THE PART PLAYED BY THE ACID OF THE GASTRIC JUICE IN THE PATHOLOGICAL PROCESSES OF GASTRIC ULCER.¹

By CHARLES BOLTON, M.D., D.Sc., F.R.C.P., *Physician to Out-patients, University College Hospital.*

Graham Research Laboratories, University of London.

(PLATES XVI.-XVIII.)

AN ulcer of the stomach originates in many different ways, and the processes giving rise to it are similar to those which are responsible for the formation of ulcers in other parts of the body. The ulcer whilst in its acute stage usually tends to heal in the normal manner; occasionally the healing is delayed for varying periods of time; and in a considerable number of cases it is completely arrested. This arrest in the healing brings about the condition known as chronic gastric ulcer. The persistent tendency of chronic gastric ulcer to remain unhealed is one of the most important problems in the pathology of the disease which requires solution.

An ulcer of the stomach, although formed in a similar manner to other ulcers, differs from them in that it is exposed to certain adverse influences during the process of gastric digestion. The *normal* gastric processes cannot exert much deterring influence upon the healing of an ulcer, because most acute gastric ulcers heal rapidly, and similarly all experimenters agree that the ulcers they have formed in animals by various means have healed equally well. However, in the case of chronic gastric ulcer, the digestive processes are *not* conducted normally, and it is an everyday experience that the subjects of this disease suffer from gastric disorders of both motion and secretion.

It is practically certain that all patients with chronic gastric ulcer suffer from attacks of food retention owing to pyloric spasm or muscular insufficiency. For such a condition to produce decidedly adverse effects it is not necessary for it to be prolonged or of a high degree. Although most of the meal may leave the stomach in the normal time, certain articles of diet are not uncommonly retained and subsequently found in the stomach mixed with almost pure gastric

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juice or with the next meal. The ordinary bismuth meal is no test of these slighter forms of intermittent retention.

Again, it has been proved that the majority of cases of chronic gastric ulcer are associated with hyperchlorhydria, and often with hypersecretion also. It is true that in a minority the percentage of HCl is found to be normal or even diminished, but this is no proof that there is not or has not been intermittent hyperchlorhydria, particularly as repeated examination of the gastric contents in any given case of gastric ulcer is not a usual procedure. If it is permanently diminished in some cases of gastric ulcer, particularly those in which the disease is of very long standing, it must be remembered that such an ulcer owing to its chronicity may be easily affected by a low degree of acidity. One of the most important points, therefore, in the pathology of gastric ulcer involves the consideration of the relation of such disorders of motion and secretion to the various pathological processes occurring in this disease.

It has naturally been considered, for many years past, that the gastric juice played an important part either in the initiation or propagation of gastric ulcer, but this idea has been held in a vague kind of way and has not been supported by any very definite evidence with regard to what precise effects this secretion produces, and what is its mode of action.

Katzenstein (1908¹), from his experiments, concluded that the *ferment* of the gastric juice was the chief destructive agent, and that this secretion could digest the wall of the stomach, because the latter was deficient in protective anti-ferment, but more recently Wolff (1909-10²) has shown that the stomach, in cases of gastric ulcer, is as rich in anti-ferment as the normal stomach, and that there is no diminution in the anti-ferment content of the blood in this disease.

For some time past I have maintained that it is the *acid* of the gastric juice which is the chief damaging factor, and from my experiments have drawn the following conclusions (1907-10³):

1. The normal gastric juice is able to attack the gastric mucous membrane which has been damaged or devitalised to a certain extent by a blood poison, the actual death of the cell not being a necessary antecedent to such attack.

2. This property it owes to the HCl contained in it, which completes the death of the tissue and thus allows of its digestion. The HCl acts in this capacity as a protoplasmic poison.

3. The ulceration produced in the presence of a hyperacid gastric juice (0.25 per cent. and upwards) is much more extensive than that produced in a stomach secreting normal juice.

4. Acute ulcer is more easily and quickly produced in the digesting than in the resting stomach, and is more extensive in the former than in the latter.

5. Motor insufficiency of the stomach, leading to undue retention

of food, delays the healing of an ulcer for at least twice the normal time, owing to necrosis of the granulation tissue of the base of the ulcer by the prolonged action of the HCl in the gastric contents.

6. For the same reason the healing time is prolonged by a diet which causes considerable secretion of gastric juice and leaves the stomach slowly; it is hastened by the opposite kind of diet.

Other experimenters have approached the question of the effects of hyperacidity upon the healing of the ulcer, but their deductions from the results of their experiments have not been in agreement, and the experiments themselves were not systematically conducted but were merely isolated observations.

Matthes (1893⁴) produced a lesion in the gastric mucous membrane 6 cms. in diameter, in each of three dogs. In one animal at the end of fourteen days he found a small ulcer 2.5 cms. in diameter. In another at the end of a month a scar was present, the lesion having completely healed. The third animal was fed with 0.5 per cent. HCl solution, and at the end of three weeks an ulcer the size of a split pea with hard edges was found on killing the animal. Litthauer (1909⁵) produced ulcers in four animals. Into one of them he repeatedly injected pyrogallic acid and into the other three pyridin, in order to produce artificial anæmia. Each dog was fed with 0.37 to 0.5 per cent. HCl solution. The animals were killed on the twelfth, forty-ninth, fifty-ninth, and sixty-third days, and in each case the ulcer was found to be healed. The days on which these ulcers healed were not ascertained. In another experiment he tied off the vessels supplying a third of the stomach with blood and fed the animal on 0.37 per cent. HCl solution. At the end of a month a deep ulcer was found in the stomach. Suzuki (1912⁶) produced an ulcer in a dog and fed it on 0.37 per cent. HCl solution. At the end of six weeks he found a scar in the stomach.

Litthauer's experiments dealt with the effects of anæmia and hyperacidity, so there are left two experiments only which were performed to test the effects of simple hyperacidity. In one a small healing ulcer was found at the end of three weeks, and in the other a scar at the end of six weeks. We thus see that no systematic experiments have hitherto been performed in regard to the effects of hyperacidity upon the healing of ulcers.

The present research was undertaken in continuation of my former experiments and refers particularly to the effects of hyperacidity alone and combined with motor insufficiency upon the healing of gastric ulcer, and to the effects of hyperacidity of the gastric juice upon the mucous membrane of the stomach.

The subject will be considered under the following headings:

I. The effects of hyperchlorhydria upon the healing of gastric ulcer. II. The effects of hyperchlorhydria, together with motor insufficiency, upon the healing of gastric ulcer. III. The effects of hyperchlorhydria upon the gastric mucous membrane.

I.

**THE EFFECTS OF HYPERCHLORHYDRIA UPON THE
HEALING OF GASTRIC ULCER.**

The animals used were monkeys, and a few experiments were done upon cats. In all cases the ulcers were produced by the local injection of a gastrototoxic serum into the wall of the stomach. The production of such an immune serum and the formation and normal healing of the resulting ulcers in the case of the cat have already been described in a former paper (1910³), and need not now be referred to. As this is the first time a gastrototoxic serum active against the monkey has been produced, I will give a short description of the process and of the formation and healing of the resulting ulcers.

The monkey was selected as the experimental animal on account of the very close resemblance which its stomach bears to that of man. The texture of the stomach wall is more delicate than that of the cat and the muscular coat is less powerful. Anatomically the position, shape, and connections of the stomach are the same as in man. The body of the stomach is vertical and turns sharply to the right at the pyloric end, the small curvature being bent at about a right angle. The uppermost portion of the fundus contains an air space. The three portions of the duodenum have also the same anatomical relation as those of the human subject. The percentage of hydrochloric acid in the gastric contents is about 0.15 to 0.2. The diet of the monkey was in all cases a vegetable one.

Production of a gastrototoxic serum active against the monkey.—The serum was produced by the repeated injection of a fresh extract of the gastric cells of the normal monkey into the goat. The stomach of one monkey was used for each injection, and subcutaneous injections were made at intervals of about ten to fourteen days. The stomach was cut out immediately after death and thoroughly washed. The mucous membrane was then scraped off on a porcelain plate with a knife, and ground up with sterilised sand in a glass mortar. An emulsion with salt solution was thus made and centrifugalised, the supernatant fluid amounting to about 50 c.c. being used for injection. All the apparatus was of course thoroughly sterilised before use. In this way three goats were immunised and the blood serum of each was found to possess strong gastrototoxic properties for the monkey's stomach. The monkeys used were chiefly *Macacus rhesus*, but also included bonnets, two young baboons, *Patas cercopithecus*, and green *cercopithecus*. There was no specificity for any definite species of monkey; so long as the animal was a monkey its stomach was susceptible to the action of the serum. The goats were bled from a vein of the ear if small amounts of serum were required, and from the jugular vein if 100 c.c. or more were to be removed. The blood was whipped and centrifugalised at once, and the serum used for injection whilst quite fresh. After about six injections the serum is ready for use. By continued injections the goat will yield a toxic serum for many months; in one case the serum was highly toxic nine months after the commencement of the injections. If the injections are stopped the toxicity of the serum soon falls. The best time to bleed the goat is about seven to ten days after the last injection.

Injection of the serum.—The blood serum was in all cases injected into the wall of the stomach on the anterior surface at about the junction of the cardiac and pyloric portions. The monkey, which had been fed about one hour previously so that digestion was proceeding, was anaesthetised with ether and the stomach drawn out of a median incision through the abdominal wall.

The point of the needle was introduced between the coats of the stomach and from 6 to 10 c.c. of serum according to its strength injected with a glass syringe, so as to produce a round patch of œdema in the stomach wall. The abdominal wound was then closed. Iodine was used to disinfect the skin after shaving, and the operation was performed under strict aseptic conditions.

Formation and healing of the ulcer.—The normal goat's serum is without action when injected in such doses into the stomach wall of the monkey. In the case of gastrototoxic serum, however, the gastrot toxin is abstracted from the serum and becomes fixed on to the tissues, more particularly the cells of the mucous membrane. The affected portion of the mucous membrane is attacked by the gastric juice and a slough is formed, which gradually separates with the formation of a cleanly punched-out ulcer, extending to various depths in proportion to the strength of the serum; perforation may occur. The ulcer is formed in about four or five days.

The stages in the healing were worked out in a series of monkeys, and the process found to be the same as in the cat, so that a very short description will suffice. When the sloughs have separated from the edges, but before they have completely separated from the base of the ulcer, the glandular cells at the edges begin to proliferate and cover the raw surface with a single layer of flat cells. These cells become cubical in shape, and from them simple tubes, which eventually form new glands, bud off and grow down into the granulation tissue. The base of the ulcer becomes covered with granulation tissue when all the sloughs have separated, and the single layer of flat epithelial cells at the periphery grows out over this tissue, and by about the twenty-first day has completely covered it. During this time the edges of the ulcer are being drawn nearer together by the contraction of the newly formed fibrous tissue in the base of the ulcer, so that an increasingly smaller surface remains to be covered. The epithelial cells covering the base now send out buds in the shape of simple tubes which proliferate in the underlying cellular stroma, and so the new mucous membrane gradually thickens as the glands become fully formed.

The following experiments illustrate the various stages in the evolution and healing of the ulcers:

Experiment 1.—*Macacus rhesus* (weight, 2600 grms.) was injected with 9 c.c. gastrototoxic serum. It died on the *third day*. There was a patch of necrotic tissue and hæmorrhage, 1 inch by $\frac{3}{4}$ inch in size, in the wall of the stomach at the site of injection which was about to separate, forming an ulcer.

Experiment 2.—BONNET MONKEY (weight, 1530 grms.) was injected with 7 c.c. gastrototoxic serum and killed on the *fifth day*. An ulcer the size of a shilling with a slough covering the base and separated from the edges was found at the site of injection. There was some lymph on the outside of the stomach fixing it to the liver. The ulcer extended through the muscular coat of the stomach.

Experiment 3.—*Macacus rhesus* (weight, 2230 grms.) was injected with 7 c.c. gastrototoxic serum. It died on the *sixth day*. An ulcer was present in the stomach the same size as that of Experiment 2. The edges and base were

clean, and there was a large perforation in the latter. There was recent lymph round the region of the ulcer and some free fluid in the abdomen.

Experiment 4.—COMMON MACAQUE (weight, 2630 grms.) was injected with 12 c.c. gastrototoxic serum and killed on the *thirteenth day*. An ulcer the size of a sixpenny-piece was present in the stomach. Its base was adherent to the liver. The edges were clean, rounded and healed, but the base itself was uncovered by epithelium, which was growing inwards from the periphery.

Experiment 5.—*Macacus rhesus* (weight, 3950 grms.) was injected with 10 c.c. gastrototoxic serum. It was killed on the *twenty-first day* following the injection. A scar was found in the stomach. It consisted of a small depressed surface surrounded by considerable puckering of the mucous membrane. On *microscopical examination* the depressed surface of the scar was seen to be completely covered with a single layer of epithelial cells (Plate XVI. Fig. 1).

Experiment 6.—*Patas cercopithecus* (weight, 2130 grms.) was injected with 12 c.c. gastrototoxic serum. The animal was killed on the *twenty-seventh day*. A healed ulcer was present in the stomach. The scar was stellate in form.

Experiment 7.—*Macacus rhesus* (weight, 2350 grms.) was injected with 9 c.c. gastrototoxic serum. At the same time the wall of the stomach around the site of injection was stitched to the liver, to prevent contraction of the base of the ulcer. The animal was given a bismuth meal, and the stomach found to empty itself in the normal time. It was killed on the *twenty-first day* following the injection. An ulcer was found in the stomach about the size of a threepenny-piece. The edges were smooth and rounded, and on *microscopical examination* were found to be covered with epithelial cells which had grown for a certain distance on to the base of the ulcer. An area in the centre of the base consisted of granulation tissue and was still uncovered by epithelium. There was no necrosis of the surface of the granulation tissue.

FIG. 1.—Tracings of the X-ray appearances of the stomach of Experiment 7 during the process of emptying, which occurred normally. The upper unshaded portion represents an air space. The less dense portion of the shadow is due to settling of the bismuth.

When, therefore, the stomach empties itself in the normal time, and the acidity of the gastric contents is normal, the ulcer may be expected to heal in three weeks or shortly after that time; but when the edges are prevented from coming together the healing occurs rather more slowly, because there is a larger area to be covered by epithelium. In the latter case the uncovered area is coated with granulation tissue as in the normal healing of the ulcer.

Production of hyperchlorhydria.—In a former series of experiments in which guinea-pigs were used, hyperchlorhydria was produced by feeding the animals upon food soaked in 0·5 or 0·6 per cent. HCl solution (1910⁷). On estimating the stomach contents it was found that the acidity varied considerably, sometimes being normal and sometimes a little above normal, namely, 0·25 to 0·3 per cent. There was no delay in the healing of these ulcers, but I did not regard the method as being satisfactory, because one could not test the effect of any given strength of acid, and further one had no guarantee what was the percentage of *free* HCl in any given case, as the food converts the free HCl into protein HCl. The damage to the stomach wall is done by free HCl, not protein HCl. In this series of experiments, therefore, a solution of HCl was introduced into the fasting stomach. This is quite an easy procedure. A wooden gag with a hole in the centre was introduced into the monkey's mouth and a rubber tube passed through it into the stomach.

In the earlier experiments the animals were given the solution once a day in the morning, one hour before being fed. In the later experiments this was done before the evening meal also. In most of the cases the amount introduced on each occasion was 50 c.c., smaller amounts occasionally being used, particularly in the earlier experiments. Various strengths of HCl were used.

In hyperchlorhydria in the human subject the total hydrochloric acid secreted varies in different cases from 0·25 to over 0·4 per cent. At the end of two hours after a test meal of meat, the percentage of free HCl in the stomach contents is more than half that of the total amount of acid secreted in about 50 per cent. of the cases, and in the rest it is somewhat less than this. This statement is based on a series of actual estimates. The proportion of free HCl to protein HCl increases till the stomach is empty, and any damage to the stomach wall is therefore done in the later stages of digestion and is proportional to the length of stay of the residual contents in the stomach. In the case of associated hypersecretion the damage done is much greater, because the gastric mucous membrane is in this case exposed to the full strength of the HCl of the gastric juice for a longer time and in the fasting stomach.

The *efficiency* of this method of producing hyperchlorhydria is not great, and the effects obtained by it must be small in comparison with those produced by hyperchlorhydria in man. The reason for this is, that the solution rapidly leaves the stomach and the degree of acidity quickly falls. In illustration of this the three following experiments may be quoted:

Rhesus (weight, 2300 grms., Experiment 12) was given by the tube 50 c.c. of a 0·39 per cent. HCl solution. In half an hour 15 c.c. of fluid were found in the stomach containing 0·12 per cent. HCl.

Rhesus (weight, 3080 grms., Experiment 10) was given by tube 50 c.c. of a 0·28 per cent. HCl solution. In half an hour 28 c.c. of fluid were found in the stomach containing 0·14 per cent. HCl.

Rhesus (weight, 3150 grms., Experiment 8) was given by tube 50 c.c. of a 0·18 per cent. solution. In half an hour 7 c.c. fluid were found in the stomach containing 0·108 per cent. HCl.

The stomachs, therefore, in these experiments were exposed to the full strength of the solution administered for a short time only. This time was apparently shorter in the case of the stronger solutions than in that of the weaker ones.

The strengths of the solutions employed were 0·18, 0·28, 0·39, 0·5, 0·9, and 1·5 per cent. The solutions were made with concentrated HCl and distilled water, and the exact strength of each solution was afterwards ascertained by titration with decinormal soda solution. Solutions of 0·5 per cent. and upwards were liable to cause vomiting, owing to the irritant action of the HCl, and in such cases the maximum effect of the HCl was not obtained.

EFFECTS OF HYPERCHLORHYDRIA.

1. *Upon extension of the ulcer.*—In no case was any regular extension of the ulcer produced. When once the sloughs had separated, the epithelium was able to grow quite well if granulation tissue were present for it to cover.

It will be seen later that only HCl of a certain strength is able to kill the healthy gastric cells. In this case, when once the ulcer was formed, the gastric cells at the edge of the ulcer were healthy, and no regular extension of the ulcer occurred. The extension of an ulcer laterally is thus seen to be due to the persistence of the original cause of the ulcer, the gastric juice acting as a contributory factor only.

2. *Upon the healing of the ulcer.*—The effect of the hyperacidity of gastric juice was to produce a definite delay in the healing of the ulcer. This delay amounted to about three or four weeks beyond the normal time. The cause of the delay in the healing was the necrotic condition of the base of the ulcer. The hydrochloric acid, although unable to attack the epithelium at the edge of the ulcer, killed off the connective tissue of the base; the superficial layer of this for various depths was rendered necrotic; hence the growth of the epithelium over the base was retarded. In the case of normal healing the base of the ulcer, although uncovered by epithelium, is composed of granulation tissue after a certain period, but in unhealed ulcers on the twenty-first day in these cases of hyperacidity the granulation tissue was replaced by a slough owing to the necrotic action of the hydrochloric acid. When healing eventually occurred, the new mucous membrane was deformed, as has been described in a former paper when delayed healing was due to motor insufficiency of the stomach.

The following experiments were conducted in order to test the effect of various strengths of HCl.

Strength of HCl Solution = 0.18 per cent.

Experiment 8.—*Macacus rhesus* (weight, 3150 grms.) was injected with 7 c.c. gastrototoxic serum. On the fifth day feeding with HCl solution was commenced. For three days one feed was given each morning, and subsequently two feeds—one in the morning and one in the evening—were given daily with a very few exceptions. The amount administered was 50 c.c. on each occasion, and twenty-three feeds in all were given. An examination with the X-rays after a bismuth meal showed that the stomach emptied itself in the normal time. The monkey was killed on the twenty-first day, and an unhealed ulcer, triangular in shape, was found in the stomach, which was adherent to the liver. The edges of the ulcer were covered with epithelium, and ~~this was growing over the base, but the centre of the latter was covered with~~

commenced as in the preceding experiment. Seventy-eight feeds were given. The stomach was found by the X-rays to empty itself in the normal time. The monkey was killed at the end of nine weeks and three days. The stomach was adherent to the liver and contained an excess of mucus. A radiating scar was present in the mucous membrane at the adherent spot.

FIG. 2.—Tracings of the X-ray appearances of the stomach of Experiment 9 during the process of emptying, which occurred normally.

Strength of HCl Solution = 0.28 per cent.

Experiment 10.—*Macacus rhesus* (weight, 3080 grms.) was injected with 7 c.c. gastrototoxic serum. Feeding with HCl solution was commenced on the fifth day after injection. On the first three days one feed a day was given, and after this period the monkey was, with one or two exceptions, fed twice a day. The volume of the feed on each occasion was 50 c.c. Twenty-three feeds were administered. The stomach was found by the X-rays to empty itself in the normal time. The monkey was killed on the twenty-first day. An unhealed ulcer, $\frac{1}{4}$ inch in size, was present in the stomach; its base was considerably contracted and in a similar condition to that of Experiment 8.

FIG. 3.—Tracings of the X-ray appearances of the stomach of Experiment 10 during the process of emptying, which occurred normally.

Experiment 11.—*Macacus rhesus* (weight, 3100 grms.) was injected with 7 c.c. gastrototoxic serum. Feeding was commenced on the sixth day after injection. On the first day one feed was given, and subsequently two each day. The amount of each feed was 50 c.c. Sixty-seven feeds were administered. The stomach was proved by the X-rays to empty itself in the normal time. The monkey was killed at the end of seven weeks. A scar was found

in the mucous membrane of the stomach, 1 inch by $\frac{3}{8}$ inch in size. The edges were raised, and the base which was covered with newly-formed mucous membrane sloped slightly to the centre. The ulcer was completely healed.

Strength of HCl solution = 0.39 per cent.

Experiment 12.—*Macacus rhesus* (weight, 2300 grms.) was injected with 8 c.c. gastrototoxic serum. Feeding with HCl solution was commenced on the fifth day. On the first three occasions one feed only was given during the day, and subsequently the animal was fed twice a day. The amount of the feeds was 50 c.c. Twenty-three feeds were administered. The stomach emptied normally. The monkey was killed on the twenty-first day. An excess of bile-stained mucus was present in the stomach. An ulcer was found with healed edges and contracting base, over which the epithelium was growing, the centre being covered with slough. The ulcer was larger than those of Experiments 8 and 10 (Plate XVI. Fig. 2).

Experiment 13.—*Macacus rhesus* (weight, 2550 grms.) was injected with 8 c.c. gastrototoxic serum. Feeding was commenced on the fifth day. In this case only one feed a day was given, the total number of feeds being seventeen. The animal was killed at the end of a month. An unhealed ulcer, lozenge-shaped and $\frac{3}{4}$ inch by $\frac{3}{8}$ inch in size, was present in the stomach. It had raised edges and the base sloped to the centre in the shape of a funnel. The whole was covered with newly-formed mucous membrane, except a slit-shaped portion in the centre where a slough was present.

Experiment 14.—*Macacus rhesus* (weight, 2800 grms.) was injected with 6 c.c. gastrototoxic serum. Feeding with 50 c.c. of HCl solution was commenced on the fifth day. For four days the feeds were administered once a day, and subsequently twice a day. One hundred and twelve feeds were administered. By X-rays the stomach was found to empty normally. The monkey was killed at the end of eleven weeks. The stomach was adherent to the liver, and there was very slight hour-glass constriction at the spot. The stomach contained a good deal of mucus. A scar was present, which was 1 inch by $\frac{1}{2}$ inch in size. The edges were raised and the base of the scar covered with newly formed mucous membrane. In the centre was a puckered knot. An hour before it was killed the animal was given 50 c.c. of milk as a test meal. The total HCl secreted was found, on analysis of the stomach contents, to be 0.057 per cent.

Strength of the HCl solution = 0.5 per cent.

Experiment 15.—*Macacus rhesus* (weight, 2830 grms.) was injected with 7 c.c. gastrototoxic serum. Feeding with 50 c.c. of the solution was commenced on the fourth day, and after the first three feeds was continued twice a day. Twenty-six feeds were administered. Vomiting occurred on several occasions. The stomach was shown to empty itself in the normal time. The monkey was killed on the twenty-third day. A healing ulcer was found in the stomach. It was well-contracted, deep, and the uncovered portion of the base was about the size of a split pea. A good deal of mucus was present in the stomach.

Experiment 16.—*Macacus rhesus* (weight, 2900 grms.) was injected with 7 c.c. gastrototoxic serum. Feeding with 50 c.c. HCl solution was commenced on the fourth day and continued twice a day after the first three doses. Vomiting occurred off and on, and was accompanied by salivation and a good deal of retching. Thirty-seven feeds were administered. The stomach emptied in the normal time. The monkey was killed on the thirtieth day. There was a good deal of mucus in the stomach and a small deep ulcer was present. It was healing slowly, oval in shape, and $\frac{3}{8}$ inch by $\frac{1}{4}$ inch in size.

Experiment 17.—*Macacus rhesus* (weight, 2260 grms.) was injected with 9 c.c. gastrototoxic serum. Feeding with 50 c.c. HCl solution was commenced on the seventh day after injection. The feeds were given once a day only, and twenty-nine in all were administered. Vomiting occurred on several occasions. By the X-rays the stomach was found to empty itself in the normal time. The monkey was killed on the fortieth day. An ulcer advanced in healing was present in the stomach. It was 1 inch by $\frac{1}{2}$ inch in size. It was funnel-shaped, with raised edges. The newly-formed mucous membrane had grown down the sides, leaving a small slit-shaped area in the centre of the base covered with slough.

Strength of HCl Solution = 0.9 per cent.

Experiment 18.—BABOON (weight, 1350 grms.).—Injected with 8 c.c. gastrototoxic serum. Feeding with HCl solution was commenced on the eighth day. The feeds were given once a day; for the first four days 30 c.c., and for the next seven 40 c.c., were given on each occasion. The monkey vomited every day. It was killed on the twenty-first day, and a healed ulcer was found in the stomach. The scar was stellate in form.

Strength of HCl Solution = 1.6 per cent

Experiment 19.—*Macacus rhesus* (weight, 2370 grms.) was injected with 8 c.c. gastrototoxic serum. Feeding was commenced on the seventh day and continued daily. Twelve doses of 20 c.c. and three of 30 c.c. were administered. The animal vomited and suffered from salivation. It was killed on the twenty-fourth day. An ulcer was present in the stomach. It was healed except for a tiny area in the centre. The stomach wall was puckered, but there were no adhesions.

Free hydrochloric acid of all the ordinary strengths found in hyperacidity of the gastric juice, in human subjects suffering from pathological conditions, was able to delay materially the healing of the ulcer, but in no case was complete arrest of healing produced. This may of course have been due to the inefficiency of the method employed, and it is quite certain that hyperchlorhydria as found in the human subject would produce a much greater effect. A solution of 0.18 per cent. strength was able to produce *some* effect. Solutions of 0.5 per cent. and upwards did not appear to produce more effect than the weaker solutions, and sometimes much less. This was due to the fact that they gave rise to vomiting in the first place; moreover, a stronger solution in the short time at its disposal can do little more than kill off the superficial granulation tissue in the same way as a weaker solution. The delay in healing in all cases was due to the same cause, namely, necrosis of the granulation tissue base of the ulcer, which prevented the epithelium growing over it. Gastric juice is the only digestive fluid which is able to digest connective tissue, and therefore disintegrate food-stuffs and organs, whose elements are bound together by that tissue. This power it owes to the hydrochloric acid contained in it. It is not surprising, therefore, that hyperacid gastric

juice should attack the connective-tissue base of an ulcer and produce the results described above.

Another method was employed to test the effect of the secretion of gastric juice in the fasting stomach upon the healing of gastric ulcer.

It is well known that *pilocarpine* on injection causes a flow of gastric juice, but I could not find in the literature on the subject whether, while the flow continues, the juice contains the normal amount of acid, and whether repeated injection of *pilocarpine* alters the acid content of the juice. A few experiments on cats were therefore conducted in order to determine these points.

METHOD.—The cat, which had been starved for twenty-four hours previously, was anaesthetised with ether. The abdomen was opened in the middle line and the stomach drawn out. Ligatures were placed round the lower end of the oesophagus and the duodenum just beyond the pylorus. An incision was made into the stomach, and any remnants of mucus carefully removed by mopping out with absorbent cotton wool. The edges of the incision were stitched to the edges of the abdominal wound so as to make a gastric fistula with a large external opening. The *pilocarpine* was injected subcutaneously or intravenously and the gastric juice collected by means of a pipette at intervals.

Experiment A.—CAT (weight, 2750 grms.).—Fistula prepared as described above, and *pilocarpine* nitrite, $\frac{1}{3}$ gr., injected into the femoral vein at 10.25 a.m. Salivation commenced in a few minutes, and the following amounts of gastric juice were collected :

At 11.45 a.m.	.	.	.	2.5 c.c.
12.45 p.m.	.	.	.	1.5 "
1.45 "	.	.	.	1.5 "
2.45 "	.	.	.	2 "
3.45 "	.	.	.	1.5 " killed.

The juice was yellowish in colour, with a few tiny brownish flakes, evidently due to minute hæmorrhages from the gastric mucous membrane. The salivation diminished considerably after the first hour. The samples of juice were mixed together and the amount of HCl estimated by the silver method. The total chlorides were found to amount to 0.1898 per cent. The total acidity was then estimated with decinormal NaOH and found to amount to 0.1825 per cent. The chloride is therefore present almost entirely as free HCl.

Experiment B.—CAT (weight, 2210 grms.).—Fistula prepared. *Pilocarpine* nitrate, $\frac{1}{3}$ gr., subcutaneously injected at 11.45 a.m. In about three minutes salivation commenced, and at the same time the gastric mucous membrane became moist. At 12.45 p.m. (one hour later) 8.5 c.c. of gastric juice had been collected when the animal died. On estimation the percentage of HCl in the juice was found to be 0.18 per cent.

Experiment C.—CAT (weight, 3390 grms.).—Fistula prepared. *Pilocarpine* nitrate, $\frac{1}{6}$ gr., subcutaneously injected at 10.50 a.m. At 12 p.m. 6 c.c. gastric juice containing 0.18 per cent. HCl, and at 1 p.m. $3\frac{1}{2}$ c.c. juice containing 0.146 per cent. HCl, were collected. The animal was then killed.

Experiment D.—CAT (weight, 2800 grms.).—Fistula prepared. *Pilocarpine* nitrate, $\frac{1}{12}$ gr., subcutaneously injected at 10.25 a.m. The following samples of gastric juice were collected.

Time.	Salivation.	Gastric Juice.	HCl.
11.30 a.m.	Profuse	2 c.c. }	0.18 per cent.
1.30 p.m.	Some	3 c.c. }	
3.30 p.m.	Very slight	3.5 c.c.	0.146 ,,
5.30 p.m.	None	2 c.c.	0.109 ,,
Animal killed . . .	...	...	...

Experiment E.—CAT (weight, 3000 grms.) was injected repeatedly with pilocarpine nitrate. Twelve injections were given in thirty-two days. Four doses of $\frac{1}{8}$ gr., seven doses of $\frac{1}{3}$ gr., and one dose of $\frac{1}{2}$ gr. were administered. Two days after the last injection the experiment was performed. A gastric fistula as described above was made, and pilocarpine nitrate, $\frac{1}{8}$ gr., subcutaneously injected. Six c.c. gastric juice containing 0.18 per cent. HCl was collected in three hours, when the animal was killed.

The amount of gastric juice secreted in response to the injection of a given dose of pilocarpine varies somewhat in quantity. The percentage of HCl present in it is constant, but it tends to diminish a little after the first hour of secretion. Repeated injections of the drug do not affect the quantity and quality of the gastric juice secreted as the result of its action. Injections of pilocarpine, therefore, may be used to test the effects of gastric juice, unadulterated with food, upon the healing of an ulcer.

With this end in view pilocarpine was repeatedly injected into a monkey, in which an ulcer had been produced.

Experiment 20.—*Macacus rhesus* (weight, 3200 grms.) was injected with 9 c.c. gastrotoxic serum. The monkey received twenty-two subcutaneous injections of pilocarpine, not more than one a day being given. The doses were as follows: $\frac{1}{8}$ gr. was injected twice, $\frac{1}{3}$ gr. eight times, $\frac{1}{2}$ gr. seven times, and $\frac{2}{3}$ gr. five times. The injections were given in the morning two hours before the first feed. The animal was killed at the end of six weeks. What appeared to the naked eye to be a linear scar, 1 inch by $\frac{1}{8}$ inch in size, with puckering of the mucous membrane on both sides of it, was present in the stomach. On *microscopic examination*, however, it was seen that the linear space was uncovered by mucous membrane, and therefore the ulcer was not yet healed. The newly formed glands were often found distended into mucous cysts.

Hypersecretion of normal gastric juice into the fasting stomach, therefore, is able to delay to some extent the healing of the ulcer. This experiment confirms the results of those recorded above, in which a 0.18 per cent. HCl solution was found to produce the same effect.

II.

EFFECTS OF HYPERCHLORHYDRIA, TOGETHER WITH MOTOR INSUFFICIENCY, UPON THE HEALING OF GASTRIC ULCER.

In a former paper it was shown that motor insufficiency, leading to retention of food in the stomach, definitely delayed the healing of

acute gastric ulcer (1910³); and that this effect was due to necrosis of the granulation tissue base of the ulcer, the growth of the epithelium over the latter being thus delayed. The prolonged action of HCl was responsible for this result. These experiments were performed upon cats. Retention of food in the stomach, for varying lengths of time, is present, as stated above, at one time or another in all cases of chronic gastric ulcer. It seemed, therefore, natural to inquire how much further delay could be produced by motor insufficiency acting in conjunction with hyperacidity.

In this series of experiments also, monkeys were used. The ulcers were produced by the method described above, and the animals were fed with solutions of HCl by the tube.

Production of motor insufficiency.—The motor insufficiency was produced by artificial duodenal obstruction. The method of obstruction of the first part of the duodenum by a piece of indiarubber tubing, which I had found to be successful in the cat, was inapplicable to the monkey. This was owing to the position of the stomach and the connections of the duodenum. The duodenum of the cat is more movable and the stomach is not slung from it as is the case in the monkey, in which animal I found that kinking resulted and complete obstruction was produced. Neither was the method of introducing a row of Lembert's sutures very successful, on account of the difficulty of judging of the degree of constriction produced, and in such a condition compensation was easily produced. The method which I finally adopted was the following.

A median incision was made in the abdomen, with strictly antiseptic precautions under ether. The stomach was drawn out and a very small gastroenterostomy clamp put on the organ so as to separate off the body, into which the contents of the stomach were squeezed, from the pyloric region. A small incision was made into the latter and a glass rod about 4 mm. in diameter was passed into the opening and through the pylorus into the duodenum. Two pieces of silver wire were passed round the first part of the duodenum immediately beyond the pylorus, and each separately twisted on the glass rod, which was firmly held in position. The degree of tightness secured was one which admitted of the glass rod being withdrawn and reintroduced fairly easily through the stenosed duodenum. The glass rod was then taken out and the incision into the stomach closed by silk sutures. The gastrototoxic serum was injected into the stomach wall, as described above, at the same operation. The animal had been given a small meal one hour before the operation.

The result of the obstruction was to produce some loss of weight and diminished appetite, and in the higher degrees a certain amount of vomiting. The animals, however, kept well in all other respects.

Estimation of the presence and the degree of retention of food.—The animals were not all of the same size and the degree of tightness of the wires varied a little, so that it was necessary to estimate the actual degree of obstruction in each case, in order to compare this with the results obtained. The method used was that of watching by the X-rays the rate of emptying of the stomach after having administered a bismuth meal. The meal was administered by the stomach tube and consisted of 1 drm. of bismuth carbonate suspended in 30 c.c. of milk. The bismuth settles a little in the stomach, but when the milk clots it becomes mixed with the clot and the outline of the stomach is very clearly and definitely shown.

Normal position, shape, and emptying of the stomach.—The outline of the stomach was drawn on the screen at intervals and then traced on oiled paper. The exact position was easily located by drawing in the diaphragm and outlines of the body wall. This was found to be much the simplest method. Radiograms

were taken in some instances. Unless taken as snapshots they were blurred, owing to the respiratory excursions, and possessed no advantage over the diagrams. The monkeys were all examined in the upright position. The shadow of the stomach consists of a vertical portion on the left of the mid-line and a shorter and narrower horizontal portion which turns to the right. There is, as in man, a fair-sized air space in the fundus. The appearance presented is practically the same as that of a baby a few weeks old. The upper part of the vertical shadow for a variable depth is usually less dense, owing to settling of the bismuth. When water instead of milk is given the bismuth settles rapidly, forming a layer in the most dependent portion of the stomach. After the milk has clotted, the bismuth is mixed with the clots and the fluid portion is uncoloured. The fluid part leaves the stomach more rapidly than the clots. The shadow becomes narrower and smaller, and finally a small black mass occupying the distal end of the pyloric region is all that can be seen; eventually this disappears. A certain amount of narrowing is quite common at the junction of the pyloric region and the body, forming various degrees of spasmodic hour-glass stomach. The movements of the stomach, as seen at the moment by the X-rays, are very sluggish, probably owing to fright. This may not be the case, because I have seen the same sort of movements in a baby, which was not frightened. The stomach commences to empty at once, and after a quarter of an hour or thereabouts bismuth may be seen in the small intestine, the coils of which become rapidly outlined as the stomach empties (Fig. 4). After a meal of 30 c.c. milk and 1 drm. of bismuth carbonate, the stomach is usually empty in from two and a half to three and a half hours, according to the size of the monkey. The larger the meal the longer the stomach takes to empty; for example, after a meal of 50 c.c. it is not empty within about five hours.

FIG. 4.—Tracings of the X-ray appearances of the stomach of a normal monkey during the process of emptying. The stomach was empty within four hours. The air space was fairly large and the stomach showed spasmodic hour-glass contraction. The bismuth meal could be seen passing out of the pylorus.

Rate of emptying in the condition of pyloric stenosis.—The rate of emptying was found to vary with the degree of obstruction. The silver wires round the duodenum could be quite easily seen with the X-rays. In the lesser degrees of obstruction the size and shape of the stomach was normal, in the higher degrees the stomach was dilated. In addition to the size of the stomach, two other points were obvious. The first was that as the food collected in the small intestine much more slowly than normal, the shadow in that organ appeared more slowly than usual, and with higher degrees of obstruction the bismuth could not be seen till it reached the large intestine. The second was, that the size of the bismuth shadow in the stomach diminished more slowly than normal and did not disappear until a varying number of hours beyond the normal time limit.

Having decided upon the methods to be employed, the following experiments were performed :

Strength of HCl Solution = 0.28 per cent.

Experiment 21.—*Macacus rhesus* (weight, 2080 grms.) was injected with 7 c.c. gastrototoxic serum, and at the same operation the duodenum was stenosed with silver wire, as described above. Feeding with the HCl solution was commenced on the fifth day after injection, 50 c.c. being administered on each occasion. A single feed was given on the fifth, seventh, and eighth days respectively, after which the animal was, with four exceptions, fed twice a day.

Twenty-one feeds in all were administered. On the fourteenth day a bismuth meal was given. The stomach emptied slowly, and after six and a quarter hours still contained a certain amount of food. The animal was killed on the twenty-first day. It was given 50 c.c. 0.28 per cent. HCl solution in the morning and killed in half an hour. The stomach contained 30 c.c. of a clear, slightly mucoid fluid, containing 0.19 per cent. free HCl.

There was a large ulcer in the stomach, 1 inch by $\frac{3}{8}$ inch in size, adherent to the liver and a little excavated in the centre; the base was covered with a yellowish slough. The edges were rounded and the mucous membrane beginning to grow over the periphery of the base (Plate XVI. Fig. 3).

FIG. 5.—Tracings of the X-ray appearances of the stomach of Experiment 21 during the process of emptying. The silver ring round the duodenum is distinctly seen. There is considerable delay in the emptying, a large amount of food being present in the stomach after six and a quarter hours. There is no dilatation of the stomach.

Strength of HCl Solution = 0.39 per cent.

Experiment 22.—BONNET MONKEY (weight, 2180 grms.) was injected with 8 c.c. gastrototoxic serum, and at the same operation the duodenum was obstructed. One feed of 50 c.c. HCl solution was administered on the fourth, fifth, sixth, and eighth days respectively after injection. After this period the feeds were given twice a day. Twenty-five feeds in all were administered. A bismuth meal was given on the seventh day. It was administered in the morning, all

food having been taken away from the animal at 6 p.m. on the previous evening. From the shape of the shadow it appeared that a certain amount of residual food had been retained all night. The stomach emptied slowly, and eight hours after administration still contained a considerable amount of food. The animal was killed on the twenty-first day after injection of the serum. A large ulcer, 1 inch by $\frac{1}{2}$ inch in size, was found in the stomach, which was adherent to the liver. The base of the ulcer was completely covered with slough. The edges were rounded and the mucous membrane was just beginning to grow over the periphery of the base (Plate XVI. Fig. 4).

FIG. 6.—Tracings of the X-ray appearances of the stomach of Experiment 22 during the process of emptying. The silver ring round the duodenum is seen. There is some dilatation of the stomach and considerable delay in the emptying, a large amount of food being retained after eight hours.

Experiment 23.—BONNET MONKEY (weight, 1580 grms.) was injected with 8 c.c. gastrototoxic serum, and at the same operation the duodenum was narrowed by silk sutures. Feeding with HCl solution was commenced on the fifth day, and continued once a day only, as the animal, although bright looking, was obviously losing ground. Five doses of 10 c.c. each were given, and then one dose of 20 c.c., and three doses of 30 c.c. The animal died on the sixteenth day. The duodenal constriction was tight. The stomach was adherent to the liver, spleen, and diaphragm. There was a large ulcer at the site of injection, with inverted edges and an excavated cavity. It was 1 inch by $\frac{3}{4}$ inch in size. Microscopic sections showed that the base was covered with slough and that the epithelium of the edge had not commenced to grow over it. A second and newly-formed ulcer was present on the posterior wall, parallel to and quite near the small curvature. It was oval in shape, longitudinally situated, $\frac{3}{4}$ inch by $\frac{1}{4}$ inch in size. It had sharply-cut edges, and the muscular coat of the stomach was exposed in the base. There were no signs of healing, and the edge showed disappearance of the gland such as occurs in

acute spreading ulcer in man. One or two tiny ulcers were forming in the immediate vicinity (Plate XVII. Fig. 5). Sections of the small commencing ulcers showed that the process of ulceration commenced as a necrotic lesion in the mucous membrane. This is a very important experiment, as it illustrates the commencement of an acute spreading ulcer in necrosis of the mucous membrane due to HCl. This point will be reverted to later.

Strength of HCl Solution = 0.9 per cent.

Experiment 24.—*Macacus rhesus* (weight, 2830 grms.) was injected with 10 c.c. gastrototoxic serum. At the same operation the duodenum was constricted with silver wire. A bismuth meal was given on the seventh day. The meal consisted of 50 c.c. milk and 1 drm. of bismuth carbonate. At the end of eight and a half hours there was a large mass of food present in the stomach. Feeding with the HCl solution was started on the eighth day, one feed a day being administered. Four doses of 30 c.c. each and seven doses of 40 c.c. each were given in all. The monkey was killed on the twenty-first day. A large ulcer with inverted edges was present in the stomach and was adherent to the liver. It was $\frac{3}{4}$ inch by $\frac{2}{3}$ inch in size. The base was white and sloughy and completely uncovered (Plate XVII. Fig. 6). On section it was found that the epithelium of the edge was just beginning to grow on to the periphery of the base. Two or three small ulcers were also present in distant parts of the stomach.

In all these experiments the ulcers were larger and less advanced in healing than in the former series of experiments in which hyperacidity alone was produced. The cause of the delay in healing was the same, namely, necrosis of the base of the ulcer, so that the mucous membrane was unable to reform. The edges of the ulcers were rounded, and there was no tendency for the latter to spread.

There was here a summation of effects, each factor—hyperacidity and food retention—contributing to delay the healing of the ulcers. It is probable that the ulcers would have eventually healed, although one cannot be quite certain on this point, as no case was examined beyond the twenty-first day.

It is quite certain that hyperacidity and motor insufficiency in man are able to produce greater effects than those described in these experiments.

It is to be noted that there were no appearances in the X-ray pictures to suggest that an ulcer was present in the stomach. This could hardly be expected to occur unless the ulcer formed a pouch on one or other curvature so as to interrupt the contour of the shadow. The ulcers in this position had no effect whatever upon the movements of the stomach.

In the case of a small baboon an hour-glass contraction of the stomach was produced. This could be seen on the X-ray screen, since the only part of the stomach behind the stricture contained food, leaving the pyloric portion empty. After a while, however, the pyloric portion filled up, the former shadow diminishing in size, and it was then quite impossible to recognise the contraction at this stage.

FIG. 7.—Tracings of the X-ray appearances of the stomach of the baboon mentioned above. The silver ring round the duodenum is seen. In the first tracing the pyloric region is quite empty, but in the second the outline of the stomach is normal. The organic hour-glass contraction had obviously been so increased by spasm as to prevent the passage of food.

The stomach contents of those animals which died from the tightness of the stricture showed a diminished amount of HCl, exact figures obtained in three cases being 0.018, 0.036, and 0.072 per cent. acid. In the lesser degrees of obstruction the acidity was unaffected, being from 0.1 to 0.2 per cent.

III.

EFFECTS OF HYPERCHLORHYDRIA UPON THE GASTRIC MUCOUS MEMBRANE.

It was found that the solutions of HCl produced certain well-marked changes in the gastric mucous membrane. These changes were worked out in the animals whose records have already been described and also in certain additional animals. A general description will be given of these changes, as it is unnecessary to refer in detail to each animal investigated. The effects of the repeated doses of HCl solutions upon the gastric mucous membrane were irritant and necrotic.

1. IRRITANT EFFECT.—This effect was manifested as a chronic inflammation of the mucous membrane. On opening the stomach an increased amount of mucus was found in it. Points of hæmorrhage were to be seen in the mucous membrane in the advanced cases, but not in the slighter cases. The mucous membrane itself was not particularly congested, but, on the contrary, was very often paler than normal. Enlarged lymph follicles could be seen under the mucous membrane scattered about the stomach like seeds, and in more advanced cases they opened on the surface by small pinholes constituting follicular ulcers (Plate XVII. Fig. 7). Another appearance presented was that of rounded patches slightly depressed below the surface of the mucous membrane and surrounded by a well-defined

rim of normal tissue. They varied in size up to about a quarter of an inch in diameter. These proved to be localised patches of gastritis (Plate XVII. Fig. 8). In no case was there any evidence that the follicular ulcers had spread by continued administration of the acid so as to form larger ulcers.

Microscopical examination of the stomach showed that the gastritis was either a more or less diffuse condition or that it was localised to patches surrounded by perfectly healthy mucous membrane. The *gastritis*, whether it was diffuse or localised, gave rise to the same appearances in all cases.

The most apparent change was the *infiltration with round cells* of the mucous membrane affected. This infiltration which existed between the glands was present in varying degrees according to the intensity of the disease. It was most marked towards the surface of the mucous membrane and less towards the bases of the glands, in the slight cases merely packing the interglandular tissue, in the more advanced cases compressing and invading the glands, which became less defined and gradually disappeared (Plate XVIII. Fig. 9).

The *surface epithelium* in early cases showed swelling with mucus, and there was often a deposit of mucus on the surface of the membrane. In the more advanced cases desquamation of the epithelium occurred, and on the surface was a layer of mucus with loose cells shrunken, deformed, and entangled in it.

In these cases the *cells of the glands* were in a similar condition to those of the surface epithelium. In advanced cases the glands had largely disappeared, and those which were left appeared as islands of cells, sometimes still arranged around the central lumen or sometimes desquamated into it and embedded in the infiltrated tissue.

There was no doubt whatever that the desquamated surface epithelial cells were renewed by the proliferation of unaffected cells, because young flattened cells could be seen on the surface in many sections. These newly-formed surface cells were no doubt desquamated in their turn. In this way the process was continued, any uncovered surfaces which might be said to constitute "erosions" being rapidly covered over, so that open ulcers were not present for very long. The *underlying tissue* consisted of small round cells and proliferated connective-tissue cells with the remains of the glands embedded in it.

The *lymphatic follicles* in the normal condition are rounded compact masses of cells situated under the muscularis mucosæ. They may also be embedded in the mucous membrane and there lie on the muscularis mucosæ, having in section a somewhat triangular shape owing to their extension upwards between the bases of the glands. In either case they become enlarged and spread upwards to the surface of the mucous membrane and also laterally. Those lying under the muscularis mucosæ burst first through that structure. By prolifera-

tion of their cells the nodules thus grow upwards, displacing and pushing aside the gastric glands, many of which are destroyed in the process. Eventually the nodule reaches the surface and bursts through the epithelium, producing a tiny acute ulcer (Plate XVIII. Fig. 10). In no case was degeneration of the cells forming the nodule observed, leading to the condition of abscess formation. The lymph cells always stained well even after the surface epithelium was destroyed.

Follicular ulcers of various sizes were thus produced, and the same process of repair as is described above was observed here. Many ulcers were found, but in many cases also the surface of the ulcer was already covered with newly-formed epithelium which had grown in from the edges of the ulcer. Extension of the ulcer either laterally or in its depth was never observed. These follicular ulcers might be found quite isolated in the midst of almost normal mucous membrane. On the other hand, their occasional presence in connexion with a local patch of gastritis gave rise to the suggestion that the patch might have arisen as an extension from the enlarged follicle. Many patches of gastritis were, however, found quite free from enlarged follicles.

This irritant effect of hydrochloric acid was produced with solutions of 0.28 per cent. in strength, and of course with any stronger solution. I have already stated that solutions of 0.5 per cent. strength and over often caused vomiting, so that the effects upon the mucous membrane varied a little, but, speaking generally, the degree and extent of the gastritis varied in proportion to the strength of the acid and the length of time over which it was administered. Quite a marked effect, however, was seen in the stomach of animals who had only received a few doses.

The regularity with which this gastritis is produced by weak solutions of HCl acting for such short periods makes it quite certain that continued hyperchlorhydria in the human subject gives rise to gastritis.

Incidentally it may be mentioned that the presence of gastritis did not affect the healing of the ulcers. This agrees with the observations of pathological anatomy. Neither were the movements of the stomach affected.

2. NECROTIC EFFECT.—So far as we have seen the usual effect is an irritant one and there is merely a separation and killing off of surface epithelial cells, the glands being destroyed as a secondary effect of the inflammatory infiltration. Hydrochloric acid, however, is able in certain strengths to kill a tract of mucous membrane for various depths, and by continuous administration to produce a spreading ulcer.

I had previously found in the case of the guinea-pig that a single dose of a solution of HCl of 0.7 to 0.9 per cent. in strength, according to the weight of the animal, was able to produce patches of necrosis in the gastric mucous membrane (1910 7). Strengths below these were

unable to do so unless the cells were also devitalised by some other cause. In the case of the monkey, stronger solutions than these are required. In the case of a bonnet monkey, weighing 1530 grms., 20 c.c. of a 1·6 per cent. HCl solution produced large patches of necrosis in the mucous membrane, stained black by altered blood.

I have found that weaker solutions than this, if continuously administered, are now and again able to produce necrosis, gradually extending in the mucous membrane and giving rise to a definite ulcer. The weakest solution which I have found to produce this effect in the monkey is one of 0·39 per cent. in strength.

Experiment 23 is an example of such a case. In this experiment an oval spreading ulcer was found, and one or two tiny ones in its vicinity. The animal had also marked duodenal obstruction. Another bonnet monkey, weighing 2800 grms., was injected with 8 c.c. gastrototoxic serum, and duodenal obstruction produced. On the fourth, fifth, and sixth days 50 c.c. HCl solution, 0·39 per cent. in strength, were administered. The animal wasted and looked ill, and was therefore killed on the seventh day. The constriction was very tight. An enormous ulcer occupying most of the anterior wall and small curvature had been produced at the site of injection. It was 2 inches by $1\frac{3}{4}$ inch in size, and exposed the liver. In addition, some necrotic ulcers quite apart from the injection were present. One was $\frac{1}{2}$ inch long, and there were two or three smaller ones. The enormous size of the ulcer, produced at the site of injection, was due to the action of the acid, aided, no doubt, by the obstruction; the presence of the smaller ulcers was entirely due to this (Plate XVIII. Fig. 12).

Another case illustrates the fact that in the condition of pyloric obstruction a gastrototoxic ulcer may be made enormous by the administration of 0·39 per cent. HCl solution in the early stages.

The monkey was a bonnet, and weighed 2230 grms. 8 c.c. gastrototoxic serum were injected and the duodenum obstructed. On the fourth, fifth, and sixth days 50 c.c. of 0·39 HCl solution were administered, and as the animal looked ill it was killed on the seventh day. The constriction was tight. A very large ulcer, $1\frac{1}{2}$ inch by 1 inch in size, with hæmorrhage into the surrounding mucous membrane, was found. It had exposed the liver over a large area and the base was perforated at one edge. General peritonitis was commencing. There were no other ulcers to be seen by the naked eye.

Experiment 24, in which 0·9 per cent. HCl was administered, showed two or three small necrotic ulcers.

A 1 per cent. solution of HCl, repeatedly administered, is able to cause such ulcers in the cat, in the absence of pyloric obstruction.

Two cats, weighing 4420 grms. and 2755 grms. respectively, were fed with HCl solution. The former received two doses of 0·33 per cent. solution and three doses of 1 per cent. solution, each amounting to 50 c.c. It was then killed. There were several patches of superficial ulceration and a considerable number of scattered points of hæmorrhage in the stomach. The latter received sixteen doses of 60 c.c. of a 1 per cent. solution of HCl and was then killed. There was much mucus in the stomach, and a considerable amount of superficial ulceration of the mucous membrane (Plate XVIII. Fig. 11).

Necrosis of the mucous membrane of the stomach, therefore, only occurs with fairly strong solutions of HCl, provided that the stomach

empties normally, but in the condition of pyloric obstruction it is liable to occur with solutions of 0.39 per cent. in strength.

Considering that such a short time is available for the action of these solutions, and that the human stomach is probably as susceptible to HCl solution as is that of the monkey or cat, it is probable that hyperacidity of, say, 0.35 to 0.4 per cent., and hypersecretion of the gastric juice, will now and again of themselves give rise to an ulcer of the stomach.

Sections of these necrotic ulcers were cut and the following points elicited. The ulcer begins as a tiny necrotic spot in the superficial mucous membrane, which separates. The necrosis spreads in all directions, and the tissue gradually separates until an ulcer involving the whole thickness of the mucous membrane is produced, quite comparable to the acute spreading ulcer in man. The smallest ulcers are circular and about as big as a pin's head. They often spread irregularly, but in the monkey, Experiment 23, the ulcer spread in the regular oval shape as described above, lying parallel to or near the small curvature on the posterior wall of the stomach.

CONCLUSIONS.

1. The gastric juice is not only concerned in the initiation of a gastric ulcer, but also in its tendency to spread and to become chronic. It is thus responsible for the anatomical peculiarities which distinguish this ulcer from ulcers in other parts of the body.

2. The gastric juice owes its destructive power primarily to the hydrochloric acid contained in it, and the damage done to the wall of the stomach varies in proportion to the strength of the acid present.

3. Although the hydrochloric acid is usually only a factor in the initiation of an ulcer, some damage being also inflicted upon the gastric cells by other means, it is occasionally, when of a percentage of 0.39 and upwards and combined with motor insufficiency, the actual cause of the ulcer.

4. The spread of an ulcer is due to persistence of the original cause, but it is more likely to spread when the gastric juice is hyperacid than when of normal acidity.

5. The gastric juice is able to attack the connective-tissue base of an ulcer by virtue of the hydrochloric acid contained in it, and, when hyperacid, to produce various degrees of delay in the healing of the ulcer as a consequence. This effect is added to when retention of food in the stomach or hypersecretion of the gastric juice is present. In this way may be explained the condition of delayed healing of acute ulcer in man.

6. It is probable that in human pathology a complete arrest in healing and a resulting chronic ulcer may be similarly brought about, since the experimental methods available for producing hyperacidity

are not so effective as the condition present in man. It must also be remembered that an ulcer heals with difficulty in proportion to its chronicity, and that the more chronic ulcers may be kept open by the normal gastric juice.

7. An important point in favour of this view is the similarity between the two conditions. The experimental ulcer is delayed in healing by the necrotic condition of its base, brought about by the hydrochloric acid, and it is precisely the fibrotic base covered with necrotic tissue which prevents the healing of human ulcer. The treatment aimed at reducing the acidity of the gastric contents and facilitating the emptying of the stomach is that which is successful in healing a human gastric ulcer.

8. Associated with chronic gastric ulcer in the human subject are commonly the two conditions—(1) hyperacidity and (2) gastritis. The association of the three conditions has in the past given rise to much speculation with regard to the relation which they bear to one another. It is proved by these experiments that continued hyperacidity gives rise to gastritis, and, on the other hand, it is well known clinically that if gastritis affects the acidity of the gastric juice the latter is diminished. It seems reasonable, therefore, to assume that the hyperacidity precedes the gastritis and causes it. Gastritis in ulcer may of course be due to irritants in the food, but the regularity of its occurrence suggests that some constant factor is usually its cause. It is obvious that a gastric ulcer does not give rise to diffuse gastritis, and it is equally obvious from these experiments that follicular ulcers, occurring as a part of gastritis, cannot become chronic by continued hyperacidity. Diffuse gastritis, therefore, is neither the cause nor the effect of the ulcer, but results from the irritant action of the hydrochloric acid, or perhaps in other cases from one of the well-known causes of the affection. We have seen that hyperacidity is concerned as a factor in each of the pathological processes of gastric ulcer, and, on the other hand, it may be stated that, although it has been suggested, proof has never been afforded that an ulcer gives rise to hyperacidity.

9. We thus see the important part which the acid of the gastric juice plays as a factor in the pathological processes of gastric ulcer. It must not, however, be supposed that the importance of this factor is the same in all cases, since there are many different types of ulcer of the stomach brought about by an equal number of different causes. The destiny of an ulcer of the stomach depends upon its cause as well as upon the adverse influences to which it is exposed.

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DESCRIPTION OF PLATES XVI.-XVIII.

PLATE XVI.

- FIG. 1.—Microphotograph of a section of the scar of Experiment 5. The fibrous tissue of the base is covered with a single layer of cubical epithelial cells, which have not yet commenced to form primitive glands. ($\times 60$.)
- FIG. 2.—Photograph of the ulcer of Experiment 12, showing the delay in healing on the twenty-first day due to administration of 0·39 per cent. HCl solution. (Slightly reduced.)
- FIG. 3.—Photograph of the ulcer of Experiment 21, showing the delay in healing on the twenty-first day due to administration of 0·28 per cent. HCl solution, together with motor insufficiency. (Slightly reduced.)
- FIG. 4.—Photograph of the ulcer of Experiment 22, showing the delay in healing on the twenty-first day due to administration of 0·39 per cent. HCl solution, together with motor insufficiency. The slough covering the base is seen to have shrunk from the edges of the ulcer. (Slightly reduced.)

PLATE XVII.

- FIG. 5.—Photograph of the stomach of Experiment 23, showing a large ulcer in the centre which was formed by the gastrotxin and which shows on the sixteenth day very little tendency to heal. The oval ulcer to the left is an acute spreading ulcer which has arisen as a necrotic patch in the mucous membrane owing to the action of the HCl of 0·39 per cent. strength. Motor insufficiency was present. One or two smaller ulcers were also present. (Slightly reduced.)
- FIG. 6.—Photograph of the ulcer of Experiment 24, showing the delay in healing on the twenty-first day due to administration of 0·9 per cent. HCl solution, together with motor insufficiency. (Slightly reduced.)
- FIG. 7.—Photograph of monkey's stomach, showing gastritis and follicular ulceration due to administration of 0·9 per cent. HCl solution. (Natural size.)
- FIG. 8.—Photograph of monkey's stomach, showing circular patches of gastritis due to administration of 0·5 per cent. HCl solution. (Natural size.)

PLATE XVIII.

- FIG. 9.—Microphotograph of section of stomach of Experiment 22, showing gastritis due to administration of 0·39 per cent. HCl solution. There is round-celled infiltration of the mucosa, destruction of the gastric glands, and desquamation of the surface epithelium. ($\times 80$.)
- FIG. 10.—Microphotograph of section through an enlarged follicle in the mucous membrane of a monkey's stomach, resulting from the administration of 0·5 per cent. HCl solution. A follicular ulcer is forming. The enlarged follicle has burst through the muscularis mucosæ and appeared at the surface of the mucous membrane. ($\times 75$.)

- FIG. 11.—Microphotograph of section of cat's stomach, mentioned on p. 154, showing the formation of a necrotic ulcer. The mucous membrane has gradually disappeared almost to the level of the muscularis mucosæ, which is covered with necrotic tissue, embedded in which are the remains of gastric glands. ($\times 60$.)
- FIG. 12.—Photograph of monkey's stomach, mentioned on p. 154. The ulcer is seen to occupy most of the anterior surface of the stomach, the base being formed of a large area of the liver covered with slough. (Reduced by about one-half.)

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.