meat the animal's stomach is not empty for about twelve hours, whereas after a full meal of milk it is empty in about three hours. In the case of meat-fed animals, therefore, the base of a gastric ulcer is more continually exposed to the action of the hydrochloric acid of the gastric juice than in the case of milk-fed animals.

I found in a series of experiments that in the case of milk-fed animals the base of the ulcer was in most cases completely covered with a single layer of epithelial cells on the twentieth day and almost completely in a minority.

In the case of meat-fed cats this stage in the healing was reached at a later period, and in these cases the delay was caused by necrosis of the granulation tissue of the base of the ulcer so that the growth of the epithelium over it was delayed. Before healing could occur it was necessary for this superficial slough to separate.

In the case of milk-fed cats the superficial base of the ulcer was formed of granulation tissue at quite an early stage, but the prolonged action of the hydrochloric acid, assisted by the more vigorous movements of the stomach in meat-fed animals, killed off the superficial portions of this tissue, and by this means delayed the growth of the epithelium over it.

EFFECTS OF MOTOR INSUFFICIENCY.

This same action of the gastric juice in delaying the healing of an ulcer can be more strikingly demonstrated by producing retention of food beyond the normal time and dilatation of the stomach by artificial pyloric stenosis. The duodenum of the cat was constricted by a short piece of rubber catheter tied on the outside. In a series of experiments of this nature I found that the healing of an ulcer was delayed according to the degree of retention of food in the stomach. One can only proceed up to a certain degree of food retention, limited by the point beyond which it is impossible to maintain the normal digestive process, owing to vomiting or extreme dilatation of the stomach with wasting and death. The delay in cases of retention of food owing to motor insufficiency I found to be about twice the normal time, or even longer than this. The delay occurred in the early stages of healing and was due to necrosis of the granulation tissue base of the ulcer, so that the epithelium was unable to grow over it.

A further change was noted—namely, that the regeneration of the mucous membrane in these cases of delay did not occur in a normal manner. The glands consisted of cells of the duct type only and were very irregularly shaped and dilated. This latter change was due to the sclerotic condition of the base resulting from the chronic irritation of the hydrochloric acid, so that the glands had not a sufficiently vascular and cellular stroma in which to proliferate. A similar condition of newly-formed mucous membrane has for a long time been known to exist in healed gastric ulcers in the human subject.

EFFECTS OF HYPERACIDITY.

So far we have been dealing with gastric juice of a normal acidity, but which has been allowed a longer time in which to act, and which has perhaps been assisted in its action by the increased peristalsis of the stomach.

We must now consider the effects of hyperacidity upon the rate of healing of an ulcer.

I had already done some experiments with guinea-pigs, the food being soaked in solutions of hydrochloric acid, but was dissatisfied with this method and the results. The following observations were made upon monkeys, the animals being fed daily by the tube with hydrochloric acid solution of different strengths. Any strength of hydrochloric acid above the normal delays the healing of an ulcer, and the amount of delay varies with the strength of the solution.

Hydrochloric acid solution above 0.5 per cent. in strength is liable to be vomited, and perhaps largely for this reason stronger solutions do not produce a proportionately greater delay. Even a 1 per cent. solution either in the monkey or the cat will not cause extension of the ulcer, and the amount of delay in the healing is not much greater than with the weaker solution. In no case was the epithelium at the edge of the ulcer destroyed, giving rise to a regular lateral extension of the ulcer. If, however, the HCl was administered during the early stages of the formation of the ulcer, the extent of the latter was

much increased. The hydrochloric acid of the gastric juice is thus only able to cause lateral extension of an ulcer the origin of which is partially due to it; the lateral spread of other ulcers in the mucous membrane is due to the persistence of the original causes of the ulcers. In all the cases the edges of the ulcers were inverted and rounded by the superficial growth of new epithelium, and the delay in healing was due to necrosis of the granulation tissue of the base. In such cases the newly formed mucous membrane was of the atypical variety. The amount of delay in the healing was from two to three times the normal period (Fig. 5). On the vegetable diet which a monkey eats, an acute ulcer of the stomach heals in three weeks.

When motor insufficiency is combined with hyperacidity a summation of effects is observed. The motor insufficiency was produced in these monkeys by constricting the first part of the duodenum with silver wire twisted upon a glass rod, 4 mm. in diameter, passed through a gastrotomy incision into the duodenum. An ulcer was also produced by injection of gastrotoxin. In three such monkeys, which were fed with strengths of 0.28, 0.39, and 0.9 per cent. hydrochloric acid solution respectively, large open ulcers were found on the twenty-first day. The bases were covered with necrotic tissue, and the epithelium had just rounded off the edges of the ulcers. All three were in very much the same condition, and their sizes were not much less than the original sizes of the ulcers (Fig. 6).

I have not observed the condition of such cases beyond the third week, but the presumption is that they would eventually heal. Another animal with a higher degree of pyloric obstruction and fed with 0.38 per cent. hydrochloric acid solution, died on the sixteenth day. A large excavated ulcer was found at the site of injection, and quite as big as the originally produced ulcer.

The delay in healing in all these cases must be ascribed to the necrotic action of the hydrochloric acid, and, as I have before remarked, in the human being the effect of hyperacidity must be considerably greater than in my experiments.

A similar condition of delayed healing of acute ulcer is found in human pathology. As a fact, one finds acute ulcers which heal readily, acute ulcers which are spreading, acute ulcers which are delayed in their healing, and definite chronic ulcers the healing of which is arrested and remains so for long periods of time.

In both the ulcers in which the healing is delayed and in chronic ulcer in which it is arrested, the same condition of the base is present—namely, necrosis of the connective tissue and secondary inflammatory thickening—and this is the reason why the ulcer is delayed or arrested in the healing. The fault is not in the epithelium, but in the connective tissue base of the ulcer. Motor insufficiency alone is able to delay the healing, and if one could efficiently produce hyperacidity even of a low degree in addition, it appears likely that a complete arrest in the healing of an experimental ulcer would be accomplished. We thus see what a very powerful factor the hydrochloric acid of the gastric juice is and what an important part it plays in the various pathological processes which constitute the life-history of a gastric ulcer.

ON GASTRIC ANALYSIS.

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THE analysis of the contents of the stomach after a test meal must always be an inexact method of achieving its object—namely, the measurement of the amount and composition of the gastric secretion. The limitations of the method are obvious. Its value must be only in so far as it gives information which may be compared with similar data, obtained under similar conditions from patients who have been found, whether at operation or *post mortem*, to present the various phenomena of gastric pathology. The value of the method must therefore obviously be the greater the more varied this information can be made, and the more perfectly the conditions of obtaining it can be standardized.

Gastric analysis, which is confined to the estimation of the chlorides, is unsatisfactory in several ways.

1. It does not differentiate between composition and quantity in the gastric secretion. If, for example, a test meal were given containing a pint of fluid, the gastric secretion might measure another pint with a chloride value of 1 per cent., or it might measure half a pint with a chloride value of 1.5 per cent., and the results of chloride analysis would be the same—namely, 0.5 per cent.

2. Directly the test meal enters the stomach it begins to leave it by the duodenum, and at the end of an hour, when the stomach tube is passed, the greater part of the meal will have left it. The product obtained with the tube will therefore consist partly of the meal, partly of gastric juice. The relative amounts of each will depend on the motor activity of the stomach, and the results of chloride analysis will vary accordingly.

3. The secreting mucous membrane of the stomach is not uniform in structure; part only—namely, the cardiac glands containing oxyntic cells—secretes hydrochloric acid. We have no justification for supposing that the gastric secretion as a whole is of constant composition as regards chloride; the cardiac portion, for instance, might initiate the secretion and the pyloric portion continue it. The results of test-meal analysis would then record only the particular composition of the combined product at the moment; in half an hour earlier or later it might have completely changed. This view has been elaborated by Sick.¹

4. The pylorus, though no doubt a powerful muscular sphincter, is not a valvular orifice. A certain amount of regurgitation of duodenal contents is permitted into the stomach through it, and the percentage of gastric HCl, possibly even of total chloride, is thereby altered.

Now, of these four points the first and the second centre upon the fact that gastric analysis by the ordinary method is not the analysis of the gastric juice, but is rather the analysis of a mixture of this with the remains of the test meal. If it were only known how much of the mixture was meal and how much was gastric juice, both difficulties would disappear, for it would become possible to calculate the actual composition of the gastric secretion. Supposing, for instance, that one obtained a fluid with a chloride percentage of 0.25 per cent., and that one knew that 25 per cent. of this fluid was derived from the fluid of the test meal; then obviously the chloride percentage of the actual gastric secretion would be $\frac{100}{75} \times 0.25$, or 0.33 per cent.

This calculated value for the actual composition of the gastric juice would be independent both of the total amount of the secreted juice, and of the rate of emptying of the stomach. Further, an idea would be obtained, though not perhaps an exact measure, of the amount of the gastric secretion, as well as its composition, as will be shown later. Finally, an indication would also be possible as to the rate of the stomach's emptying, and therefore of its motility.

These results can be attained by adding to the test meal some substance at a known concentration, and then by estimating the concentration of the substance subsequently in the fluid obtained for analysis. Suppose, for instance, that it be given at a concentration of 1 per cent., and the fluid removed be found to contain it at a concentration of 0.5 per cent., it follows that the fluid removed must consist of equal parts of the fluid of the meal, and of gastric juice. Suppose, then, that the chloride percentage of the fluid be 0.25 per cent., the chloride percentage of the gastric juice itself will be 0.5 per cent.

Various substances have been suggested from time to time for addition to the Ewald test breakfast, with a view to obtaining a measure of the gastric motility. These methods, since their object is now more satisfactorily achieved by x-ray examination with bismuth, have lately been dropped, for their wider application to the estimating of the composition of the secreted gastric juice has not apparently been made. Boas² first used a solution of chlorophyll in water, and subsequently estimated it colorimetrically. Mathieu³ used oil of sweet almonds in emulsion in the test meal and then weighed the ethereal extract. Roux and Laboulais⁴ used disodium phosphate, estimating it afterwards by titration against uranium

acetate. Meunier⁵ added to the test meal a minute quantity of an iron salt, and estimated with sulphocyanide. None of these methods are at all satisfactory; their technique is difficult, their sources of error great; in Boas's and Meunier's methods the meal must be one of water, for the tea in the standard meal (Ewald) would interfere with the estimations; Roux and Laboulais's substance interferes with and upsets the reaction of the gastric contents; Mathieu's method is laborious and inexact. For this work the substance used has been urea. To an ordinary test breakfast, consisting of toast and a pint of tea, 5.72 grams of urea are added, making a 1 per cent. solution. The concentration of the urea in the fluid subsequently obtained indicates the degree of dilution by gastric juice which the fluid of the meal has undergone. The estimation of the urea by an ordinary hypobromite method is vitiated by a slight error due to the presence in the gastric content of proteoses; a more exact figure would be obtained by the use of the urease method of urea estimation, first suggested by Marshall, jun.,⁶ and this method, as adapted by Plimmer and Skelton,⁷ has been utilized in some of the present experiments.

The conditions in which this refinement of gastric analysis would appear to have value are, then, first, where there is abnormally rapid or abnormally slow emptying of the stomach through the pylorus; and, secondly, where an increased or decreased secretion simulates or is indistinguishable from an increased or decreased acidity.

1. Delayed evacuation of the stomach (pyloric stenosis), or accelerated evacuation (hypertonus). These conditions introduce an element of confusion into the interpretation of gastric analyses, for the fluid analysed will contain in the one case an abnormally high proportion, and in the other case an abnormally low proportion, of the fluids of the meal. In pyloric stenosis the acidity is greater than it appears, for much of the administered fluid is present; in hypertonus the acidity of the gastric juice is practically the same as it appears, for practically all of the administered fluid will have left the stomach. If urea be added to the meal, as described, and subsequently estimated, and the volume of the gastric contents at the end of an hour be also measured, the total amount of urea remaining in the stomach at the end of that time can be calculated. Suppose, for instance, that 5.72 grams of urea be administered, and 100 c.cm. of gastric contents be obtained, with a urea concentration of 0.2 per cent., then it is plain that only 0.2 gram out of the original 5.72 grams of urea, or 3 per cent., can still be left in the stomach. The rate of emptying of the stomach, then, will be 97 per cent. in an hour. By these means it is found that in the normal stomach only 2 or 3 per cent. of the original meal remains in the stomach at the end of an hour, and hence the results of simple chloride analysis are approximately correct; while if there is pyloric stenosis the remnants of the meal may amount to 30 per cent. or more, and hence the figure on chloride analysis will be very far from indicating the actual composition of the gastric secretion. The following cases will illustrate the degrees of difference which are met with:

Subject.	Volume of Contents Obtained.	Urea %	Total Urea in Stomach (out of 5.72 Grams Administered).	Meal Left in Stomach at Moment of Emptying.	Condition.
A. 21	40 c.cm.	0.13	0.052 gram	0.9 %	Hypertonus.
T.B.H.	75 c.cm.	0.17	0.15 gram	2 %	Normal.
A. 0	300 c.cm.	0.63	1.89 grams	33 %	Pyloric stenosis.

Since the proportion of the meal-constituent in the gastric content varies in this way and to this degree, it follows that in cases of pyloric stenosis the actual acidity of the gastric juice will be obtained by multiplying the figure obtained by a large factor, while in the absence of stenosis, and in the opposite condition, this will not be the case; the figure obtained will represent fairly accurately the actual composition of the gastric juice. The factor by which it will be necessary to multiply the figure obtained

from analysis, is given by the percentage of urea found on estimation. Thus, in the three cases already quoted:

Subject.	Condition.	Active HCl on Analysis.	Urea % (1 % administered).	Calculated Active HCl of the Gastric Juice.	Diagnosis.
A. 21	Hypertonus	0.32	0.13	0.37	Hyperchlorhydria.
T.B.H.	Normal	0.16	0.17	0.19	Normal.
A. 30	Pyloric stenosis	0.15	0.63	0.41	Hyperchlorhydria.

In the last of these three cases, though the chloride is apparently only normal, it is actually very much above normal, for the gastric juice has been diluted with a larger proportion of the original meal than has been the case in the other two instances. By calculation from the urea value obtained, the actual hyperacidity of the gastric juice is demonstrated.

The condition of delayed emptying of the stomach does not always depend upon pyloric stenosis. It may often be due to atony, or to psychical causes. The danger of error in the simple gastric analysis in all these cases is equally great.

2. Increase in the quantity of the gastric secretion (hypersecretion), or deficiency (hyposecretion). These factors, whatever their pathological cause or clinical significance, must obviously have the effect of masking or of simulating changes in the actual composition of the gastric juice. The conditions of altered composition and of altered amount of the juice are, in fact, rarely differentiated. The possibility, indeed, of hyperacidity, as distinct from hypersecretion, has been called into question. From the standpoint of simple gastric analysis hyperacidity and hypersecretion will be indistinguishable. The above-mentioned urea method affords a simple means of determining the composition of the gastric secretion, and inferring its amount. When there is much gastric secretion the proportion of urea will be low; when it is scanty the proportion will be higher. Increased motility of the stomach, and increased secretion will therefore have the same effect of causing a low urea figure—that is, of increasing the ratio, gastric juice: residue of meal, in the gastric content. The more active the stomach movements, the more copious its secretion, the more closely does the analysed gastric content approximate to the composition of the actual secretion. When the movements are sluggish, or the quantity of secretion deficient, the deviation from this becomes wide, and it is in these cases that error is likely to be made in the interpretation of obtained figures. In a case, for instance, of suppression of the gastric secretion, the fluid obtained for analysis will consist almost entirely of the fluid of the meal, for but little gastric juice will have been added to it. Hence the figures of analysis will represent, not the true composition of the gastric secretion, but rather the composition of the administered tea, mixed with a small proportion of added juice. It is obviously desirable that we should know in these cases what is the nature of the fluid with which we are dealing. To take typical cases:

Subject.	On Analysis. Active HCl %.	Urea % (1% administered).	Calculated Active HCl of Gastric Secretion.	Condition.
A. 42	0.01	0.50	0.02	Hypoacidity.
T.B.H.	0.16	0.17	0.19	Normal.
S 44	0.02	0.94	0.35	Hyposecretion

It would, of course, be a mistake to suppose that these cases represented the conditions which they typify in extreme purity. The first of the cases, for instance, has some hyposecretion as well as hypoacidity, for the urea value in his case, though very much lower than in the third, is yet considerably higher than in the normal. The two conditions are often, in fact usually, associated; but it is none the less important to be able to distinguish between them. The gastric content of a case of carcinoma of the stomach, for example, in which HCl is often absent owing to neutralization of the secretion, would at once be

distinguished from the so-called primary achylia gastrica, where the gastric mucous membrane has completely atrophied and the gastric secretion is absent. The clinical associations of hypoacidity, however, as opposed to those of hyposecretion, remain to be worked out.

The effect of a marked diminution in the quantity of the gastric secretion will be similarly great in cases where the acidity is increased. The figure on analysis may lie within normal limits, owing to the abnormally large proportion of the fluid of the meal still present, and yet the actual acidity may be very much above normal. Similarly, if the secretion is much increased in amount, as in the so-called cases of gastrosuccorhoea, the fluid for analysis will be practically pure gastric juice, and an excessively high value for its acidity may hence be inferred. The urea method affords a comparatively simple method of distinguishing these two conditions of increased acidity, and increased secretion. Again, to take typical instances:

Subject.	On Analysis. Active HCl %	Urea % (1 % administered).	Calculated Active HCl of Gastric Secretion.	Condition.
C. 11	0.28	0.16	0.33	Hypersecretion
T.B.H.	0.16	0.17	0.19	Normal.
A. 12	0.20	0.61	0.51	Hyperacidity.

Here, again, the conditions of hypersecretion and hyperacidity are not necessarily opposed to one another; they are commonly associated together, owing to a common cause. In the first of these three cases, for instance, there is some hyperacidity as well as hypersecretion. But these cases illustrate how a simple gastric analysis may fail to represent the actual condition of the gastric secretion. For in the first case analysis gives a higher figure for active hydrochloric acid than in the third; yet by reason of the fact that the secretion in the third case is so much the less abundant (as shown by the higher urea value), the acidity in the third case is actually the higher of the two.

It is sometimes found in the analysis of gastric contents, after urea has been added to the test meal, that the acidity of the fluid to phenolphthalein has disappeared. Its reaction may even have become alkaline. The figure for the active hydrochloric acid, however, remains in these cases unaltered. The cause for this is manifestly the formation of ammonia from the urea. Dr. J. H. Ryffel suggests that this is due to gastric sepsis, and, since it is only rarely observed, may indicate the presence of a special organism.

CONCLUSIONS.

1. The interpretation of the figures obtained by gastric analysis after a test meal is, by reason of the number of factors involved, a matter of great complexity. Any additional means of standardizing results is therefore desirable. Such means is afforded by adding to the meal a fixed proportion of some inert substance, such as urea, whose proportion can be estimated subsequently in the gastric content.

2. It is then possible to arrive by calculation at an approximation to the figures for the actual composition of the secreted gastric juice, as opposed to those of the mixture of this with the remnants of the fluid of the meal.

3. By this method it is possible also to eliminate the disturbing influences of an abnormally rapid or an abnormally slow rate of emptying of the stomach into the duodenum.

4. The conditions of hyperacidity and of hypoacidity can then be differentiated from those respectively of hypersecretion and hyposecretion.

This work has been carried on with the constant advice and help of Dr. Ryffel, and many of the analysis figures obtained and quoted were made by him in the routine analysis of gastric contents from ward cases. My cordial thanks are due to him for the use of these figures, and more still for his kind assistance.

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