man, age 72, had an advanced cancer of the stomach with ascites and masses in the liver. When examined it was possible to obtain only small amounts (see table 10) of a brownish foul fluid containing considerable granular debris. The specimens were centrifuged and the supernatant fluid tested. The fluid itself contained a considerable amount of protein precipitable by trichloroacetic acid. This was measured and a correction was made. The table shows that even in the presence of an advanced sloughing carcinoma with total absence of acid, pepsin was still present in readily demonstrable amounts.

SUMMARY

A series of observations on the application in the clinic of a quantitative method of pepsin estimation are reported. The curves of pepsin concentration and of total pepsin output before and after stimulation by histamine are described. In normal people the concentration of pepsin falls markedly after stimulation and follows closely the curve of nitrogen concentration. The total output of pepsin is usually increased.

Aberrations from the normal are illustrated and it is pointed out that even in pernicious anemia of long standing and in advanced cancer of the stomach, some pepsin may still be secreted. Estimation of pepsin may turn out to be a more delicate index of gastric damage, in certain types of cases, than determinations of acidity.

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