A STUDY OF THE MODE OF ACTION OF GASTRO-TOXIN AND THE HEALING OF GASTROTOXIC ULCERS.¹

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(PLATE XXIII.)

IN a former paper (¹) I was able to demonstrate that the serum formed by immunising the rabbit with the gastric cells of the guinea-pig, or with those of another rabbit, on injection into the guinea-pig's peritoneum produced general symptoms of intoxication and patches of necrosis in the mucous membrane of the stomach, which were stained black by altered blood pigment, and which subsequently developed into gastric ulcers.

The present communication will deal with the two following points:—

1. The way in which the blood-stained patches of necrosis are produced.

2. The subsequent changes which occur in the ulcers under normal and pathological conditions.

A preliminary report on some of the main results of this series of experiments was communicated to the Pathological Section of the Royal Society of Medicine in 1908 (²).

I. MODE OF ACTION OF GASTROTOXIN.

The presence in the necrotic patches of altered blood pigment seemed to indicate that the gastric juice played an important part in the production of the lesions, which might have been brought about in one of the two following ways:—

1. By the direct action of the gastrot toxin on the gastric cells, the hæmorrhage being secondary to digestion of the mucous membrane by the gastric juice.

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2. By a destructive action of the poison upon the capillary wall, the hæmorrhage being the primary condition, and the cell necrosis a secondary effect of the gastric juice.

It was decided, therefore, to put the gastric juice out of action whilst the poison was acting. This is quite easy to do, since the poison acts within a few hours.

The method, which consists in passing a soft rubber catheter down the œsophagus of the guinea-pig and filling its stomach with a weak alkaline solution, and the results of this experiment, were described in a former paper (1907³). It was found that neutralisation of the gastric juice prevented the occurrence of any lesion in the stomach. The alkaline solution employed had a volume of about 14 c.c. to 20 c.c., and contained 1 per cent. sodium bicarbonate or any strength above this. Solutions of soda of strengths below 1 per cent. will partially, but not completely, prevent the necrosis occurring. Control animals were in each experiment injected with the same dose of the same serum and in all cases showed the usual lesions.

It was quite evident from these experiments that the first hypothesis was correct, and that the hæmorrhage was a secondary condition, because, if the hæmorrhage had been the primary lesion, neutralisation of the gastric juice would not have prevented its occurrence.

The gastrotoxin therefore directly produces some change in the gastric cells, leading to digestion of the mucous membrane in patches, which are stained dark brown or black by hæmatin formed from the hæmoglobin of the blood in the capillaries by the action of the acid of the gastric juice.

Initial Change in the Gastric Cells.

A series of animals was injected with the serum and the animals were killed at different stages (*e.g.* at the end of one hour, two hours, and so on), so as to obtain microscopic sections of the necrotic patches in the course of formation.

Some of the blocks were hardened in formalin, and the sections stained with hæmatoxylin and eosin. Others were fixed in a mixture of picric acid, formalin, and acetic acid, and the sections stained with eosin and toluidin-blue, or with safranin, or fuchsin. No distinct change, however, in the cells preceding digestion could be found. All the cells around a necrotic patch which were about to be attacked stained perfectly well and appeared quite normal.

Sections of stomachs in which the gastric juice had been previously neutralised showed the cells to be normal, although the animals had been killed by the serum.

It is evident, therefore, that the actual necrosis of the cells, as seen under the microscope, is brought about by the action of the gastric juice acting upon a cell in some way changed, but showing no microscopic deviation from the normal. With regard to the nature of this change in the cells rendering them susceptible to the action of the gastric juice, two hypotheses present themselves as follows:—

1. The normal cells possess a specific resisting power (possibly of the nature of an antibody), which is destroyed by the gastrototoxin.

2. The cells are damaged or in some way devitalised, and therefore are unable to resist the action of the gastric juice.

In order to settle which of these hypotheses was correct I tested the action of other poisons.

In a previous paper (1906 ⁴) I was able to show that hepatotoxin, enterotoxin, and hæmolysin were all able to produce necrosis of the mucous membrane of the stomach indistinguishable from that produced by gastrototoxin. In the same paper it was pointed out that none of these cytotoxins was strictly specific, but that each acted with greatest intensity upon the tissue against which it was formed whilst possessing a slight action upon other tissues of the body. I have now been able to show that the above three cytotoxins produce their effects upon the stomach in exactly the same way as does gastrototoxin. This was shown by the method of neutralisation of the gastric juice by sodium bicarbonate. In all the cases the alkali was able to prevent the stomach lesions occurring; thereby showing that the poisons acted directly upon the stomach cells and did not cause ulceration by first producing a hæmorrhage. I referred to this fact in the paper published in December 1908, and in June 1909 Rehfuß (⁵), using my neutralisation method, proved that the venom of *Heloderma suspectum* produced gastric ulceration in the same way.

It seems quite clear from this that the second hypothesis is correct, namely, that it is a question of devitalisation of the cell, which then becomes digested, for hepatotoxin, enterotoxin, and hæmolysin cannot be supposed to have any influence in removing or destroying any supposed specific resisting power possessed by the gastric cells against digestion by the gastric juice. This observation is important from several points of view. It establishes the principle that self-digestion of the gastric mucous membrane may be brought about by a poison circulating in the blood, and it also raises the question whether there may not be many endogenous and also exogenous poisons (*e.g.* bacterial or otherwise) which by their action on the gastric cells through the blood stream may so devitalise them as to initiate self-digestion. Whether the cell is actually killed by the poison or not does not seem to me of much importance. The point is that the cell can be so altered by a poison circulating in the blood that it is digested.

It is well known that acute gastric ulcer in the human being is associated with many different diseases of bacterial origin, and that necrosis of the gastric mucous membrane may be brought about by bacterial poisons irrespective of the actual presence of the micro-organism, as in Péron's case (1897 ⁶) and in the experimental work of Enriquez and Hallion (1893 ⁷), to quote instances. Many bacteria on injection give rise to ulceration of the stomach, and a great deal of

work has been done in this direction, but the details of this do not concern us here.

These experiments also show that a hæmolytic serum prepared by the injection of washed red blood corpuscles probably contains many protoplasmic poisons, for in addition to its actions upon the red blood corpuscles, and upon the capillary wall by its hæmorrhagin, it is also able to damage the gastric cells. It does this although no hæmorrhages are to be found anywhere in the body, the capillary endothelium not being sufficiently damaged to allow of the escape of blood, the gastric cells being necrosed because they happen to be exposed to the action of the acid gastric juice. It is not intended in this short report to discuss fully the literature on the subject, and it is sufficient to state that it is now well known that hæmolysin will act on many tissues of the body.

This demonstrated action upon the gastric cells of a poison circulating in the blood suggested that certain substances introduced into the cavity of the stomach might produce a similar effect, or, if too weak to produce self-digestion alone, that they might, if combined with the administration of gastrotoxin, increase the effect produced by this poison.

Effects of Hyperacidity of the Gastric Juice.

The first substance experimented with was hydrochloric acid. The *normal acidity* of the stomach contents of the guinea-pig was estimated at varying periods of time after it had eaten a test meal of oats, bran, and green vegetables.

The animal was killed, and the stomach contents made into a suspension with 50 c.c. distilled water. The volume of the contents was thus determined. The suspension was diluted with water until its volume formed a simple multiple of that of the stomach contents. The suspension was allowed to stand for twelve hours and then filtered. The percentages of the total chlorides and of the inorganic chlorides in the filtrate were determined by the silver nitrate method, and the percentage of active HCl found by deducting the latter from the former. By this method the following results were obtained in twelve animals:—

Time after Test Meal.	Percentage of Active HCl.
1 hour	0·126, 0·1008.
2 hours	0·144, 0·09, 0·108, 0·126, 0·144.
3 „	0·216, 0·234, 0·187.
4 „	0·252, 0·205.

The increase in acidity is due to the fact that a guinea-pig eats a very large test meal in a short time if previously starved, so that the food does not become uniformly saturated with acid till about three hours after the meal. The amount of HCl is very similar to that found in the human subject.

Effects of Hyperacidity of the Gastric Juice alone.

Twenty-four guinea-pigs were fed with solutions of HCl of various strengths by stomach tube, the animals having been previously starved overnight. It was found that no effect was produced with solutions up to a certain point, but beyond this point necrosis of the mucous membrane and ulceration were produced, the lesions macroscopically differing in no particular from those produced by gastrotoxin.

The acid used was commercial HCl, which by titration with decinormal soda solution was found to contain about 34 per cent. HCl. About 20 or 25 c.c. of the solutions were introduced in each case. The weights of the animals varied from about 300 to 600 grms.

The results obtained were very uniform. Solutions of strengths below 0.7 per cent. HCl produced no lesion in any animal, small or large. Above 0.7 per cent. lesions occurred in the smaller animals, and above 0.9 per cent. in the larger animals. Solutions of 1, 1.16, and 1.3 per cent. strengths converted the whole mucous membrane into a black mass.

Effects of Hyperacidity combined with Gastrotoxin.

A series of twenty-two experiments was done in the same way as I described in connection with the neutralisation experiments. The dilute acid solution was introduced into the stomach by an œsophageal tube, and the gastrotoxic serum at once injected into the peritoneal cavity. In each experiment a control guinea-pig was injected with the same amount of the same serum at the same time, and the two experiments subsequently compared.

In my first paper (1904¹) I pointed out that the lesions produced by gastrotoxin were not invariably of exactly the same extent in guinea-pigs of the same weights, but this error becomes negligible when a sufficient number of experiments is done.

The strengths of the HCl solution in each case were such as had been found to be innocuous alone (*e.g.* below 0.7 per cent.). Solutions of strengths above 0.3 per cent. were found to increase markedly the lesions; below this strength the result was sometimes an increase, and at 0.2 per cent. the solution produced no effect whatever. Three of these experiments were described in the paper quoted above (1907³), the HCl referred to in that paper being commercial HCl. This result indicates that if the percentage amount of HCl in the stomach contents of the guinea-pig rises above normal, the lesions produced by gastrotoxin will be more marked than if the acidity of the stomach contents be normal.

How does the Hyperacidity produce this Effect?

In answer to this question two hypotheses are available—

1. The HCl increases the peptic activity of the gastric juice.
2. The HCl acts as an additional protoplasmic poison.

The first hypothesis is unlikely, because it is well known that only within small limits will an increase of HCl assist in the digestion of certain food-stuffs. There is a definite amount of acidity for optimum activity of the gastric juice, and this varies for the different

kinds of protein to be digested. The whole question probably turns on what strength of acid will most easily cause swelling of the tissue to be digested. It seems, therefore, that the second hypothesis is correct, and that the HCl increases the tendency to digestion of the mucous membrane by acting as a protoplasmic poison. In the higher strengths (*e.g.* above 0·7 per cent.) it is able alone to poison the gastric cells and bring about self-digestion; in the lower strengths (*e.g.* below 0·7 per cent.) it adds its quota to that of the gastrototoxic serum, and the result is a summation of effects.

This hypothesis is supported by certain experiments in which I have introduced other protoplasmic poisons into the guinea-pig's stomach.

These experiments will now be considered.

Effects of the Introduction of other Acids alone.

Three acids have been used—commercial sulphuric, glacial acetic, and lactic acids. These were introduced into the stomach by œsophageal tube under the same conditions and in the same amounts as in the case of the HCl.

Commercial sulphuric acid.—Black patches of necrosis are produced with all strengths above 0·9 per cent.; below this no lesion results.

Glacial acetic acid.—Necrotic patches and ulcers are produced by a 2·5 per cent. solution, and solutions of all strengths above this. A 2 per cent. (and below this) solution produces no lesions.

Lactic acid.—This acid is not so potent as the former. In all guinea-pigs no lesion whatever results when 4 per cent. or weaker solutions are used. Solutions of 6 per cent. strength or above this cause lesions in small animals (400 grms.). Larger animals require a rather higher percentage. The whole mucous membrane may be brown in colour, with distributed black patches.

Effects of these Acids combined with Gastrototoxin.

The strengths of the acids used were such as had been found to be innocuous alone. The acids were introduced into the stomach as before, and gastrototoxin was at the same time injected into the peritoneum. Controls were in all cases injected with the gastrototoxic serum.

Commercial sulphuric acid.—Solutions of 0·6, 0·7, and 0·8 per cent. strengths increase the lesions produced by gastrototoxin, but 0·5 per cent. and under appear to have no effect.

Glacial acetic acid.—A 0·5 per cent. solution or any strength above this markedly increases the gastrototoxic lesions.

Lactic acid.—3 and 4 per cent. solutions increase the effect of gastrototoxin.

Effects of Acids combined with Hepatotoxin, Enterotoxin, and Hæmolysin.

Briefly stated, it has been found that the acids in inert solutions increase the effects produced by these three cytotoxins in exactly the same way as they do those of gastrototoxin.

Effects of the Introduction of other Protoplasmic Poisons.

Bile salts and formic aldehyde were used. They are powerful protoplasmic poisons, and produce much the same effect upon the mucous membrane

of the stomach. The lesions produced are quite different from those caused by acids. The stomach is found to be much congested, the mucous membrane is dull red and raw looking, and there is considerable secretion of mucus. With weaker solutions a black patch or two may be seen. Digestion of the mucous membrane does not occur, because the cells are probably protected by the increased secretion of mucus, and probably also by stoppage of the secretion of gastric juice.

Sodium taurocholate produces the above effects in 3 per cent. solution. Combined with gastrotoxin inert solutions commonly cause a marked inflammatory reaction; if this does not occur the gastrotoxic lesions are increased (Plate XXIII. Fig. 1).

The weakest strength of *formic aldehyde* which is able to produce such lesions is 0.3 per cent. Combined with gastrotoxin inert solutions produce precisely the same effects as does sodium taurocholate.

From all these experiments it appears that self-digestion of the mucous membrane of the stomach may be brought about by poisons devitalising the gastric cells, either through the blood stream or by attacking them from the free surface of the mucous membrane, and that in either case the lesions produced are precisely the same. It is of great significance that certain substances, in themselves innocuous when introduced into the stomach, are, however, able to add their quota to that of a devitalising influence affecting the cells through the blood, and so produce self-digestion. This is of special importance in relation to hydrochloric acid, since any increase above the normal markedly predisposes to self-digestion. The percentage of HCl in the human stomach rarely rises above 0.35 per cent. But the *total acidity* may rise to 0.6 or 0.7 per cent., and it has been demonstrated that other acids besides HCl (lactic, etc.) are also able to produce a devitalising influence on the gastric cells, so that here is a condition especially predisposing to self-digestion. Again, vinegar contains 4 per cent. glacial acetic acid, and 0.5 per cent. solution of this acid is capable of increasing the gastrotoxic lesions, so that the drinking of vinegar, which is occasionally seen in a certain class of persons, is quite likely to cause gastric ulceration, especially if associated with some poisoning of the cells through the blood.

The fact that the above acids are able to increase the devitalising action of gastrotoxin lends support to the view that the latter substance does not actually kill the gastric cells, but markedly affects their vitality. It is, of course, difficult to prove this point, but it certainly appears as if the actual death of the cell were not a necessary antecedent to digestion.

II. THE HEALING OF GASTROTOXIC ULCERS.

It has been shown that gastrotoxin is not a specific poison for the gastric cells, but that it acts on other tissues and produces general symptoms of intoxication. The method of injection into the peritoneal cavity or blood stream is therefore an unsuitable one to employ for

the study of the changes occurring in the ulcers, because so many animals die from the effects of the poison upon other tissues. It is of no use giving small doses, as the poison is taken up by so many organs of the body that it is soon neutralised, and I have shown that repeated injection of the serum gives rise to immunity to the gastrot toxin (⁸). I have therefore used the method of local injection of the serum into the stomach wall, and in this way a true acute gastric ulcer, in all respects comparable to that seen in the human subject, may be produced.

Method.—The guinea-pig is previously starved for some fifteen or eighteen hours, so that the stomach wall is not too thin and the stomach can be properly manipulated. The organ is by no means empty, and after this period of starvation it usually contains variable amounts of highly acid food remnants. If the stomach were absolutely empty and the glands resting it is probable that ulceration would not be produced, as the necrosis of the epithelium depends upon digestion by the gastric juice.

Ether is administered, the abdomen is opened in the middle line under strict antiseptic precautions, and the stomach drawn out. A hypodermic needle is inserted under the peritoneal coat of the stomach, and from $1\frac{1}{2}$ to 2 c.c. gastrototoxic serum injected so as to form a blister under the peritoneum. The size of this blister should not be less than that of a shilling. More or less serum escapes when the needle is withdrawn, but not much, as it is enclosed in the meshes of the tissues, forming a local oedema. The stomach is replaced and the abdominal muscles and peritoneum united by silk, the skin being separately sutured. A collodion dressing is applied, and the wound heals by first intention.

Mode of action.—I have been able to show that the action is a toxic one, and not a mechanical effect resulting from pressure. In order to do this it is merely necessary to inject an innocuous fluid and note the result. I have injected normal rabbit's serum, normal guinea-pig's serum, and physiological salt solution. In each case the solution is absorbed without leaving any trace of necrosis or ulceration.

It is, of course, possible to produce slight mechanical ulceration by injecting massive amounts of neutral fluids, and this is easier to do in the case of normal rabbit's serum, because it is very slightly toxic for the guinea-pig's tissues, but it is surprising to what an extent the mucous membrane and peritoneal coat may be separated without any harm whatever resulting; such a method of producing ulceration is, however, quite useless, as one can never predict what is likely to happen, the whole may be completely absorbed, the mucous membrane may rupture, a slight ulcer may result, or the animal may die.

The activity of the gastrot toxin in producing an ulcer by the method of local injection varies exactly with its activity in producing lesions when carried to the stomach by the blood. As I have mentioned before, individual rabbits vary in the strength of the serum they produce. The best time for collecting the serum for this purpose is, as I have pointed out in former papers, from four to six weeks after

the commencement of immunisation, and after a few months the serum is not of much potency.

Formation.—The gastrototoxic serum soaks into the overlying mucous membrane, which is then digested at this spot by the gastric juice and forms a slough. There is always more or less hæmorrhage under the mucous membrane, which depends on mechanical injury to the vessels during the injection. By about the third or fifth day the necrosed portion has become disintegrated and separated, and a clearly defined ulcer is formed having for its base the peritoneum, which is more or less covered with the remains of the muscular coat. There is no doubt that the necrosed tissue becomes secondarily infected with bacteria from the food, and that in this way adhesions with neighbouring organs and thickening of the base of the ulcer is produced; at the same time irritation of the base of the ulcer by the gastric juice may probably produce a like result. The size of the ulcer is considerably less than the size of the blister which has been produced in the first instance. During the formation of the ulcer the peritoneum may give way and septic peritonitis result, or it may become adherent to the liver or other organ and a subdiaphragmatic abscess result.

Healing.—The healing was first studied in animals on a normal diet (oats, bran, and green vegetables). The conclusions have been drawn by observing the different stages in the healing in some forty guinea-pigs. A certain number of the animals died during the formation of the ulcers as described above. In all the cases the ulcer was produced upon the anterior wall of the stomach at about its centre. The ulcer commences to heal at once, and gradually shrinks, becoming smaller and smaller until it is completely healed.

Sometimes there is practically no thickening left, the ulcer having disappeared except for a slight puckering of the mucous membrane, which may have a stellate character. At other times there is considerable thickening of the peritoneum, and a definite nodule is left to mark the site of the ulcer. The base of the scar may be firmly adherent to a neighbouring structure, or loose and completely organised adhesions may occur with the intestines, omentum, liver, and abdominal wall. In all cases the ulcer heals in from fourteen to twenty-eight days. The actual time of healing depends to a large extent on the size of the ulcer, and probably upon the amount of inflammatory reaction set up, which in its turn may depend upon the extent to which the ulcer has been secondarily invaded by bacteria or irritated by the gastric juice. It is impossible to make all the ulcers of exactly the same size, since the serum does not always spread out over exactly the same area, and more escapes from the puncture in some cases than in others, so that a slight variation occurs in the exact time of healing; but this only amounts to a few days, and I repeat that in all cases healing promptly occurs.

Cohnheim (⁸), using a modification of a method first introduced by

Panum (1862⁹), found that the gastric ulcers, produced in dogs by injection of chromate of lead into one of the gastric branches of the splenic artery so as to give rise to an area of infarction, healed within three weeks. Many other experimenters, from Quinke (10) in 1875 to Litthauer (11) in 1909, have directly injured the gastric mucous membrane by various means, and also found that the lesions so produced healed within a few weeks. Acute ulcers of the stomach are by no means uncommon in the human subject; they do not necessarily give rise to symptoms, and they heal as experimental ulcers do. Chronic gastric ulcer, however, is a common malady, the ulcer may persist for months or even years, and it may extend.

Since ulcers formed by the process of self-digestion are initially acute, there must be present some unknown condition or conditions preventing the healing of such chronic ulcers. I have performed the following experiments with the object of discovering such conditions.

Effects of position.—I have produced ulcers quite close to the *cardiac orifice* in nine guinea-pigs and have found that, the animals being otherwise normal, the ulcers all healed up in about three weeks.

Pyloric ulcers were formed in ten animals, and were found to heal up in precisely the same time. Whether the serum be injected into the *anterior* or *posterior* wall does not at all matter, the resulting ulcers heal up in the prescribed time.

Effects of hyperacidity of the gastric juice.—Ulcers were produced in twenty-four guinea-pigs. Half the animals were put on a normal diet and half on an acid diet. The animals were killed at various stages, and in each case the stomachs of those on an acid diet were compared with those on a normal diet.

This investigation showed that the ulcers in the animals fed on an acid diet passed through precisely the same stages as those in the animals fed on a normal diet, and that they healed up in the same time. On the whole, they appeared to be in a rather more advanced condition of healing than the corresponding ulcers in the animals fed on a normal diet. The acid diet consisted of green vegetables, bran, and oats soaked in 2 per cent. commercial HCl (1 = 0·6 per cent. HCl) (Plate XXIII. Fig. 2). The animals do not like this food, but they will eat it when they are hungry.

In order to show that it is possible to keep the percentage of HCl in the gastric contents above the normal by this means a series of animals was fed on food soaked in 0·5 per cent. HCl and the stomach contents estimated each hour, with the following result:—

Time after Test Meal.	Percentage of HCl.
1 hour	0·3240
2 hours	0·2793
3 „	0·234
4 „	0·2916
5 „	0·3168

Five animals in which pyloric ulcers had been produced were put on food soaked in HCl combined with albumin. The ulcers of these animals passed through the usual stages, and healed during the third week.

A moderate increase in the acidity of the gastric juice such as occurs in the human being will not therefore delay the healing of an ulcer. Several observers, especially Matthes (1893¹²), have been credited with proving that hyperacidity delays the healing of an ulcer. Matthes only describes one experiment in which he stitched a porcelain ring to the peritoneal layer of the stomach and cut off the enclosed mucous membrane measuring 6 cm. in diameter. The dog was given a 0·5 per cent. solution of HCl daily by tube, and at the expiration of three weeks was killed. An unhealed area the size of a split-pea was found at the autopsy. The lesion of the control animal was healed in four weeks. The evidence afforded by this experiment of the influence of hyperacidity in delaying the healing of an ulcer does not appear to me to be very weighty, especially in view of the recent experiments of Litthauer (1909¹¹), who found hyperacidity without influence.

Gastric ulcer in the human being may or may not be associated with hyperacidity of the gastric contents.

It has been shown above that hyperacidity of the gastric contents is capable of increasing the tendency to ulceration, and since it has been shown that hyperacidity will not of itself delay the healing of gastric ulcer in the guinea-pig, it seemed of interest to determine what was the effect of the presence of gastric ulcer upon the acidity of the gastric juice.

*Effects of Acute Gastric Ulcer upon the Acidity of the
Stomach Contents.*

Ulcers were produced in nineteen guinea-pigs. These animals were given test meals at various stages of the healing process, and the stomach contents were examined two hours later. The normal percentage of HCl two hours after a test meal as stated above is from 0·09 to 0·144. The following results were obtained :—

Day of Disease.	Condition of Ulcer.	Percentage of Active HCl.
5	Large, necrotic, base tore	Nil.
5	Small, clean base	0·2772
6	Large, necrotic, base tore	0·036
6	Large, sloughy base, adherent	0·054
6	Medium, clean	0·108
7	Large, sloughy base	0·0576
8	Large, slough, small abscess	Nil.
8	Large, adherent, thickened, clean	0·0972
8	2 pin-point, almost healed, ulcers	0·09
9	Large, clean	0·1872
10	Small, adherent, base tore	0·07
11	Medium, adherent, clean	0·144
11	Pin-point, almost healed	0·144
11	Medium, base necrotic	0·126
14	Large, clean	0·216
14	Medium, clean	0·324
18	Small, adherent, almost healed	0·144
19	Small, almost healed	0·144
20	Healed, thickening	0·18

It appears that when the ulcer is in the stage of formation and before the base has been cleanly digested there is a diminution in the active HCl in the gastric contents. If this were due to neutralisation of the HCl by the alkaline discharge from the ulcer the inorganic chlorides would be correspondingly increased.

As a fact in the above experiments the inorganic chlorides remained about normal in all cases, and there was no such correspondence to be seen; so that in the early stages there is a diminished secretion of HCl. When the base of the ulcer is clean and it is in process of healing there may be an increase in the HCl secreted, but it is more likely that the HCl will be normal in amount, especially if the ulcer be almost healed.

Effects of Diminution of the Acidity of the Gastric Juice.

Gastric ulcers were produced in twenty-five guinea-pigs, and the animals were then placed on an alkaline diet consisting of oats, bran, and green vegetables soaked in 4 per cent. solution of sodium bicarbonate. The ulcers in these animals were compared with controls at various stages. In all cases the ulcers showed evidence of healing, but in the early stages there was perhaps more sloughy material attached to the base of the ulcers, and in the later stages slightly more tendency to thickening and adhesions than in the animals on a normal diet. In many cases the ulcers also seemed to be in not quite such an advanced stage of healing as were the control ulcers.

However, if any delay occurred in the healing process it was only a question of a few days, and in no case did a chronic ulcer result. I have mentioned above that when the gastric juice is hyperacid the ulcers appear to heal more rapidly; this is probably due to the fact that the food is better disinfected. When the acidity of the gastric juice is diminished the food is not so well disinfected and there is a greater tendency to bacterial infection, and perhaps a slight lengthening of the healing time, but this is of no material importance. Diminished acidity of the stomach contents probably also leads to a loss of tone in the muscular coats, which may be of some influence.

The following table shows that it is possible to keep the gastric contents alkaline or neutral for longer periods of time than are normal by feeding animals on food soaked in soda solution, although it is impossible by this means to render the contents permanently alkaline. The animals were fed on food soaked in 4 per cent. sodium bicarbonate solution, and the stomach contents examined at different intervals.

Time after Test Meal.	Percentage of HCl.
1 hour	Absent.
2 hours	"
3 "	"
4 "	0·072.
5 "	0·2016, 0·126, 0·252.

As a matter of fact, at any period of digestion, although the contents of the stomach are alkaline, there is always a layer in contact with the

stomach wall giving an acid reaction; when the contents are mixed for estimation this layer of acid is neutralised by the alkali.

It used to be taught that the giving of an alkali increased the secretion of HCl; later Pawlow showed that it inhibited it.

These experiments appear to indicate, however, that the HCl is merely neutralised by the alkali, forming NaCl till the whole alkali is used up, and then the acidity of the gastric contents becomes normal. So that the only effect is to cause a delay in the digestive process.

Effects of Bacterial Feeding.

The above results suggested that perhaps a secondary bacterial infection of the ulcer might be responsible for its chronicity.

Two series of experiments were therefore conducted. In the first series seven animals, in which ulcers had been produced, were fed on food soaked in fresh cultures of *Bacillus pyocyaneus*, and the ulcers compared with those of control animals.

In the second series six animals, in which ulcers had been produced, were fed on alkaline food soaked in fresh cultures of *B. coli communis*, and their ulcers likewise compared with those of control animals fed on a normal diet.

In both series of experiments the ulcers healed as usual, whether the animals were fed on normal or infected diet, and no chronic ulcer ever resulted. In the animals fed on *B. coli* there were perhaps more thickening and adhesions than in those fed on normal diet.

It appears, therefore, that so long as the stomach empties itself in the normal time, or, in other words, so long as there is no motor insufficiency, it is impossible to affect the healing of a gastric ulcer materially by an alteration in the acidity of the gastric juice such as occurs in the human subject or by feeding on moderately infected food.

CONCLUSIONS.

1. Gastrototoxic serum damages functionally the gastric cells, and the actual necrosis and ulceration of the mucous membrane is brought about by the gastric juice, the process being one of self-digestion.

2. All the other cytotoxic sera examined are capable of damaging the gastric cells in a similar manner, but to a less extent, and of initiating self-digestion.

The possibility is therefore established that certain endogenous poisons, and probably also certain exogenous poisons (*e.g.* bacterial poisons, and so on), may exist in the blood and be capable of so devitalising the gastric cells as to initiate self-digestion. An endogenous poison, potentially able to attack the stomach of the animal forming it, may be produced, as I have proved, by immunising the rabbit with rabbit's gastric cells.

3. Certain substances introduced in excess with the food may act in like manner as protoplasmic poisons.

4. These substances, if innocuous alone, are nevertheless capable

Fig 1

Fig 2A

Fig 2B

Fig 2C

of adding their quota to a devitalising influence acting through the blood stream, and of thereby increasing the effect of the latter. Hyperacidity of the gastric juice is able to act in this manner.

5. Acute gastric ulcers heal within a few weeks, whether the gastric juice be normal or increased or diminished in acidity to the extent which may be found in man.

6. The presence of an acute sloughing ulcer in the stomach is associated with a diminution in the acidity of the gastric contents, and when the ulcer is healing the acidity is normal. Hyperacidity may occasionally occur.

7. If the motor power of the stomach be normal, neither *B. pyocyaneus* nor *B. coli communis*, even though the gastric contents be diminished in acidity, are able to delay the healing of gastric ulcer.

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DESCRIPTION OF PLATE XXIII.

FIG. 1.—Demonstrates the influence of bile salts in increasing gastrototoxic lesions in the guinea-pig. *Upper stomach*.—Twenty c.c. of a 1 per cent. solution of sodium taurocholate were introduced into the stomach, and 10 c.c. gastrototoxic serum then injected into the peritoneum. Marked necrosis. *Lower stomach*.—Control animal. Ten c.c. gastrototoxic serum were injected into the peritoneum. Slight necrosis.

FIG. 2.—Illustrates the healing of gastric ulcer in the guinea-pig on a hydrochloric acid diet (0.6 per cent.). (a) *Sixth day*.—There is a little altered blood at the base of the ulcer, and a little bruising around it. (b) *Thirteenth day*.—A small triangular-shaped ulcer, which is rapidly healing, is present. (c) *Fourteenth day*.—A small nodule of fibrous tissue is all that remains.