THE ACID CONTROL OF THE PYLORUS.

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THREE years ago I called attention to the fact that when the different food-stuffs, uniform in amount and consistency, are fed, they are discharged through the pylorus at different rates. At that time I offered in explanation of this differential discharge a
theory 1 which accorded with the facts then established. Later I reported further observations on the discharge of the three food-stuffs, singly and in combinations, and stated that a discussion of these observations and an account of explanatory experiments would be deferred to a later paper. 2 They are presented in the following pages. 3

Opposing views have been set forth as to the manner in which the stomach empties. The statements of Richet 4 and of Rossbach, 5 that gastric contents are first thoroughly mixed with gastric juice and after three or four hours or more are passed rapidly into the duodenum, have given way before contrary results obtained under more natural conditions. Clinical studies with the stomach tube, 3 observations on the undisturbed subject by means of the X-rays, 7 and investigations through duodenal fistulae, 6 combine to prove that the stomach is emptied progressively during the course of gastric digestion. The observations by means of X-rays and the investigations through duodenal openings have further demonstrated that the chyme does not pass through the pylorus in a continuous small stream, nor at the approach of every peristaltic wave, but occurs occasionally, at irregular intervals.

DISCUSSION OF PREVIOUS VIEWS AS TO THE CONTROL OF GASTRIC EVACUATION.

Both mechanical and chemical agencies have been invoked to explain the emptying of the stomach. These agencies have been supposed by some investigators to act in the stomach, by others to act in the intestine. It is necessary, first, to consider these views and the evidence adduced in their favor.

1 CANNON: This journal, 1904, x, p. xviii.
2 CANNON: Ibid., xii, p. 418.
3 Some of this evidence has been reported in previous communications (see CANNON: Journal of the American Medical Association, 1905, xlv, p. 15; This journal, 1906, xv, p. xxv).
5 ROSSBACH: Deutsches Archiv für klinische Medicin, 1890, xvi, pp 296, 317.
7 CANNON: This journal, 1898, i, pp. 368, 369, 377.
Mechanical agencies in the stomach. — The claim has been made by those who believe that chyme is discharged only after several hours of gastric digestion, that the pyloric sphincter, although able to withstand the recurrent peristaltic pressure in the earlier stages of chymification, is overcome by the more intense constrictions in the later stages.¹ As already stated, the proof is conclusive that a delay of several hours in the discharge from the stomach is abnormal. The moving constriction-rings do indeed press deeper into the gastric contents as digestion proceeds, but this late augmentation of contraction does not explain the normal gradual exit during earlier stages of chymification. In these earlier stages I have many times looked carefully for any relation between the moment of discharge and any momentarily greater intensity of peristalsis. Wave after wave passes with almost no perceptible variation of depth. Yet, as the waves are passing with such notable uniformity, the pylorus may open before the pressure of an approaching constriction, and the mass in the antrum, then released, will be driven forth into the duodenum. The next wave, and perhaps many thereafter, of approximately the same depth, may fail to press the food onward.² The occasional discharge of chyme from the stomach cannot therefore be attributed to an occasional increase of intensity of the peristaltic constrictions.

Mechanical agencies in the intestine. — In 1897 v. Mering³ reported that the introduction of a large amount of milk into a duodenal fistula checked the exit of water from the stomach. The next year Marbaix⁴ published a paper on evacuation of the stomach as affected by a state of repletion of various parts of the intestine. He found that in the upper half of the small intestine a state of repletion, induced by injections through fistula, inhibited the discharge from the stomach.⁵ In order to cause the reflex, however, even in the first fourth of the intestine, the injected liquid had to

¹ See Lesshaft: Archiv für pathologische Anatomie und Physiologie und für klinische Medicin, 1882, lxxxvii, p. 80.
² Cannon: This Journal, 1896, i, p. 369.
⁴ Marbaix: La cellule, 1898, xiv, p. 251.
⁵ An investigation of the motor functions of the stomach after pyloroplasty (see Cannon and Blake: Annals of surgery, 1905, xli, p. 707) has proved that although the upper part of the small intestine may become filled with food, there is no cessation of peristalsis. The effect noted by v. Mering and Marbaix would therefore probably be due to closure of the pyloric sphincter.
occupy a considerable extent of gut. For example, filling the gut from 10 cm. to 25 cm. beyond the pylorus caused no inhibition of the discharge. But much less than 15 cm. of continuous content is normally present in the upper intestinal tract. A radiograph and tracings of X-ray shadows already published show that the intestinal contents are normally disposed in separate short masses. Under natural conditions, therefore, the extensive uninterrupted surface of contact required by v. Mering’s and Marbaix’s explanation, in order to prevent a continuous outpouring from the stomach, does not exist. As the continuous outpouring nevertheless does not occur, their results do not explain the normal control of gastric discharge.

Von Mering’s and Marbaix’s results are confirmed by Tobler’s observation that the rapid inflation of a balloon in the duodenum checks the passage of food from the stomach. This experiment, like v. Mering’s and Marbaix’s, does not explain normal conditions, because, as already shown, chyme normally gathers in the duodenum gradually, by repeated small additions, and even when accumulated lies as a slender strand which does not distend the gut. Each strand thus formed is soon hurried forward some distance along the tube, thus clearing the duodenum for new accumulations.

Though the passage of food from the stomach may be checked by artificially filling a long piece of the upper intestine or by sudden distention of the gut at one point, such conditions cannot account for any natural control of gastric discharge from the intestinal side, because such conditions are not normally found. The evidence, therefore, is opposed to the conception that mechanical agencies, acting either in the stomach or in the intestine, play an important part in controlling the normal gastric evacuation.

Chemical agencies in the stomach. — More than twenty years ago Ewald and Boas found, by use of the stomach tube on man, that there was a considerable development of free hydrochloric acid before the gastric contents began to be notably diminished in amount. Where the acid may have had its effect — whether on peristalsis or on the pyloric sphincter — was not determined.

1 Cannon: This journal, 1902, vi, p. 255; and 1904, xii, p. 389.
3 Cannon: This journal, 1902, vi, p. 262.
4 Ewald and Boas: Loc. cit., p. 364.
5 Hammarsten’s statement that HCl seems to act as a stimulus to open the pylorus (Lehrbuch der physiologischen Chemie, 3d ed., Wiesbaden, 1895, p. 246)
Penzoldt has studied extensively the periods during which various common foods remain in the stomach, and has noted that foods delaying the appearance of free hydrochloric acid remain longest. Verhaegen, on the other hand, has declared that it matters little for the passage through the pylorus whether the food is acid or neutral.

As a basis for explaining the factors in control of gastric evacuation, Penzoldt’s results are inconclusive. In general the foods used were not fairly representative food-stuffs, but were often complicated mixtures. The amounts given at different times were not equal, nor was the consistency uniform. For his judgments Penzoldt was dependent on securing remnants of the gastric contents by means of the stomach tube, — a procedure not distinguishing the differences in the chemical reaction of the food in the two ends of the stomach, and furnishing no data as to the progressive rate at which the stomach is emptied. Ignorance of the effects of varying composition of foods, varying amounts and varying consistencies, and ignorance of the rapidity of gastric discharge as digestion proceeds, renders it difficult to arrive at exact conclusions from Penzoldt’s results.

In the presence of strong opposing evidence Verhaegen’s contention that neither acidity nor neutrality of the chyme has any effect on the emptying of the stomach, may reasonably be doubted, for his observations were made with the stomach tube on only four individuals, two of whom were pathologic.

Chemical agencies in the duodenum. — In 1893 Hirsch observed that solutions of inorganic acids left the stomach slowly, and he concluded that the slow exit was due to the stimulating effect of the acid on the mucosa of the duodenum. Later Serdjukow, one of Pawlow’s students, inhibited gastric evacuation by introducing acid into the duodenum through a fistula, thus confirming the conclusion of Hirsch. Tobler’s results also substantiate it.

was an inference from the observations of EWALD and BOAS (Personal communication). The statement does not occur in later editions.

2 Verhaegen: La cellule, 1897, xii, p. 69.
3 Hirsch: Centralblatt für klinische Medicin, 1893, xiv, p. 383.
5 Tobler: Loc. cit., p. 198.
The main defect of all the above methods as means for determining the nature of the chemical control of gastric discharge is their failure to distinguish between the two factors concerned in the passage of food through the pylorus. Before pointing out how essential the distinction is, it will be well to consider the part played by each of the two factors.

**The Two Factors Concerned in Gastric Evacuation.**

One of the two factors necessary for the emptying of the stomach is the pressure to which the food at the pylorus is subjected by recurring peristaltic waves; the other is the action of the pyloric sphincter. Not until the X-ray method was used to study the mechanical processes in digestion was it possible to watch, under normal conditions, both the movement of gastric peristalsis and the exit of food through the pylorus. Until the application of the X-ray method, therefore, a clear distinction between the normal effects of these two factors could not be made.

That the natural passage of food through the pylorus is occasional might be due to occasional peristaltic constrictions, or occasional specially strong peristaltic constrictions, pressing the gastric contents against an easily opened pylorus; or, on the other hand, the occasional passage might be due to an occasional relaxation of the pylorus in the presence of a fairly constant pressure.

It is true that some of the investigators whose work has already been mentioned have ascribed the control of gastric discharge solely to the action of the pyloric sphincter. Marbaix, for example, writes of the influence of the repletion of the intestine on the closure of the pylorus. His evidence for this limitation is not clear. Von Mering, on the other hand, recognized that intestinal repletion might check gastric discharge by stopping gastric peristalsis, and he resected the pylorus in order to differentiate, if possible, between the peristaltic and the pyloric factors. The failure to make this differentiation is the essential flaw, from the point of view of this paper, in the methods of Ewald and Boas, Penzoldt, Hirsch, Serdjukow, and Tobler. Their results, therefore, while significant, cannot serve for a conclusive determination of the control of gastric evacuation.

The possible confusion of the two factors is illustrated in Paw-
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low's report of Serdjukow's experiments. He states, without giving evidence, that acid chyme entering the duodenum reflexly occludes the pyloric orifice "and at the same time reflexly inhibits the propulsive movements of the organ (stomach)." Clearly the occlusion of the pyloric orifice alone would account for Serdjukow's results. What is the evidence that peristalsis also is affected?

In my first paper on the stomach 1 stated 2 that gastric peristaltic waves in normal conditions are continuously running, so long as food remains. Hundreds of observations made since that time on various animals — mainly on cats, but also on dogs, guinea pigs, and white rats — and likewise records of stomach sounds in man 3 have confirmed the view that peristalsis continues uninterruptedly until the stomach is swept clear of its contents. In my experience, neither ejaculation of acid chyme, nor stretching of the duodenum with food pressed through the cut pylorus (see footnote, p. 285), has any tendency to interrupt the sequence of waves.

The continuously passing peristaltic waves of the stomach, as remarked in discussion of mechanical agencies in the stomach, do not show from moment to moment notable variation of intensity. One of the two factors concerned in gastric discharge — the pressure in the antrum — is therefore recurrently constant. The control of the discharge, consequently, must reside with the other factor, i. e., with the action of the pyloric sphincter. If the sphincter holds tight, the recurring waves churn the food in the antrum; if the sphincter relaxes, these waves press the food out into the duodenum. The pylorus is the "keeper of the gate."

THE FACTS TO BE EXPLAINED.

The discharge from the stomach, as already demonstrated, is occasional. The foregoing analysis proves that this occasional discharge must be due to occasional relaxations of the pyloric sphincter. To explain the action of the pylorus, therefore, it is necessary to consider agencies which maintain an intermittent closure, — which usually keep the passage shut, yet open it at intervals to allow portions of the chyme to depart. None of the researches on

2 Cannon: This journal, 1898, i, p. 367.
3 Cannon: Ibid., 1903, viii, p. xxii; and 1905, xiv, p. 344.
the control of gastric evacuation, discussed in the preceding pages, were definitely concerned with this intermittent closure. Further investigation was desirable to explain the repeated opening and shutting of the pyloric orifice.

To explain also the differences in the rate of discharge of different food-stuffs from the stomach further investigation was necessary. In the report of the research mentioned at the beginning of this paper I called attention to the fact that when representative carbohydrate, proteid, and fat foods, of uniform amount and consistency, are separately fed, the carbohydrates begin to leave the stomach soon after ingestion (within ten minutes) and are passed out rapidly; proteids commonly do not leave the stomach at all during the first half hour and sometimes not for an hour, then they are expelled only slowly; and fats, because of a continuous slow exit, remain in the stomach for a long period. Since the major portion of a diet is more likely to be composed of carbohydrate or proteid or of the two combined, than of fat, it becomes especially important to understand the difference in the mechanical treatment of these two main food-stuffs. What is the pyloric mechanism whereby carbohydrates, not digested by the gastric juice, are permitted to pass quickly into the small intestine to be digested, whereas proteids, digested in the stomach, are there retained to undergo digestion?

A Theory of the Control of the Pylorus.

The investigators whose views have been presented have regarded factors in the stomach, or factors in the intestine, as controlling gastric evacuation. An interaction of agencies in the two situations has not been considered. The theory referred to at the beginning of this paper, propounded to explain the differential discharge of the different food-stuffs, is based on evidence of opposed effects from a single stimulus acting first in the stomach and later in the duodenum.

1 Marbaix's declaration that when any food is introduced into the stomach a portion passes directly into the empty intestine, and immediately causes v. Mering's reflex (Marbaix: Loc. cit., p 296), I have never been able to verify. Animals that had fasted several days were given lean beef mixed with bismuth subnitrate, which they eagerly devoured. Radiographs taken a half-hour later showed that in spite of continuous peristalsis there was no sign of food in the intestine.
The first statement in the theory is that acid coming to the pylorus causes a relaxation of the sphincter. Thus would be explained why the initial discharge is longer delayed when proteids are fed than when carbohydrates are fed. Both carbohydrate and proteid stimulate gastric secretion in abundance, as researches on dogs by Pawlow and his co-workers, and as clinical studies on men have shown. Inasmuch as carbohydrates do not unite chemically with the acid, free acid is at once present in the stomach; and carbohydrates would therefore begin almost immediately to pass through the pylorus. Proteids, on the other hand, join with the acid and thus retard for some time the development of an acid reaction; the proteid discharge would therefore be retarded.

But acid on the stomach side of the pylorus is not the only determinant of pyloric action. This is proved by feeding carbohydrate food moistened with 0.4 per cent hydrochloric acid. The rate of discharge is not increased. If acid in the stomach is the stimulus relaxing the pylorus, why in this case is the rate of discharge not increased? The observations of Hirsch and Serdjukow now have their bearing. Since it has been shown that acid in the duodenum does not stop gastric peristalsis, the acid reflex from the duodenum must affect the pyloric sphincter. The second statement in the theory naturally follows,—acid in the duodenum closes the pylorus.

It is probable that the pyloric sphincter has normally a greater or less degree of tonic contraction, with occasional relaxations. Certainly it has a tonic contraction persistently strong for some time after food enters the stomach; when proteid, for example, is fed, peristaltic constrictions may press the food against the pylorus repeatedly for an hour (approximately 300 waves) without forcing food through the orifice.

The whole theory of the acid control of the pylorus may now be stated. The pylorus is tonically closed when food is ingested, and remains closed against recurring pressure. The appearance of acid at the pylorus causes the sphincter to relax. The pressing peristaltic waves now force some of the acid chyme into the duodenum. The acid in the duodenum at once tightens the sphincter against further exit. The same acid also stimulates the flow of
alkaline pancreatic juice. Since no inorganic acid is normally present beyond the first few centimetres of the small intestine, and since the acid reaction of the contents in this uppermost region is replaced throughout the rest of the small intestine by practically a neutral reaction, the acid chyme must be neutralized soon after its emergence from the stomach. As neutralization proceeds, the stimulus closing the pylorus is weakened; now the acid in the stomach is able again to relax the sphincter. Again the acid food goes forth, and immediately closes the passage behind it until the duodenal processes have undergone their slower change. And thus, repeatedly, until the stomach is empty. What is the evidence for this theory?

**Experimental Evidence for the Acid Control of the Pylorus.**

As the acid of the gastric juice, according to the theory, may have two opposing effects on the pylorus, it will be well to present first the evidence that acid in the antrum causes the pylorus to open, and second the evidence that acid in the duodenum causes the pylorus to be kept closed.

**A. That acid in the stomach opens the pylorus.** — The evidence for this first half of the theory will be presented under several headings, as follows:

1. *Delaying the appearance of hydrochloric acid delays the initial discharge.* — Observations on the gastric discharge of different food-stuffs, of the same amount and consistency, proved that carbohydrates begin to leave the stomach early and are passed out rapidly. In terms of the above theory this quick exit is due to the early appearance of acid in the stomach. The appearance of acid can be delayed if the carbohydrates are first moistened with sodium bicarbonate. The acid would first be neutralized by the alkaline food near the secreting surface and in the churning antrum; and only after some time would free acid appear in considerable amount. If

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1 Bayliss and Starling: Centralblatt für Physiologie, 1901, xv, p. 682.
2 Moore and Bergin: This journal, 1900, iii, p. 325.
3 Munk: Centralblatt für Physiologie, 1902, xvi, p. 33.
4 Cohnheim, in his summary of the factors controlling the discharge of food from the stomach (Nagel's Handbuch der Physiologie des Menschen, Braunschweig, 1907, ii, p. 564), mentions the theory here propounded, but states that my evidence for it is not convincing. It is fair to note that this present paper gives for the first time the evidence in a complete and detailed form.
the theory is correct, this postponement of the appearance of acid should delay beyond the normal time the initial discharge of the food.

Crackers, rice, and mashed potatoes were chosen as representative carbohydrate foods. The rice was steamed and dried, and the mashed potato was also dried before being used. In all cases one per cent sodium bicarbonate was added to the dried food until a mush was made, of the same consistency as in the standard cases. The carbohydrates thus prepared were mixed with subnitrate of bismuth and fed, as in the standard cases, in 25 c.c. amounts.

In the following figures are presented the average aggregate length of the food-masses in the small intestine, as seen by the Röntgen rays, after feeding potato, rice, and crackers moistened with water (four cases each), and moistened with sodium bicarbonate (four cases each). The figures for the first two hours of observation are given, since they are most significant in judging the rate of discharge.

<table>
<thead>
<tr>
<th>Hours . . . .</th>
<th>POTATO.</th>
<th>RICE.</th>
<th>CRACKERS.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>½ 1 2</td>
<td>½ 1 2</td>
<td>½ 1 2</td>
</tr>
<tr>
<td>With water¹</td>
<td>9.5 31</td>
<td>43.0 16.5 29</td>
<td>36.0 11 22 35.5</td>
</tr>
<tr>
<td>With 1% NaHCO₃</td>
<td>1.0 11</td>
<td>26.5 1.5 14 29.5</td>
<td>1 8 23.0</td>
</tr>
</tbody>
</table>

The average figures for twelve cases in which the three carbohydrates wet with water were fed, and the twelve cases in which they were fed wet with sodium bicarbonate, are represented graphically in Fig. 1.

¹ See CANNON: This journal, 1904, xii, p. 397. For a description of the method used, see p. 388.
Comparison of the results of feeding carbohydrate food in the two conditions shows that at the end of a half-hour there had emerged only about one tenth as much of the food wet with the alkaline solution as of the same food wet with water (in six of the twelve cases no alkaline food had left the stomach); at the end of an hour, from a third to a half as much; and in two hours, from about a half to five sixths as much. In other words, there has been a marked retardation in the discharge of carbohydrates wet with the alkaline solution. This result is in harmony with the observation by Jaworski on man, that alkalinity of the contents delays the emptying of the stomach.¹

Sodium bicarbonate delays the appearance of acid in two ways: it checks the secretion of the gastric juice,² and for a time it unites with the acid of the gastric juice as rapidly as it is poured out. The evidence here presented shows that experimental conditions delaying the appearance of hydrochloric acid delay the discharge from the stomach.

¹ Jaworski: Zeitschrift für Biologie, 1883, xix, p. 444.
² Pavlov: Loc. cit., p. 95. Evidence will be presented later in this paper that conditions not favoring gastric secretion are accompanied by low pyloric tonus, and that under these circumstances gastric evacuation may be very rapid. That carbohydrate foods mixed with NaHCO₃ may be close to the line between a retention at the pylorus till an acid reaction develops, and a swift discharge because the pyloric tonus is low, is indicated by observations on “flaked rice” moistened with NaHCO₃. Three cases gave the following figures:

<table>
<thead>
<tr>
<th>Centimetres of food masses</th>
<th>0.0</th>
<th>11.0</th>
<th>19.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>5.5</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td>7.0</td>
<td>22.0</td>
<td></td>
</tr>
</tbody>
</table>

Four other cases, fed in the same manner the same amount with the same consistency, yielded the following figures:

<table>
<thead>
<tr>
<th>Centimetres of food masses</th>
<th>21.0</th>
<th>27.0</th>
<th>40.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.5</td>
<td>34.0</td>
<td>47.0</td>
<td></td>
</tr>
<tr>
<td>20.0</td>
<td>36.5</td>
<td>43.5</td>
<td></td>
</tr>
<tr>
<td>14.5</td>
<td>41.5</td>
<td>52.0</td>
<td></td>
</tr>
</tbody>
</table>

These latter figures were extraordinary, and can only be compared with the results of feeding raw egg-white, which likewise does not readily excite gastric secretion (see page 313).
2. Hastening the appearance of hydrochloric acid hastens the initial discharge. — Proteids normally begin to leave the stomach only after an interval of about a half-hour after feeding, and then continue going out at a much slower rate than do carbohydrates. According to the theory, as already stated, the slow passage of proteids from the stomach is due to their union with the acid of the gastric juice, which prevents the rapid development of a marked acid state.

Evidence as to this supposition may be secured by feeding proteid food that has previously been changed to acid proteid. Fibrin, lean beef, and fowl, freed from fat, were chosen as representative proteid foods. They were mixed with ten per cent hydrochloric acid and allowed to stand until changed to acid proteid. The free acid was dialyzed away until test showed none present. As the change to acid proteid was accompanied by swelling of the original substance, approximately the same proteid content was preserved by feeding the acid proteid in twice the standard amount. Doubling the amount of the natural proteid notably retards the outgo from the stomach; if changing the natural to acid proteid has no effect on the outgo from the stomach, doubling the amount should likewise retard the outgo, certainly should not accelerate it.

Fibrin, fowl, and lean beef were fed as acid proteids in 50 c.c. amounts and with the same consistency as in the standard cases. A comparison of the rate of discharge of the natural proteid foods, and the rate of discharge of the same foods given as acid proteids is exhibited in the following table. The figures represent the total length of the food-masses in the small intestine at the indicated intervals after feeding. In each instance the figures are averages of four cases.

1 See Cannon: This journal, 1904, xii, p. 409.
In Fig. 2 are presented the curves for the average figures of the twelve cases in which the natural proteids were fed and the twelve cases in which these same foods were given as acid proteids.

The figures of the foregoing table show that at the end of a half-hour the stomach had discharged from five to ten times as much acid proteid as natural proteid; three to ten times as much at the end of an hour; and in two hours about twice as much acid proteid as natural proteid. Evidently the change to acid proteid and the feeding in increased amount resulted not in slowing, but in remarkably accelerating the exit from the stomach. The proteid in these cases, already united with hydrochloric acid, does not unite with the hydrochloric acid of the gastric juice. The hydrochloric acid of the gastric juice secreted on the acid proteid is at once free acid. Free acid appears earlier, therefore, than when the natural proteid is fed. The evidence given above shows that when experimental conditions hasten the appearance of free acid, the discharge from the stomach is correspondingly hastened.

3. The appearance of acid in the antrum closely precedes the initial discharge. Although in the experimental conditions already described the emergence of food from the stomach has occurred as if acid were present to open the pylorus, this judgment is only an inference, — there has been no demonstration that acid was present when the first food passed into the duodenum. It is desirable to determine more exactly the relation between the first development of acid and the first exit of the food. This can be done by establishing in the antrum, close to the pylorus, a fistula.

An antrum fistula holding a simple flanged cannula with a removable plug was established in several cats. The cats recovered readily from the operation and were usually in very good health.

1 Whenever an operation is mentioned or suggested in this paper, it is understood, of course, that the operation was performed under complete general anaesthesia.
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In order that the food could be seen with the X-rays when it first entered the duodenum, it was always mixed with bismuth subnitrate. Various methods were used to determine the first appearance of acid in the antrum. The method causing least disturbance was that used when potato was fed. Mixed with the mashed potato (25 c.c.) were 20 drops of dimethylamidoazobenzol — an amount staining the white potato orange and showing a clearly marked change to pink when hydrochloric acid developed. As soon as the potato was given (usually by stomach tube), the plug was removed from the cylinder of the cannula and replaced by a glass syringe. The syringe consisted of a piece of glass tubing about 25 cm. long into which was passed a close-fitting glass rod 5 cm. longer. Half of a short length of rubber tubing was stretched over the upper end of the glass tube; the other half firmly encircled the projecting rod. Thus the joint was made tight. The glass tube, which slipped snugly into the cannula, was held in place by a ring of rubber tubing stretched around both the cannula and the syringe. By pulling up the rod the thin mushy contents of the antrum were drawn into the glass tube. Then any change of color could be noted. If the original orange color still persisted, the rod was pushed down again, and thus the food was restored normally to the stomach. Usually such observations were made every four minutes; during the intervals X-ray observations showed whether food had yet been passed into the duodenum. When lean beef was fed, the color change could not be clearly seen, and it was necessary to remove through the cannula a sample of the antrum contents in a small pipette. The contents were tested for acid with Congo-red, dimethylamidoazobenzol, and tropaolin 00. The difficulty of this method was the liability of loss of food whenever the plug of the cannula was removed.

In some of the following cases the conditions varied from the normal. These cases are reported, however, because of their double value: they not only present direct evidence that an acid reaction in the antrum precedes the initial gastric discharge, but they also bring to the theory of the acid control of the pylorus the support arising from the concomitant variation of these two processes.

A cat suffering from a severe inflammation of the nose and eyes was given 25 c.c. mashed potato mixed with bismuth subnitrate and dimethylamidoazobenzol, as above described. The animal was examined alternately during fifty-five minutes after feeding, for the presence of acid and for food discharged
from the stomach. There was no sign of acid, and although usually carbo-
hydrate food begins to leave the stomach in about ten minutes, there was no
discharge.\footnote{When animals are thus afflicted with “distemper,” food has been observed to
stagnate all day in the stomach (see CANNON and MURPHY, Annals of surgery,
1906, xlili, p. 534).}

Five days later the same cat, in much better health though not yet well, was
again examined in the same manner. Gastric peristalsis was seen five minutes
after the feeding. Nineteen minutes later no food had left the stomach, and
the previous examination for acid had revealed no sign of change. At twenty-
one minutes the potato drawn into the syringe was pink. As soon as the
X-rays could be applied, the fluoroscope showed that there was food in the
duodenum.

A few days later the digestion of some meat was interrupted in the same cat,
now in good health, by pulling out through the fistula the larger pieces of the
gastric contents, flushing out the remnants, and then washing the stomach from
a stomach tube through the fistula until there was no acid reaction in the wash
water. The cat was at once given potato as before. As soon as she was looked
at with the X-rays gastric peristaltic waves were seen. Five minutes after the
feeding the potato in the syringe was pink, and a minute later the X-rays
showed that some potato had passed the pylorus.

Other observations after feeding potato have confirmed these results,— an
acid reaction of the antrum contents was always noted before the food emerged
from the stomach.

Observations after feeding lean beef gave similar results. The
following cases are significant:

A cat finished eating voluntarily 25 c.c. lean beef mixed with 5 gm. sub-
nitrate of bismuth at 2.16 P.M. At 2.49 gastric peristalsis was prominent; but
no food had left the stomach, and the test for acid in the antrum contents was
negative. At 3.00 o’clock the condition was unchanged. Then a small amount
of 0.4 per cent HCl was introduced into the antrum through the fistula.\footnote{In none of these injections was the amount introduced sufficient to flood
the antrum or even to dilute the gastric contents so as markedly to alter their
consistency.} Within a minute thereafter there were two discharges of food into the duodenum.
As there was no further emergence for some time, a little food was removed and
tested. It gave no clear acid reaction. A small amount of 0.4 per cent HCl
was again introduced into the antrum towards the pylorus, and again food
emerged. Nothing more left the stomach for ten minutes. Then the food
was once more tested, with no clear sign of acid. The introduction of more
acid caused another discharge through the pylorus. It was now 3.40. Nothing
left the stomach during the next five minutes, although deep strong peristaltic waves had been passing continuously and pressing the gastric contents into the cannula whenever the plug was removed. An hour and a half had elapsed and only a very small amount of food had left the stomach, and that had left only when acid had been experimentally introduced. This was an unusual delay. The plug was now removed, and the peristaltic pressure permitted to drive out the gastric contents through the cannula. There was no sign of an acid reaction. It seemed as if the stomach had not been actively secreting. Certainly the acid introduced gave only a temporary and local acidity.

Twenty-five cubic centimetres of the same meat which the cat ate were now tested for alkalinity. More than 10 c.c. of 0.4 per cent HCl were added, and the reaction was still alkaline to Congo-paper blue with 0.4 per cent HCl. Strong HCl was now added; 20 drops were required before a neutral point was reached. Evidently the meat for some unknown reason was strongly alkaline.

It was later found that by mistake the meat had been boiled in a receptacle in which some instruments had previously been boiled with sodium carbonate, and which had not been cleaned.

Another cat with a fistula in the antrum finished eating, with evident relish, 25 c.c. boiled and shredded lean beef plus 5 gm. bismuth subnitrate at 12.05 P.M. At 12.14–15 she was fastened to the holder and examined. The reaction of the antrum contents was not acid, and nothing had left the stomach. At 12.22–23 nothing had left, but the Congo test had changed from a light to a dark red. At 12.30–31 the Congo test showed a still stronger acid change, and at 12.36, when examined by the X-rays, the intestine contained food some distance from the stomach.

The same cat several days later was offered the same kind of food, which she refused to eat. The food was then given to her by spoon, but with much difficulty, for she pushed out the food with her tongue and only received it all finally after repeated refusals. Ten minutes after the last mouthful was swallowed she was fastened to the board and examined as in the previous experiment. She was restless, she mewed and frequently tossed about. For an hour after the feeding the contents did not become acid, and although peristaltic waves were at times clearly seen, no food passed the pylorus. That emotional states inhibit the flow of gastric juice has been pointed out by Bickel.1 In this experiment it is probable that there was no psychic secretion at the time of eating, and that subsequent secretion was inhibited while the animal was fastened down. The absence of an acid reaction was attended by a failure of discharge from the stomach.

1 BICKEL: Deutsche medicinische Wochenschrift, 1905, xxxi, p. 1829.
The above cases prove that a delay in the appearance of acid in the antrum contents, as tested through a gastric fistula close to the pylorus, is associated with a similar delay in the passage of food from the stomach; that this may occur in spite of vigorous gastric peristalsis; that in these circumstances the introduction of a small amount of acid near the pylorus causes immediately the exit of food through the pylorus; and that whether potato or beef is fed, and whether in the same animal the discharge begins at the usual time or is much retarded, the first delivery of food into the duodenum is normally preceded by the development of an acid reaction in the antrum.

These conclusions from observations on the gastric contents through a fistula in the antrum are completely confirmed by recent studies of the reaction of the discharged chyme. Tobler, London and Sulima, and London and Polowzowa have tested the chyme collected from a duodenal fistula close to the pylorus. Tobler fed lean beef to his dogs. The repeatedly discharged gastric contents are acid from the beginning, and continue during digestion to be "stark sauer." London and Sulima record that when cooked egg-albumin is fed, the discharge from the pylorus is initiated by the pouring forth of an acid fluid. The same condition is recorded by London and Polowzowa after feeding white bread.

4. Hydrochloric acid opens the pylorus of the excised stomach. — Magnus has shown that pieces of the small intestine, removed from the body and placed in continuously oxygenated Ringer's solution, will remain alive and, so long as Auerbach's plexus is intact, will manifest the typical local reflex. In a recently published investigation I have given evidence that the mechanism in control of the differential discharge through the pylorus is independent of the central nervous system. It seemed probable, because of the rapidity of closure of the pylorus after food emerged, that the controlling

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1 All these observers report that a few drops of alkaline mucus flow from the cannula soon after observation begins. This flow does not seem to be associated with the repeated gastric discharge.
2 Tobler: Loc. cit., p. 197.
5 Magnus: Archiv für die gesammte Physiologie, 1904, cii, p. 362.
6 Cannon: This journal, 1906, xvii, p. 429.
mechanism resides in the local nerve plexus, and is similar to the
typical reaction of the intestinal wall. On this supposition the fol-
lowing experiment has been repeatedly performed.

A cat, which had fasted for twenty-four or thirty-six hours, was killed by
etherization. A cut above the cardia and another just below the pylorus
separated the stomach from the rest of the alimentary canal. The stomach,
which was empty,1 was cleared of its attachments and placed in warm Ringer's
solution (38° C.), through which oxygen continuously bubbled.

A glass tube, with a short rubber tube and a water manometer attached, was
tied into the cardiac orifice. A small amount of 0.4 per cent HCl, made blue
by the changed Congo-red, was introduced through the tube into the cardiac
end of the stomach, which was held lower than the pyloric end. The stomach
was now inflated with air until the air bubbled through the pylorus. The rub-
ter tube was next tightly clamped. When the air had ceased escaping from
the stomach, i.e., when the pyloric tonus withstood the intragastric pressure,
the cardiac end of the stomach was gently and slowly turned until the acid
came to the pylorus. In a moment the blue fluid poured forth into the
Ringer's solution. The pylorus had opened.

It might be supposed that the acid coming into the antrum caused
an increased tonus of the gastric musculature and that thus the
pyloric orifice was forced open. The manometer, however, does
not show any increase of intragastric pressure. Furthermore the
stomach can be tipped so that the acid fluid enters the antrum, but
does not come to the pylorus. This does not lead to the driving out
of more air, — the acid does not notably stimulate contraction of the
gastric wall. The opening of the pylorus, therefore, is due to the
presence of the acid.

A one per cent sodium bicarbonate solution colored red, similarly
brought to the pylorus, does not begin to emerge for a considerably
longer time, and then usually drifts out into the Ringer's solution
as if slowly diffusing.

It is justifiable to conclude that in the living excised stomach
free acid coming to the pylorus causes the pylorus to open.

B. That acid in the duodenum keeps the pylorus closed. — The sup-
port for this, the second half of the theory, has already been sug-
gested in part in discussing the experiments on the inhibition of

1 It is important that the stomach be taken while not digesting. In my experi-
ence, if digestion has been going on, the excised stomach exhibits peristalsis as
soon as inflated.
gastric discharge by acid in the duodenum. As other observations to the same effect are to be described under the above heading, a brief restatement of the previous experiments and their results will not be out of place, and will serve to bring all the evidence together.

1. *Acid in the duodenum inhibits gastric discharge.* — In 1893, Hirsch, as already noted, found that inorganic acids left the stomach slowly. When he isolated the stomach, however, the acids departed as rapidly as any other fluid. He explained this difference by assuming that the stomach is controlled by acid reflexes from the duodenum. Serdjukow modified Hirsch's experiment by introducing through a duodenal fistula small quantities of acid solutions or pure gastric juice. By repeated injections it was possible to prevent discharge from the stomach for an unlimited time. Tobler's observations were closer to the normal conditions. He allowed a dog with duodenal fistula to eat 100 gm. lean beef. The chyme as it emerged was caused to leave the duodenum through the artificial opening. The stomach was thus emptied in about two hours and fifteen to thirty minutes. The next day the dog was given the same amount of the same kind of food, but whenever a portion of the chyme came through the fistula from the stomach, a similar portion of the chyme of the day before was injected through the fistula towards the intestines. The result was that the chyme left the stomach at considerably longer intervals and was more thoroughly digested. The time of digestion thus became lengthened to three hours and three hours and a half. Tobler's observations have been completely confirmed by Lang.

The evidence of Hirsch, Serdjukow, Tobler, and Lang proves definitely that acid chyme in the duodenum checks the outgo from the stomach. Since gastric peristalsis, as previously shown in this paper, is not stopped by the discharge of acid chyme, the effect must be due to the action of the pyloric sphincter. Acid in the duodenum causes pyloric contraction.

2. *Absence of the normal alkaline secretions from the duodenum retards gastric discharge.* — Pawlow records that the passage of acid solutions out of the stomach is remarkably slower in dogs with

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a pancreatic fistula than in those without one. In order to test whether the discharge of normal gastric contents was likewise retarded by a similar condition in the duodenum, the following experiment was performed. The larger pancreatic duct and also the bile duct were tied so as to prevent the flow of the secretions into the intestine. After several days the animals were given the standard amount of mashed potato and bismuth subnitrate, with the usual consistency. The outgo from the stomach was determined as before by measuring the length of the food-masses in the small intestine. The figures of the following table give the total length of these masses at the times indicated, in normal conditions (four cases) and also after tying the larger pancreatic and the bile ducts (four cases).

<table>
<thead>
<tr>
<th>POTATO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours . . . . . . . . . . .</td>
</tr>
<tr>
<td>½</td>
</tr>
<tr>
<td>Normal conditions . . . . .</td>
</tr>
<tr>
<td>9.5</td>
</tr>
<tr>
<td>Pancreatic and bile ducts tided</td>
</tr>
<tr>
<td>0.0</td>
</tr>
</tbody>
</table>

The observations recorded in this table are represented graphically in Fig. 3. These observations were made six and twelve days after the operation. It is obvious that there has been a very marked checking of the normally rapid outgo of the potato from the stomach; nothing out in a half-hour, a fourth the normal amount in an hour, and a third the normal at the end of two hours.

Why there should be no exit of the food during the first half-hour

is not clear, but the very slow increase of the intestinal contents thereafter — from 7.5 to 14.5 cm. in the second hour of digestion, compared with the increase from 10 to 31.5 cm. in the second half-hour in the normal state — is in harmony with the observation that acid in the duodenum closes the pylorus.

Under normal conditions acid in the duodenum stimulates the secretion of pancreatic juice and bile. These alkaline fluids must neutralize the acid chyme, for an acid reaction is not found beyond the first few centimetres of the small intestine. The neutralizing of the acid removes the stimulus keeping the pylorus closed. If the alkaline fluids are prevented from entering the intestine, the acid is necessarily neutralized more slowly, the pylorus is kept closed during longer periods, and the emptying of the stomach therefore occurs at a slower rate.

3. **Destroying continuity between stomach and duodenum hastens gastric discharge.** — Additional evidence as to the relations between the duodenum and the pylorus in the control of gastric evacuation may be secured by setting aside the duodenum and causing the stomach to empty into a lower part of the gut. The intestine was cut through about 1.5 cm. beyond the pyloric furrow, and again about 30 cm. beyond. The upper end of this separated portion was turned in and closed with stitches; the lower end was joined to the gut near the ileocolic opening by an end-to-side junction. The upper end of the main part of the intestine was now united to the small remnant of duodenum contiguous to the pylorus by the simple and effective F. G. Connell suture. Thus the stomach emptied not into the duodenum, but into a piece of the intestine formerly 30 cm. beyond.

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1 See page 292.

2 See F. G. CONNELL: Journal of the American Medical Association, 1901, xxxvii, p. 952. My thanks are due to Dr. F. T. MURPHY for indispensable aid in this operation.
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The following figures give the average aggregate length of the food-masses in the small intestine, at the times indicated, after feeding shredded lean beef of standard amount and consistency, in four normal cases and in four cases with duodenum set aside. From two to nineteen days had elapsed since the operation.

<table>
<thead>
<tr>
<th>Hours . . . .</th>
<th>½</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal conditions</td>
<td>1.5</td>
<td>2.5</td>
<td>16.0</td>
</tr>
<tr>
<td>Duodenum set aside</td>
<td>1.5</td>
<td>16.0</td>
<td>31.5</td>
</tr>
</tbody>
</table>

These results are represented graphically in Fig. 4. Reference to the table and to Fig. 4 shows at once the difference between the factor which acts inside the stomach and the factor which acts in the duodenum to control the pylorus. Both conditions reported in the above table display the typical retardation of the initial discharge characteristic of proteids. Setting aside the duodenum evidently did not change that. That retardation, according to the conclusions already reported, is an affair of the stomach alone. And the figures in the above table serve to confirm those conclusions.

When the food begins to emerge, the results are suddenly quite different. Instead of 3 cm. at the end of an hour, 16 cm.; and twice the normal amount at the end of two hours — such is the effect of destroying the continuity between stomach and duodenum. After the first delay (in one case no food left the stomach for an hour) proteid is poured forth at a remarkably rapid rate.

The above results were secured before the completion of the research on the passage of different food-stuffs from the stomach deprived of its extrinsic nerves, to which reference has been made.¹ That research proved that the differential discharge from the stomach is under local control. As the investigations of Magnus had shown that the local control of intestinal reflexes resides in Auerbach's plexus, it seemed probable that merely cutting a ring around the intestine as close as possible to the pylorus, and deep enough to sever both muscular coats, would yield information as to the path of influence from duodenum to stomach. A ring was cut as above described, and the separated edges of the muscular coats were then

¹ See CANNON: This journal, 1906, xvii, p. 429.
held together by only the mucosa and the submucous connective
tissue. When proteid was fed, there was again the initial delay —
nothing out at the end of a half-hour — and this was followed by
an exit almost as rapid as when the duodenum was set aside. The
conclusion may be drawn that the influence from duodenum to
pylorus runs through a local reflex, mediated by the myenteric
plexus. As Bayliss and Starling have shown that reflex augmenta-
tion of intestinal contraction may occur from 1 to 6 cm. above a
stimulated point,¹ it is clear that acid chyme may be effective
through a considerable extent of the duodenum in causing reflex
pyloric contraction.

EVIDENCE FOR THE ACID CONTROL DERIVED FROM PREVIOUS
OBSERVATIONS ON GASTRIC DISCHARGE.

As already explained (p. 287), the data as to the discharge from
the stomach, secured by use of the stomach tube, are of little service
for the present investigation, because they do not indicate the rate
of gastric evacuation from time to time during digestion. The
method used in my earlier research on the discharge of the different
food-stuffs from the stomach ² gave characteristic curves of the
rates at which proteids, carbohydrates, and fats pass the pylorus.
The present investigation was undertaken to explain these charac-
teristic rates of discharge. To what extent do the results of the earlier
research agree with the other evidence that acid in the stomach
signals the opening of the pylorus?

Proteids. — In the earlier research above referred to, X-ray ob-
servations showed that proteids frequently did not begin to leave
the stomach during the first half-hour, and that after they began to
leave they departed slowly (see curve of natural proteids, Fig. 2).
Although in comparing results of different investigations the factor
of food consistency cannot be closely estimated, yet observations
through duodenal fistulae on the passage of proteid chyme from the
stomach support in general the X-ray observations. Thus, for
example, Moritz ³ noted that the exit of the gastric contents began
about three quarters of an hour after his dog finished eating 200 gm.
raw meat. And Lang reports that the first slight discharges of the

¹ Bayliss and Starling: Journal of physiology, 1899, xxiv, p. 112.
² Cannon: This journal, 1904, xii, p. 387.
³ Moritz: Zeitschrift für Biologie, 1901, xii, p. 574.
gastric contents did not occur for at least fifteen minutes after
feeding his dogs 200 gm. fibrin.\textsuperscript{1} Peristalsis starts almost immediately after the ingestion of food. The dog's stomach has about
four waves per minute.\textsuperscript{2} It is clear that in these cases of duodenal
fistula the food has been churned by numerous peristaltic waves,
and these waves have repeatedly pressed food upon the pylorus,
before the sphincter has relaxed and permitted an exit into the
duodenum. The evidence that the exit does not occur until the con-
tents of the antrum are acid has already been given. The first acid
secreted unites with the proteid. The relatively long delay of the
initial discharge of proteid from the stomach is thus accounted for
by a relatively slow development of a marked acid reaction in the
food which is pressed up to the pylorus.

Doubling the amount of proteid food strikingly delays the initial
discharge of the proteid from the stomach \textsuperscript{3} — a result explicable
on the ground that the increased amount of proteid to become acidi-
fied in the antrum necessarily delays the proper acid reaction for
opening the pylorus.

The continued comparatively slow outgo of proteid into the in-
testine can also be explained. As proved in my first paper on the
stomach, mixing currents do not run throughout the cavity. The
mixing occurs only in the pyloric end; the centre of the mass in
the cardiac end long remains unchanged in reaction.\textsuperscript{4} Since the
antrum does not secrete acid, all the acidity of its contents is due to
acid pressed in from the cardiac end. But unchanged proteid, stored
in the cardiac end, is also continuously being pressed into the antrum.
There is thus continuous utilization of the imported acid. Since it
is altogether probable that a certain degree of acidity is necessary
for opening the pylorus, the fresh proteid masses, by uniting with
the acid and thus reducing the acid reaction, would naturally dimin-
ish the rate of exit from the stomach. That this factor is important
in checking the rapid outgo of proteid food is indicated by the fact
that acid proteids, not demanding large amounts of acid, pass the
pylorus with almost carbohydrate rapidity (\textit{cf.} Figs. 1 and 2).

Doubtless also the proteid discharge continues to be slow because

\textsuperscript{1} \textit{Lang}: \textit{Loc. cit.}, p. 229.
\textsuperscript{2} \textit{Roux and Balthazard}: \textit{Archives de physiologic}, 1898, xxx, p. 89.
\textsuperscript{3} \textit{Cannon}: \textit{This journal}, 1904, xii, p. 410.
\textsuperscript{4} \textit{Cannon}: \textit{Ibid.}, 1898, i, p. 378. \textit{See also Grützner}: \textit{Archiv für die gesammte
Physiologie}, 1905, cvi, p. 463.
proteid chyme presents a greater amount of acid for neutralization than does carbohydrate chyme. Tobler and Lang have shown that acid proteid in the duodenum will check gastric evacuation.\(^1\) Khigine’s results prove that when 200 gm. flesh are fed to a dog, 50 per cent more gastric juice is secreted during the first four hours of digestion than is secreted in the same time when the same amount of bread is fed.\(^2\) The neutralizing of the larger amount of acid in the duodenum would necessarily require a longer time, and would result in a slower rate of discharge than would be expected when bread is fed.\(^3\)

Penzoldt’s observation that, with due regard to the effects of variation in quantity, those flesh foods with which there is an earlier appearance of acid remain a shorter time in the stomach than those with which the acid appears later; and likewise his observation that of the vegetables legumes, which are richest in proteid and can unite with much acid, are longest delayed in the stomach, — these observations\(^4\) made on man are in agreement with the supposition that the pylorus remains closed until acid appears. The statements of Roux and Balthazard,\(^5\) and of Moritz,\(^6\) based on animal experimentation, that raw meat remains in the stomach a long time and leaves slowly, confirm Penzoldt’s results. On the other hand, Cahn’s\(^7\) contention that emptying of the stomach begins with peptonization, and Roux’s\(^8\) declaration that concentrated peptone seems to accelerate evacuation, do not oppose the idea of the acid control of the pylorus in normal conditions, for when proteid is fed, acid would be present by the time peptonization had occurred in any considerable amount. To suppose that peptone is required for pyloric relaxation is manifestly unwarranted, — the pylorus opens

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\(^2\) Khigine: Archives des sciences biologiques, St. Petersburg, 1895, iii, p. 461; see also Pawlow: "Loc. cit., p. 33."

\(^3\) Khigine’s figures show slight gastric secretion continuing for ten hours after the ingestion of 200 gm. bread, but continuing only eight hours after the ingestion of 200 gm. flesh. I cannot believe that the bread was longer in the stomach than the meat; all observations on the evacuation of the stomach indicate that carbohydrate departs much earlier than the same amount of proteid.


\(^5\) Roux and Balthazard: "Loc. cit., p. 91."

\(^6\) Moritz: "Loc. cit., p. 369."

\(^7\) Cahn: Zeitschrift für klinische Medicin, 1887, xii, p. 41.

\(^8\) Roux: Comptes rendus, Société de Biologie, 1901, liii, p. 846.
early when carbohydrates are fed, yet under the circumstances no peptone can have been formed.

Carbohydrates. — With reference to the departure of carbohydrates from the stomach it is of interest to recall Marbaix's suggestion. He noted that potatoes leave the human stomach rapidly, and that gastric juice cannot attack them to any extent; he pointed out that an important question lay here. The testimony that the delay in the discharge of carbohydrates from the stomach is usually not great, that in conditions of diminished acidity they are more easily borne than meat, that test meals mainly carbohydrate leave the stomach earlier than those containing meat, all points to the possibility that acid on the gastric side of the pylorus signals the relaxation of the sphincter.

A portion of the curve showing the rate of discharge of typical carbohydrate foods (the curve for the first two hours of digestion) is reproduced in Fig. 1. The original curve, published in 1904, corresponds remarkably to that recently published by London and Polowzowa, representing the hourly percentage volume of gastric evacuation collected from a duodenal fistula after feeding white bread. The two curves almost exactly coincide during the first two hours of digestion; thereafter my curve, although similar in shape, is naturally somewhat higher, since it represents not merely the discharge, but the accumulation of the discharge in the small intestine, minus the amount absorbed or passed into the large intestine. The method of study used by London and Polowzowa completely corroborates the X-ray method which I used. Both methods show that carbohydrate foods begin to leave the stomach soon after ingestion. I noted them in the duodenum ten minutes after ingestion; eight to twelve minutes is the time given by London and Polowzowa before the bread chyme emerges, acid in reaction. The carbohydrate foods, once started, pass out rapidly; indeed, they remain in the stomach only about half as long as the same amount of proteid food having the same consistency.

As previously intimated, this early and rapid exit is in accord with the other evidence that acid in the antrum relaxes the pyloric

1 Marbaix: Loc. cit., p. 299.
3 Schüle: Therapeutisches Monatschrift, 1899, xiii, p. 601.
4 Cannon: This journal, 1904, xii, p. 398.
sphincter. It is well known that carbohydrate food stimulates the flow of gastric juice. But carbohydrates do not unite with the acid. Hydrochloric acid is consequently at once present to open the pylorus. And the acid is secreted as rapidly as the duodenum can receive the chyme, for the giving of carbohydrate already mixed with acid, does not increase the rate of the passage into the intestine.

**Combinations of the food-stuffs.** — In the research on the passage of different food-stuffs from the stomach it was found that when carbohydrate was fed first and proteid second, the proteid, filling the cardiac end of the stomach, did not materially check the departure of carbohydrate food, lying in the antrum; but proteid in the antrum, when proteid food is fed first and carbohydrate second, results in the characteristic slow discharge. The proteid holds back the carbohydrate occupying chiefly the cardiac end. In the former case the carbohydrate content of the antrum did not retard the development there of an acid reaction; in the latter case the proteid did retard that development. This observation indicates that the acid, which opens the pylorus, acts close to the pylorus, — a conclusion which is sustained by the effects of acid in the excised stomach (see p. 301).

When carbohydrates and proteids were mixed in equal parts, the mixed food did not leave the stomach so slowly as the proteids, nor so rapidly as the carbohydrates; the discharge was intermediate in rapidity. This result was to be expected, for a large proportion of proteid was present to unite with the acid secreted, and this would tend to retard the discharge in the manner already discussed (see p. 307).

In a mixture of fats and proteids in equal parts the presence of the fat caused the mixture to leave the stomach even more slowly than the proteid alone. This result also is in accord with the supposition that acid opens the pylorus, for fat alone inhibits, and fat mixed with proteid notably retards and diminishes, the flow of gastric juice. Moreover the development of an acid reaction is checked by the union of the acid with the proteid. It is quite natural that this combination of food-stuffs should be slowest of all to pass from the stomach.

Fat mixed with carbohydrate in equal amounts caused the carbo-

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1 Pawlow: *Loc. cit.*, pp. 36, 100.
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hydrates to pass the pylorus at a rate slower than their normal. In this case the fats again undoubtedly retarded and diminished the gastric secretion, but the carbohydrates, unlike the proteids, did not further hinder the appearance of an acid reaction. The checking of the outgo can therefore be explained solely by the effect of the fats in diminishing the secretion of gastric juice.

A review of the evidence presented in this section shows that observations on the rate of discharge of proteids, carbohydrates, fats, and combinations of these food-stuffs, can be readily explained on the assumption that acid in the stomach opens the pylorus and acid in the duodenum closes it. This fitness of the theory to explain the peculiar differences in the gastric discharge of the different food-stuffs, makes it still more probable as a statement of the normal mechanism of the pyloric passage.

Observations Not Accordant with the Acid Control.

The argument has been suggested against an acid control of the pylorus, that other sphincters of the alimentary canal are not thus controlled, and therefore it is unnecessary to assume such control for the pyloric sphincter. The pyloric sphincter, however, is in several respects unlike any other in the alimentary canal: (1) peristaltic waves are rhythmically pushing food against it (five or six times per minute in the cat), sometimes for half or three quarters of an hour, without causing relaxation; (2) the pylorus has on either side a secretion of opposite reaction — acid above, alkaline below — a condition unlike any other alimentary sphincter except the cardia. Because of these peculiarities it is unjustifiable to argue from the control of other sphincters as to the control of the pylorus, especially since the local changes in chemical reaction can explain the normal pyloric functioning.

It has also been urged that much of the gastric contents must escape before it is conceivable that any great proportion of acid is present. This objection to the acid control fails to take into account the important difference between the two ends of the stomach. What may be true of the bulk of the food lying in the cardiac end may not be at all true of food in the antrum. A small amount of food in the antrum may be thoroughly mixed with acid

1 A research yet unpublished shows that the cardia may be kept tonically closed during gastric digestion by the acid gastric contents.
when merely the surface of the mass in the cardiac end has been slightly acidified. As has been previously shown in this paper (see pp. 301, 310), it is the acid reaction of the food at the pylorus that is significant in causing the sphincter to relax.

The discharge of water. — Another objection to the idea that acid on the stomach side opens the pylorus is the fact that water is very rapidly discharged. For example, Moritz, in studying by means of a duodenal fistula the emptying of the stomach, noted that water begins to enter the intestine almost as soon as it enters the stomach; it may pass out in single gushes or continuously. In thirty minutes 500 c.c. of water may go from the stomach into the intestine. Similar results have also been reported by other observers who have studied the exit of water from the stomach. Not only water, but likewise physiological salt solution, may go out rapidly.

It should be noted, in the first place, that water and salt solution are very different in consistency from the foods ordinarily taken into the stomach. Furthermore, water and salt solution produce only a very slight, if any, secretion of gastric juice. When only 100 or 150 c.c. of water are injected, very often not the least trace of secretion occurs. "It is only a prolonged and widely spread contact of the water with the gastric mucous membrane, which gives a constant and positive result (secretion)." The rapid exit of water from the stomach would preclude the conditions which make it even a feeble stimulant of gastric secretion. The failure of water to excite any noteworthy amount of gastric juice favors a rapid exit, so far as the duodenal reflex is concerned, for the acid stimulus closing the pylorus is thereby absent. Within the stomach water certainly has an effect on the pyloric sphincter very different from foods which evoke an abundant flow of gastric juice. When such foods are given, scores of peristaltic waves may sweep up to the pylorus before the sphincter relaxes; but when water is given, it begins to leave the stomach at once.

It seems probable that a state of increased pyloric tonus accompanies the conditions favoring secretion of gastric juice. Pawlow has

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1 Cannon: This journal, 1898, i, pp. 378, 379.
2 Moritz: Zeitschrift für Biologie, 1901, xlii, p. 584.
5 Pawlow: Loc. cit., p. 94.
shown that the psychic secretion of gastric juice is due to impulses coming to the stomach by way of the vagi. Vagus stimulation also produces an augmentation of the contraction of the pyloric sphincter. Vagus impulses, therefore, cause the initial flow of gastric juice — the psychic secretion — and they also cause increased pyloric tonus. Water does not present the conditions for psychic secretion: it is not chewed with a relish; it is swallowed rapidly; it does not satisfy appetite; and once in the stomach, it begins to pass immediately through the pylorus, as if the sphincter were in a relaxed state. The fact that water may pour through the pylorus not rhythmically but fairly continuously (see p. 312) points definitely to a diminished pyloric tonus. This fact and the failure to stimulate gastric secretion seem related to each other. In these facts may be found a probable explanation of the rapid discharge of water from the stomach.

The discharge of egg-albumin. — In the same class with water is raw egg-white. In my observations on the rate of discharge of different food-stuffs from the stomach, I pointed out that egg-albumin formed an exception to the general rule that proteid passes out from the stomach slowly. Since then this observation has been confirmed by Loudon and Sulima in a study on dogs with duodenal fistula. They found that raw egg-albumin begins to pass the pylorus immediately after ingestion; it emerges in large gushes at intervals of four or five seconds. These gushes are therefore too frequent to correspond to the occurrence of peristaltic waves. For about twenty minutes the egg white issues from the stomach with an alkaline reaction; then the reaction becomes acid, and the discharge naturally is more seldom (one to three minute intervals) and
less abundant.\textsuperscript{1} In this connection it is of interest that Pawlow found fluid egg-white no more effective in exciting gastric secretion than an equal volume of water.\textsuperscript{2} Like water, fluid egg white does not offer the conditions for arousing psychic secretion; and attending that condition there is a state of diminished pyloric tonus, as evidenced by discharges through the pylorus much more frequent than the peristaltic waves in the dog's stomach. The rapid passage of fluid egg-white from the stomach would therefore be explained in the same manner that the rapid outgo of water is explained.\textsuperscript{3}

According to the results of my earlier investigations, however, egg-white coagulated by heat also left the stomach at a rapid rate. This observation likewise has been confirmed by London and Sulima. They found, however, that, unlike fluid egg-white, the coagulated form did not begin to leave the stomach immediately, but several minutes after ingestion. When the gastric discharge began, its reaction was acid. First the discharge had only fine particles of the egg-albumin, but later these were much larger.\textsuperscript{4} These unchanged particles are significant, for they indicate that the acid has been secreted more rapidly than it could unite with the compact coagulum of the egg-albumin.\textsuperscript{5} This failure of the acid to unite with albumin as soon as secreted brings about the same condition that prevails when carbohydrates are fed, — there is an early appearance of free acid in the stomach. London and Sulima report large amounts of free hydrochloric acid in the chyme of coagulated egg-white.\textsuperscript{6} Moritz, Tobler, and Lang, on the other hand, declare that although the chyme of beef and fibrin is acid in reaction, it does not contain free hydrochloric acid.\textsuperscript{7} This difference in the rapidity of union with the acid as it is secreted would account for the difference in the rate of discharge of these proteids. The slow union of acid with coagulated egg-white and the resultant early appearance of free acid in the stomach explains the rapid departure of this food.

\textsuperscript{1} London and Sulima: Zeitschrift für physiologische Chemie, 1905, xlvi, p. 233.
\textsuperscript{2} Pawlow: Loc. cit., p. 96.
\textsuperscript{3} The very rapid exit of a rice preparation moistened with NaHCO\textsubscript{3} (which hinders gastric secretion) may be similarly explained (see p. 294).
\textsuperscript{5} See Fermi: Loc. cit., p. 59.
\textsuperscript{6} London and Sulima: Loc. cit., p. 212.
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The discharge of fats.—In the research on the passage of the different food-stuffs from the stomach, X-ray observations showed that fats remain long in the stomach. The discharge begins slowly and continues at about the rate at which the fat leaves the small intestine by absorption and by passage into the large intestine. These results of X-ray examination are in entire accord with those of Zawilski,1 Frank,2 Matthes and Marquadsen,3 Boldireff,4 Carnot and Chassevant,5 and Levites,6 who used various other methods.

In attempting to understand the discharge of fats, it is necessary, first, to consider their effects both in the stomach and in the duodenum. Observations by Lobassow 7 and Fermi 8 have shown that fat in the stomach does not stimulate the flow of gastric juice. On the other hand, according to Lintwarew,9 fat in the duodenum, like acid, may cause a prolonged checking of the gastric discharge.

As already shown, there is reason to believe that the taking of food not causing a flow of gastric juice is accompanied by a state of low pyloric tonus. This condition seems to be as true of fats as of water and fluid egg-white, for Boldireff has reported that when fats are fed in considerable amount, a mixture of pancreatic juice, bile, and intestinal secretion flows back into the stomach.10 This result could not occur unless at times the pyloric sphincter were in a relaxed state, and unless at times the pressure in the stomach were less than that in the duodenum. In this connection it is of interest to recall that of the three food-stuffs fats produce the slowest rate of gastric peristalsis11 and commonly the weakest (i. e., the shallowest) waves.

As noted earlier in this paper, fats differ from carbohydrates and proteids in very seldom constituting the chief elements of a diet.

1 ZAWILSKI: Arbeiten aus dem physiologischen Anstalt zur Leipzig, 1876, p. 156.
3 MATTHES and MARQUADSEN: Verhandlungen des Congresses fur innere Medizin, 1898, xvi, p. 364.
4 BOLDIREFF: Centralblatt fur Physiologie, 1904, xviii, p. 457.
5 CARNOT and CHASSEVANT: Loc. cit., p. 866.
7 See Pawlow: Loc. cit., p. 97.
8 FERMI: Loc. cit., p. 76.
9 LINTWAREW: Biochemisches Centralblatt, 1903, 1, p. 96.
11 CANNON: This journal, 1904, xii, p. 392.
They differ also in not arousing gastric secretion. They are further peculiar in acting by themselves in the duodenum, not only to inhibit gastric evacuation, but also to stimulate the flow of pancreatic juice. Clearly fats do not require the secretion of gastric juice for changes in the stomach, or for the control of their exit into the intestine, or for the stimulation of a pancreatic secretion specially favorable to their digestion.

It may be that fats have also a special relation to the pyloric mechanism. But the alternative possibility of an acid control, even when fats alone are fed, should not be overlooked. Fatty acid may be set free in considerable amount in the stomach by gastric lipase, if the fat is fed as an emulsion. A separation of fatty acid also occurs when in the early stages of fat digestion pancreatic juice enters the stomach. If the failure of fats to excite gastric secretion would place them at first with fluid egg-white as substances readily passed through an easily opened pylorus, the later development of acid in the fats contained in the stomach might cause them to control their own discharge like other foods developing an acid reaction of the gastric contents.

In the duodenum it is noteworthy that fats are changed with an effect quite unlike that of the other food-stuffs. Fats cause the pancreatic juice to flow, but the pancreatic juice, instead of diminishing the acidity of the duodenal contents, increases the acidity by separating a still greater amount of fatty acid. Even when dissolved in bile the fatty acids give the solution an acid reaction. To this increasing acidity of the contents of the upper intestine, and also to the weak and sluggish gastric peristalsis which fats evoke, may reasonably be attributed the fact that fats pass from the stomach only as fast as they are absorbed or carried into the large intestine.

Pathological cases. — It may be urged that certain cases of pathological secretion of gastric juice — cases of hypo- and hyperchlorhydria, and of achylia gastrica, for example — do not yield results accordant with the acid control of the pylorus. Thus in achylia

1 DOLINSKY: Archives des sciences biologiques, St. Petersburg, 1895, iii, p. 424.
2 VOLHARD: Zeitschrift für klinische Medicin, 1901, xliii, p. 429.
3 See LEVITES: Loc. cit., p. 276.
4 See LEVITES: Loc. cit., p. 279.
5 MOORE and ROCKWOOD: Journal of physiology, 1897, xxi, p. 64.
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The absence of acid does not lead to a retention of food in the stomach. But gastric evacuation in the absence of an acid reaction is only one problem to be settled in achylia gastrica,—pancreatic secretion without the natural acid stimulus in the duodenum must also be investigated and explained. As shown by these examples, the discovery of natural relations at once reveals the character of disturbed relations. If in spite of disturbed relations the processes concerned continue to be serviceable to the organism as a whole, an adaptation to the new conditions must have occurred. The ability of organs to adapt their functioning gradually to pathological states is well known in many instances. This adaptation, however, must be studied by itself as a special subject. Thus, after the normal physiology of the pylorus is made clear, it becomes of interest to know to what extent and in what manner disturbances in the stomach and duodenum are attended by changes in pyloric reflexes which are compensatory. Undoubtedly other factors may modify the usual mechanism. Already it has been shown that the pylorus may remain tightly closed against persistent peristalsis for five or six hours, if serious injury is done to the duodenum. But this is a pathological state. It is with the normal physiology of the pylorus that the present research is primarily concerned.

In the foregoing consideration of evidence not in accord with the acid control of the pylorus, it has been necessary to assume that the ingestion of material not stimulating a flow of gastric juice is attended by a weaker tonus of the pyloric sphincter than that prevailing when food is eaten with relish. It has also been necessary to assume that if acid is secreted on proteid more rapidly than the proteid can change to acid proteid, the free acid will then cause a rapid emergence of the food from the stomach. For both these assumptions evidence is presented. If these assumptions are granted, the conclusion remains valid that acid in the stomach opens, and in the duodenum closes, the pyloric sphincter.

Inferential Support for the Acid Control from Other Processes in the Pyloric Region.

The evidence that the appearance of acid at the pylorus is the signal for the relaxation of the pyloric sphincter receives strong

support from the relation of this process to other processes in the automatic mechanisms of the stomach and duodenum.

As is well known, the acid of the gastric juice is secreted only in the cardiac end of the stomach. Edkins has reported experiments showing that the condition for the continuance of gastric secretion after the initial psychic secretion, and thus the condition for the continuance of gastric digestion, lies in a chemical stimulation of the glands through the blood stream. The chemical stimulant is produced, not by the mucous membrane of the cardiac end of the stomach, but by that of the pyloric end. It is not produced by the mucosa alone, but by the action upon the mucosa of acid, peptone, or sugar solutions. Evidently on this basis, if the pylorus opened as soon as food entered the stomach, the food would pass from the antrum without presenting to the mucosa of the antrum the acid requisite for maintaining the secretion of gastric juice. That the processes in the stomach may advance in an orderly manner, therefore, it is necessary that the food be retained until the portion in the antrum is acid.

The processes in the duodenum likewise require that food shall be checked at the pylorus until acid in reaction. If the food were allowed to depart before becoming acid, it could not stimulate chemically the duodenal reflex. The pylorus consequently would not be held closed, and the upper small intestine would be crowded full of food through an uncontrolled pyloric sphincter. Furthermore, the chyme, unless held back until acid, would not, on entering the duodenum, excite the flow of pancreatic juice and bile. Thus, if the pylorus relaxed at the approach of the first peristaltic wave (after meat had been fed, for example), the food would not only go out from the antrum wholly undigested by gastric juice, but would bear no provision for being digested by the pancreatic juice. In order that the pancreatic juice may be caused to flow and may have time to become mixed thoroughly with the chyme without being overwhelmed by fresh discharges from the stomach, food must be retained in the antrum until acid in reaction.

If it is granted that the antrum contents must be acid before being permitted to pass the pylorus, it is of interest to note how favorably the stomach is arranged for the utilization of its secretions. Evidence has previously been presented that in order to open the

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1 Edkins: Journal of physiology, 1906, xxxiv, p. 133.
2 In this discussion the somewhat variant case of the fats is not regarded.
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sphincter the acid must be at the pylorus. Clearly, if the antrum secreted acid, the acid would at once open the pylorus and let out the food (meat, for example) before the gastric juice had had opportunity to digest it. But the antrum, in which the acid stimulus acts, does not itself secrete acid. The acid and the food with an acid reaction must be brought from the cardiac end of the stomach and thoroughly mixed with the contents of the antrum before the pylorus relaxes. The necessity of importing the acid into the antrum insures a thorough mixing of the food with the gastric juice before the food departs, and provides time for gastric digestion.

The acid control of the pylorus is therefore an arrangement whereby the food is held in the stomach until provision is made for the continuance of gastric secretion, until the gastric juice has had time to act, and until the food can bear with it the acid needed for processes in the duodenum. In the duodenum the acid chyme stimulates the flow of pancreatic juice and bile, and holds the pylorus closed until this chyme has been thoroughly mixed with these digestive fluids. This thorough mixing stops gastric digestion, injurious to the action of the pancreatic ferments, by neutralizing the acid. As the acid is neutralized, the stimulus holding the pylorus closed is weakened, and then the acid in the stomach is again effective in causing the pylorus to open.

The acid control of the pylorus here described receives further inferential support from the fact that the acid affects the pyloric sphincter just as a stimulus in the intestine affects the intestinal muscle. Bayliss and Starling have shown that in the intestinal wall is a local reflex, such that a stimulus causes a contraction above the stimulated point and a relaxation below. The action of acid on the two sides of the pylorus is in exact agreement with this so-called "law of the intestine"; the acid when above causes a relaxation of the sphincter which is below, and the acid when below causes a contraction of the sphincter which is above. As already noted (see footnote, p. 311), the cardia also obeys this law. It is not impossible that throughout the portion of the alimentary canal consisting of smooth muscle, this reflex is the mechanism for orderly action.

SUMMARY.

The stomach is emptied progressively during the course of gastric digestion, by occasional discharges through the pylorus.

1 Bayliss and Starling: Journal of physiology, 1899, xxiv, p. 142.
Mechanical agencies, either in the stomach or in the intestine, play an unimportant part in controlling gastric evacuation; for (1) the occasional discharges through the pylorus are not the result of momentarily deepened peristalsis, and (2) the upper intestine in normal conditions is not sufficiently filled or distended to check the outgo from the stomach.

Observations on chemical conditions in the stomach have hitherto been defective for judging the mechanism of the pylorus, because the food given at different times has not been identical in amount nor uniform in consistency, and the difference in the chemical reaction of the two ends of the stomach has not been distinguished. Furthermore, these studies, like the observations of Hirsch, Serdjukow, and Tobler, that acid in the duodenum checks gastric discharge, have failed to distinguish between two factors always concerned in the passage of food through the pylorus.

The two factors are (1) the pressure at the pylorus due to recurrent peristalsis, and (2) the action of the pyloric sphincter. The X-ray method shows that during gastric digestion peristaltic waves are passing, not occasionally, but continuously. Since the discharge from the stomach is not continuous, but occasional, the control must rest with the pyloric sphincter.

It is necessary to explain the intermittent closure of the pylorus; the usual closure, and the occasional opening. It is also necessary to explain why, for example, carbohydrates begin to leave the stomach early and depart rapidly, whereas proteids of the same amount and consistency begin to leave the stomach only after some time, and then depart slowly.

These facts can be explained on the theory that acid in the antrum opens the pylorus, acid in the duodenum closes it. Because the acid in the duodenum is soon neutralized, the closure of the pylorus is intermittent.

That acid in the antrum signals the opening of the pylorus is indicated by the following evidence: (1) moistening carbohydrates with NaHCO₃ retards their normally rapid exit from the stomach; (2) feeding proteids as acid proteids remarkably hastens their normally slow exit; (3) observations through a fistula in the antrum show that an acid reaction closely precedes the initial passage of food through the pylorus, that the introduction of acid causes pyloric opening, and that delaying the acid reaction causes retention of the food in the stomach in spite of strong peristalsis;
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(4) when the stomach is excised and kept alive in oxygenated Ringer's solution, the pylorus is opened by acid on the gastric side.

That acid in the duodenum keeps the pylorus closed is shown by the following evidence: (1) acid in the duodenum inhibits gastric discharge (observations of Hirsch, Serdjukow, and Tobler), and as shown above, the effect is not due to stoppage of peristalsis, but to closure of the pylorus; (2) the stomach empties more slowly than normally when the tying of pancreatic and bile ducts prevents alkaline fluids from neutralizing the acid chyme in the duodenum; (3) the discharge of proteid becomes rapid if the pylorus is sutured to the intestine below the duodenum, or if a ring is cut through the muscular coats immediately beyond the pylorus. The effect from the duodenum is thus a local reflex mediated, like movements of the small intestine, by Auerbach's plexus.

Evidence for the acid control of the pylorus is also found in the application of the theory to previous observations on gastric discharge. Proteids leave the stomach only after considerable delay, and then emerge slowly; this fact can be explained (1) by the slow development of a marked acid reaction in the stomach due to the preliminary union of acid with proteid, and (2) by the large amount of acid borne into the duodenum by proteid chyme. Carbohydrates leave the stomach early and rapidly,—a result to be expected, since the acid secreted upon them does not unite with them, and is at once present to open the pylorus. The peculiar rates of discharge of combinations of these food-stuffs are also readily explained on the theory above stated. This fitness of the theory to explain established facts gives it additional support.

The rapid exit of water through the pylorus without change of reaction, and the similar rapid exit of raw egg-white,—facts not in accord with the acid control—are accounted for on the assumption that conditions not favoring gastric secretion are attended by a low pyloric tonus, and vice versa. Reasons are given for this assumption. The rapid exit of coagulated egg-white, exceptional among proteids, is explained by its slow union with the secreted acid. Fats leave the stomach very slowly. Like water and raw egg-white, they do not stimulate gastric secretion; but they may become acid in the stomach by the separation of fatty acid. Their very slow exit can probably be accounted for largely by the fact that when fats are fed, the pancreatic juice, instead of decreasing, increases the acidity of the duodenal contents.
Strong support for the acid control is found in its relation to other processes in the stomach and duodenum. The retention of food in the stomach until the antrum contents are acid is necessary (1) for the proper continuance of gastric secretion and (2) for the accomplishment of gastric digestion. Such retention is also necessary in order (3) that the chyme emerging into the duodenum may bear with it the acid required to cause the flow of pancreatic juice and bile, and (4) that the pylorus may be held closed until these important secretions are thoroughly mixed with the acid chyme.

The facts presented bring the pyloric mechanism under the "law of the intestine," -- the acid when above (in the antrum) causes a relaxation of the sphincter which is below, and the acid when below (in the duodenum) causes a contraction of the sphincter which is above.