ASPECTS OF THE PATHOGENESIS AND HEALING OF
GASTRIC EROSIONS AND ULCERS

A THESIS PRESENTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY IN THE
UNIVERSITY OF EDINBURGH.

OCTOBER, 1959.

by
"If I set out to prove something, I am no real scientist – I have to learn to follow where the facts lead me – I have to learn to whip my prejudices".

Spallanzani. 1729 - 1799.

"The man who confesses his ignorance shows it once; he who tries to conceal it shows it many times".

Japanese proverb.
CONTENTS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>DEFINITION OF GASTRIC &quot;EROSION&quot; AND &quot;ULCER&quot;</td>
<td>3</td>
</tr>
<tr>
<td>HUMAN GASTRIC ULCERS AND EROSIONS</td>
<td>4</td>
</tr>
<tr>
<td>GASTRIC EROSIONS AND ULCERS IN ANIMALS</td>
<td>25</td>
</tr>
<tr>
<td>SYSTEMIC DISORDERS AND LOCAL HEALING</td>
<td>59</td>
</tr>
<tr>
<td>LOCAL IRRITANTS AND THE STOMACH</td>
<td>67</td>
</tr>
<tr>
<td>&quot;RING&quot; BURNS AND THE HEALING OF GASTRIC ULCERS</td>
<td>79</td>
</tr>
<tr>
<td>FURTHER ATTEMPTS TO DELAY HEALING IN GASTRIC ULCERS</td>
<td>86</td>
</tr>
<tr>
<td>ALCOHOL AND THE STOMACH</td>
<td>119</td>
</tr>
<tr>
<td>HYDROCHLORIC ACID AND GASTRIC ULCER</td>
<td>143</td>
</tr>
<tr>
<td>HISTAMINE AND THE STOMACH</td>
<td>165</td>
</tr>
<tr>
<td>TWO ORIGINAL METHODS OF PRODUCING GASTRIC ULCERS</td>
<td>184</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>216</td>
</tr>
</tbody>
</table>
ACKNOWLEDGMENTS

I am grateful to Professor G. L. Montgomery for his interest, encouragement and criticism, to Mr. T. C. Dodds for help with the illustrations, to Mr. James Waugh for technical assistance, to Mr. William Robb for help with animals and to Miss Kathleen Gray for secretarial aid. I am also grateful to the Editors of Gastroenterologia (Basel) for use of figs. 86 and 87.
For nearly a century the subject of peptic ulceration has fascinated and baffled investigators. The extent of the medical literature on various aspects of the ulcer problem indicates its complexity, while the chaos of conflicting experimental and clinical data points to the need for truly fundamental knowledge. This common and serious condition remains an enigma and although accumulated information has led to improvements in treatment, the latter remains crude, unreliable and possibly associated with harmful complications.

Popular opinion supports the naive suggestion that the problem is merely one of hyperchlorhydria but a critical survey of the literature shows that, in fact, very little progress has been made in our understanding of peptic ulceration as regards acidity or other factors such as vascularity, mucin or nerve-supply and it would therefore seem appropriate to broaden our conception of the pathogenesis. Is there any reason, for example, why one should assume a common causal pathway for all types of peptic ulcer. Three fundamental questions require an answer. They are: (1) what are the factors which cause ulcers, (2) which factors favour the localization of ulcers to certain sites and (3), what are the factors which maintain chronicity, viz. delay healing. In this investigation, special emphasis is placed on the aspect of healing of gastric/
gastric erosions and ulcers. In man and animals, defects of the mucosa of stomach or duodenum are normally repaired rapidly but in patients with chronic peptic ulceration there is failure of an acute ulcer to heal. This failure, as Cohnheim (1882) first stressed, is the root of the problem. No-one has yet explained satisfactorily why it exists.

Some people are critical of the use of animals for research into the pathogenesis of chronic peptic ulcer. They assume that, because spontaneous peptic ulcers are rare in animals, experimental results are not significant in relation to humans. However, from a controlled research point of view, such immunity from spontaneous ulceration is a major advantage. The results of animal experiments may or may not be of clinical importance but are, nevertheless, of general biological importance and interest.

DEFINITION OF GASTRIC "EROSION" AND "ULCER"

The following terminology is used in this work:

(1) An erosion is a circumscribed mucosal defect which does not penetrate the muscularis mucosae.

(2) An ulcer is a circumscribed defect which extends through the muscularis mucosae.

1. Site: usually the lesser curve.
2. Number: usually solitary.
3. Size and Shape: majority not more than about 1 cm. in diameter and round or oval.
4. Base: is formed of dense fibrous tissue, covered by a thinner layer of granulation tissue and a narrow necrotic and palisaded zone at the surface (fig. 2).

There is no obvious lack of an epithelial covering at the margin and, moreover, the surrounding mucosa is abnormal; instead of being regularly arranged, the glands are disarranged and there is always some degree of inflammatory change in this marginal part of mucous membrane.

Another feature - one which is only rarely described - is that normal glands of body type are never seen immediately around an chronic ulcer. Indeed, where such an ulcer is present in a part of the stomach where body glands are normally present, these glands are few or absent for several millimetres around the ulcer and the glands that are present immediately around the ulcer are pyloric or intestinal.
HUMAN GASTRIC ULCERS AND EROSIONS.

CHRONIC GASTRIC ULCERS IN HUMANS

Fig. 1 illustrates the characters of a chronic gastric ulcer in a section.

The typical chronic ulcer has several well-recognized features which have a peculiar and, as yet, unexplained significance. The best-known are:

1. **Site**: usually the lesser curve.
2. **Number**: usually solitary.
3. **Size and shape**: majority not more than about 1 cm. in diameter and round or oval.
4. **Floor** is formed of dense fibrous tissue, covered by a thinner layer of granulation tissue and a narrow necrotic and purulent zone at the surface (Fig. 2).

There is an obvious lack of an epithelial covering at the surface and, moreover, the surrounding mucosa is abnormal: instead of being regularly arranged, the glands are irregular and there is always some degree of inflammatory change in this marginal part of mucous membrane. Another feature - one which is only rarely described - is that normal glands of body type are never seen immediately around a chronic ulcer. Indeed, where such an ulcer is present in a part of the stomach where body glands are normally present, these glands are few or absent for several millimetres around the ulcer and the glands that are present immediately around the ulcer are pyloric or intestinal/
FIG. 1. SECTION OF CHRONIC GASTRIC ULCER
H. and E. x 2.

FIG. 2. PART OF THE FLOOR OF THE ULCER IN
FIG. 1. H. and E. x 40.
intestinal in type; this change in the mucosal pattern is one that develops in the healing of both gastric erosions and ulcers (figs. 3 and 4) and suggests that either the stomach lesion was larger in area at some earlier date or, alternatively, that in a chronic ulcer and its surrounding fringe of mucosa there is an uneasy balance between injury and repair. Suggestive evidence of previous injury is also provided by the frequent finding of fibrous thickening beneath the marginal mucosa, sometimes for a breadth of several millimetres.

Consideration of these characters of chronic gastric ulcers forms a practical basis for an initial experimental approach in animals and it is surprising that many of these highly-interesting and significant structural features have been either overlooked or ignored. Some of the sorts of question that can be posed from a detailed study of the structure of chronic gastric ulcers will now be briefly mentioned:

1. Is chronicity in a gastric ulcer due to a failure of epithelial covering; if so, is the defect in the failure of epithelium to grow or is the growing epithelium abnormally sensitive to chemical or mechanical damage?

Alternatively:

2. Is chronicity in a gastric ulcer primarily a function of the nature of the ulcer floor?

The factors that control the adhesion of growing/
FIG. 3. MUCOSA AROUND THE ULCER ILLUSTRATED IN FIGS. 1 AND 2. THE GLANDS ARE PYLORIC AND MARKED CHRONIC GASTRITIS WITH INTESTINAL METAPLASIA IS PRESENT. H. and E. x 40.

FIG. 4. NORMAL GASTRIC MUCOSA: (A) BODY TYPE AND (B) PYLORIC TYPE. H. and E. x 40.
8.

growing epithelium to a surface are ill-understood and it is a reasonable postulate that epithelial growth is not possible over a floor which is necrotic, purulent or densely fibrous.

3. Does the ordinary chronic gastric ulcer possess general features which are fundamentally different from an ordinary chronic ulcer elsewhere in the body, e.g. in the skin? If not, is the chronicity, in both instances, dependent upon the large size of the initial acute lesion?

4. If acid-pepsin is so important in the pathogenesis of chronic peptic ulcers, is there conclusive proof of its alleged essential role in this context? Special mention will be made in a later section of the possible relationship between acid-pepsin and gastric erosion and ulceration but it is appropriate to mention here that there are several observations which seriously cast doubt on the correctness of the popular theory (regarded by many as a matter of fact!) that chronic gastric ulcer is the result of HCl-pepsin digestion alone: first, the focal nature of the lesion; secondly, the fact that, in many instances of gastric ulceration, the secretion levels of acid-pepsin are within normal limits, unlike the high levels found/
found as a rule in patients with a chronic duodenal ulcer; finally, the histological evidence of digestion is remarkably slight in the ordinary chronic gastric ulcer.

Much instructive and possibly useful information can thus be gained from a detailed study of the structure of human gastric ulcers and in most of the animal experiments that will be described a serious and sustained effort has been made to glean some information which might explain this structure.

**ACUTE (AND SUBACUTE) GASTRIC EROSIONS AND ULCERS IN THE HUMAN**

Any chronic ulcer could not have been chronic de novo. Every chronic gastric ulcer must therefore have developed from an acute or subacute lesion and it is pertinent at this stage to refer to such an earlier lesion. Acute or subacute peptic ulcers and erosions are rarely observed clinically, unless they bleed or perforate but, nevertheless, they account for a considerable minority of cases of severe haematemesis or melaena (Illingworth, 1953). They may be single or multiple and form defects of variable depth and area but are usually shallow and only a millimetre or two in diameter. Many are haemorrhagic. Microscopically, the lesions are necrotic with variable acute or subacute inflammatory reactions. They may occur in any part of the stomach, including the lesser curve. Except for an alleged association in some few cases with cortisone (or similar/
similar steroid) therapy or with burns, the aetiology is unknown but it is usually believed that acid-pepsin is not primarily essential for the production of these lesions.

Similar lesions are not uncommonly found routinely at autopsy, especially in patients who have died with infections, haemorrhagic disorders or malignant disease. Stewart (1929) found a 3% incidence of acute lesions in 4000 consecutive autopsies and many other investigators have reported a similar percentage. Many post-mortem specimens of stomach, however, have undergone autolysis and this change makes the identification of small mucosal lesions difficult or impossible. An accurate assessment of the incidence of lesions can therefore be made only in very fresh stomach specimens or, alternatively, in specimens which have been fixed very shortly after death - within 1/2 hour as a rule. The author in 1949 carefully examined a personal random series of 62 adult autopsy subjects in which the stomach had been fixed with formalin immediately after death. Acute ulcers were found in 4 (6%) and acute erosions in 18 (30%) stomachs in the series.

Such lesions are also recognisable in resected stomach specimens from patients who have a gastric or duodenal ulcer or both. In stomach specimens the author found acute or subacute erosions or ulcers in 19.8%.

There is satisfactory evidence that acute or subacute erosions or ulcers heal in normal subjects but, in subjects with chronic peptic ulcer, for reasons which are not at present/
present understood, one (or occasionally more than one) of these lesions fails to heal and a chronic ulcer then develops. It is interesting to note, however, that healed lesions of this kind, particularly small erosions, may be present in resected stomach specimens from peptic ulcer patients, and in the latter the author has found a very high percentage of healed erosions, also some healed ulcers, particularly in the antrum and pylorus: there were healed erosions in 129 (50.5%) and healed ulcers in 13 (5.1%) of 255 resected stomach specimens from peptic ulcer patients.

The incidence of these lesions in personally-studied series is given in table 1 and their appearances are illustrated in figs. 5 - 21.
TABLE 1.

INCIDENCE OF ACUTE, SUBACUTE AND HEALED EROSIONS AND ULCERS IN 255 RESECTED STOMACHS

210 Patients had D.U., 33 G.U., 3 Both D.U. & G.U.,
6 Stomal Ulcer and 3 Unexplained haematemesis.

<table>
<thead>
<tr>
<th></th>
<th>ACUTE OR SUBACUTE</th>
<th>HEALED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single</td>
<td>Multiple</td>
</tr>
<tr>
<td>EROSIONS</td>
<td>15 (5.9%)</td>
<td>22 (8.7%)</td>
</tr>
<tr>
<td>ULCERS</td>
<td>8 (3.1%)</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td></td>
<td>9 (3.5%)</td>
<td>120 (4.7%)</td>
</tr>
<tr>
<td></td>
<td>11 (4.4%)</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

50 (19.8%)        142 (55.6%)
FIG. 5. MULTIPLE ACUTE GASTRIC ULCERS. AUTOPSY SPECIMEN. NATURAL SIZE.

FIG. 6. SECTION OF ONE OF THE ULCERS IN FIG. 5. SHOWING THE ACUTELY INFLAMED FLOOR. H. and E. x 70.
FIG. 7. SUBACUTE GASTRIC ULCERS. GASTRECTOMY SPECIMEN. NATURAL SIZE.

FIG. 8. SECTION OF ONE OF THE ULCERS IN FIG. 7. SHOWING GRANULATION TISSUE IN FLOOR. H. and E. x 70.
FIG. 9. MULTIPLE ACUTE HAEMORRHAGIC EROSIONS IN GASTRIC MUCOSA OF A MAN OF 37. x 1.5.

FIG. 10. (A) MULTIPLE ACUTE EROSIONS IN THE GASTRIC MUCOSA OF A PREMATURE INFANT. x 2.5. (B) SECTION OF ONE OF THE EROSIONS. H. and E. x 90.
FIG. 11. (A) SUPERFICIAL AND (B) DEEP EROSIONS FROM A PARTIAL GASTRECTOMY SPECIMEN. H. and E. x 65.
FIG. 12. HEALED PYLORIC EROSION. 
H. and E. x 40.

FIG. 13. HEALED PYLORIC EROSION FROM THE SAME STOMACH AS THE LESION IN FIG. 12. NOTE THE PATTERN OF "CHRONIC ATROPHIC GASTRITIS". 
H. and E. x 40.
FIG. 14. (A) SECTION OF ANTRAL REGION OF STOMACH SHOWING HEALED EROSION.
(B) RELATIVELY NORMAL ANTRAL MUCOSA FROM SAME STOMACH. H. and E. x 70.
FIG. 15. (A) & (B). TWO SECTIONS FROM THE SAME STOMACH SHOWING SIGNS OF HEALED EROSION IN THE MUCOSA, ALSO A MARKED LYMPHOCYTOSIS. H. and E. x 40.
FIG. 16. (A) & (B). HEALED GASTRIC EROSIONS. 
H. and E. x 40.
FIG. 17. (A) & (B). HEALED GASTRIC EROSIONS. IN (B) A SMALL ACUTE EROSION IS ALSO PRESENT (c.f. FIG. 11, FROM THE SAME STOMACH). H. and E. x 65.
FIG. 18. HEALED GASTRIC EROSION AND MARKED HYPERPLASTIC THICKENING IN THE MARGINAL MUCOSA. H. and E. x 40.

FIG. 19. HEALED GASTRIC EROSION WITH MARKED INTESTINAL METAPLASIA. NOTE NORMAL BODY GLANDS ON THE RIGHT. (c.f. FIGS. 17 & 11 FROM THE SAME STOMACH). H. and E. x 65.
FIG. 20. HEALED GASTRIC EROSION WITH MARKED INTESTINAL METAPLASIA: VIRTUALLY THE APPEARANCE OF "CHRONIC ATROPHIC GASTRITIS". H. and E. x 40.

FIG. 21 (A) & (B). RANDOM SECTIONS FROM A PATIENT WITH GASTRIC CARCINOMA. BOTH SHOW FEATURES OF "CHRONIC ATROPHIC GASTRITIS" (? RELATED TO PREVIOUS EROSION). IN (B) MARKED EPITHELIAL HYPERPLASIA IS ALSO SEEN. H. and E. x 40.
REFERENCES


for to the rare occurrence of peptic ulcers in captive canines, dogs, guinea and harvans. Bougard (1962) described frequent ulcers in weaning calves. Fox (1933) observed the unusual occurrence of chronic gastric ulcers in domestic rabbits, Primatida, Insectivora, Urates and Hyracoidea. Schroeder and Wagesforth (1939) found a high incidence of chronic ulcer in Californian seals. Peptic ulcers have been reported in dogs (Muscare, 1933; Grauprecht, 1936; Koller, 1936) and rats (Piper, 1938) but not in guinea pigs (Smith and McClure, 1940) or hamsters (Ophelia, 1946).

EXPERIMENTAL LESIONS

There are very many methods of producing acute peptic erosions and ulcers in experimental animals, including direct physical or chemical trauma, the parenchyma administration of toxic agents, nerve injury, hormonal imbalance, and nutritional disturbances. Greggie (1916) listed more than 200 methods, mostly involving physical or chemical trauma. The subject has been reviewed by McGavin (1929), Lind (1937) and Toy, Genneman and Burch (1950).

Lundberg (1935) lists the following methods which might have a human counterpart:

1. Administration of acids and alkalies
2. Nerve injury
3. Chemical agents
4. Hormonal imbalance
5. Nutritional disturbances
GASTRIC EROSIONS AND ULCERS IN ANIMALS

SPONTANEOUS LESIONS

Spontaneous peptic ulceration is rare amongst domestic, laboratory and wild animals. Hutrya and Marek (1913) refer to the rare occurrence of peptic ulcer in adult cattle, dogs, swine and horses. Bongert (1912) found gastric ulcers in weaning calves. Fox (1923) reported the occasional occurrence of chronic gastric ulcer in Primates, Carnivora, Primipedia, Insectivora, Ungulata and Hyrdoces. Schroeder and Wegeforth (1935) found a high incidence of chronic ulcer in Californian seals. Peptic ulcers have been reported in dogs (Rosenow, 1923; Overgaard, 1934; Keller, 1936) and rats (Singer, 1913), but not in guinea-pigs (Smith and McConkey, 1933) or rabbits (Ophüls, 1906).

EXPERIMENTAL LESIONS

There are very many methods of producing acute peptic erosions and ulcers in experimental animals, including direct physical or chemical trauma, the parenteral administration of toxic agents, nerve injury, hormonal imbalance and nutritional disturbances. Greggio (1916) listed more than 100 methods, mostly involving physical or chemical trauma. The subject has been reviewed by McCann (1929), Aird (1949) and Ivy, Grossman and Bachrach (1950).

Sandweiss (1951) lists the following methods which might have a human counterpart:

1/
1. Dietary deficiency, especially vitamins and proteins.
2. Administration of hormones.
4. Injury to the nervous system.
5. Body injury by burning.
6. Injection of toxins and drugs, e.g. histamine, cinchophen.
7. Operation on the gastro-intestinal tract which causes the prevention of dilution, buffering and neutralization of evacuated gastric contents.

In most reported cases of experimental peptic erosion and ulceration, the lesions have healed rapidly and their relationship to the problem of peptic ulcer in man has not been at all clear. Leriche (1931) has pointed out that there is no difficulty in producing an ulcerative lesion but no method has produced ulcers which display the evolution of the disease in man while, according to Ivy (1946) one can state with confidence that there is only one type of ulcer which occurs in man, the counterpart of which has been produced experimentally and that is the post-operative gastro-jejunal ulcer, which is due primarily to acid acting on a mucosa (jejunal) more susceptible to acid than the gastric or duodenal mucosa.

As far as the stomach is concerned, it may be stated that while the experimental ulcer corresponds to the acute ulcer/
ulcer as seen in the human, no published experimental method has so far succeeded in producing a chronic ulcer similar to that seen in man. In view of the absence of spontaneous chronic gastric ulcer in laboratory animals, any experimental method which produces chronicity in gastric ulcers will clearly have special significance.

HEALING OF DEFECTS

The study of the healing of defects in the gastrointestinal tract has not been as thorough as the subject warrants. Most investigations have been on the dog. No essential difference between the healing of an acute peptic ulcer in man and that described for the dog and cat has been found (Stewart, 1922; Caylor, 1926; Kennedy, 1926).

Acute ulcers produced by cauterization heal in the same time as ulcers produced by excision. Such ulcers have been produced with a hot iron in the stomach or duodenum of rabbits by Quincke (1875), Yano (1925), Nakano (1932) and Oda (1936). Cohnheim (1822) also produced acute lesions of the stomach of rabbits by burning.

By burning the stomach wall under standardized conditions, and later fixing the organ with a constant volume of fixative, it is possible to obtain an accurate assessment of the progressive healing of gastric defects (Wynn Williams, 1953). This method, which has been applied to the study of the normal healing processes of acute/
acute gastric ulcers in guinea-pigs, rabbits and rats, and has been used in an attempt to determine possible modifying factors of the healing process, will now be described.

A STANDARDIZED CAUTERY METHOD IN GASTRIC ULCER STUDIES.

The animal is given a general anaesthetic and the abdomen opened through a midline incision. The stomach is withdrawn from the abdomen and an incision made in its anterior wall, at right-angles to the longitudinal axis of the stomach (fig. 22A). The posterior wall of the stomach is then applied to this newly-made aperture by a finger placed behind the stomach and an elected site on the exposed mucosa is cauterized with a stainless steel cylinder (figs. 22B and 23). Cylinders are of variable diameter, e.g. 1.0 to 18.0 mm., and they are heated for a constant time, e.g. 20 to 30 seconds, in a small flame of constant temperature. The brand is applied, with slight pressure, to the mucosa until the sensation of uncomfortable heat is just felt by the underlying finger-pad. After burning, the aperture in the anterior wall of the stomach is closed with a purse-string suture (fig. 22C), the stomach is returned to the abdomen and the abdominal wall is closed in two layers.

The burn is a well-defined circular lesion. The whole operation is simple to perform and occupies, as a rule, no more than 20 minutes. When it is desired to ascertain the progress of healing at a given time after operation, the animal is killed and its duodenum and oesophagus are each tied/
PRODUCTION OF CAUTERY ULCER IN STOMACH: STAGES IN THE OPERATION

(a) Ventral view of gastrostomy
(b) Sectional view of gastrostomy
(c) Ulcer produced

FIG. 22.
FIG. 23. BRANDS FOR PRODUCING ULCERS. NATURAL SIZE.

They are columnar. It is commonly stated in reports and text-books that such epithelium can grow only a fine connective tissue base, but it has been observed many times in these experiments that the cells can and do grow over necrotic debris, providing the latter forms a uniform, compact layer on the ulcer floor. This epithelial covering is probably of considerable importance in the healing of ulcers.
tied with a ligature. The stomach is then injected with a constant volume of fixative, the amount being appropriate to the size of animal, e.g. 3 - 10 ml. for young adult rats, 30 - 40 ml. for young adult guinea-pigs and 60 - 80 ml. for young adult rabbits; then the stomach is removed and immersed in fixative for 24 hours; finally, it is opened and the mucosa washed very gently with a small stream of water. The healing or healed lesion is usually easily identifiable on a relatively flat background (figs. 24-30). In the rabbit, a nodule of hyperplastic epithelium is often found at the site of healed ulcers (fig. 31).

NORMAL HEALING PROCESSES

The basic pattern of healing is identical in all 3 animal species. It comprises 2 components: epithelial regeneration and connective tissue formation. The former begins within 24 hours of injury, when a delicate film of epithelium, one cell thick, grows over the ulcer floor from the adjacent gastric pits ("foveolae"). At first, the cells are flat, later they become cuboidal and, finally, they are columnar. It is commonly stated in reports and text-books that such epithelium can grow only a firm connective tissue base, but it has been observed many times in these experiments that the cells can and do grow over necrotic debris, providing the latter forms a uniform, compact layer on the ulcer floor. This epithelial covering is probably of considerable importance in the healing of acute/
FIG. 24. ULCER, INITIALLY 12 mm. DIAMETER, IN GUINEA-PIG STOMACH. 6 DAYS AFTER PRODUCTION. x 6.
FIG. 25. ULCER, INITIALLY 18 mm. DIAMETER, IN GUINEA-PIG STOMACH 27 DAYS AFTER PRODUCTION. x 6.
FIG. 26. ULCER, INITIALLY 12 mm. DIAMETER, IN GUINEA-PIG STOMACH 20 DAYS AFTER PRODUCTION. x 6.
FIG. 27. HEALED ULCER, INITIALLY 12 mm. DIAMETER, IN GUINEA-PIG STOMACH 23 DAYS AFTER PRODUCTION.
FIG. 28. ULCER, INITIALLY 4 mm. DIAMETER, IN GUINEA-PIG STOMACH 4 DAYS AFTER PRODUCTION. x 6.
FIG. 29. ULCER, INITIALLY 4 mm. DIAMETER, IN GUINEA-PIG STOMACH, 8 DAYS AFTER PRODUCTION. x 6.
FIG. 30. ALMOST HEALED ULCER IN GUINEA-PIG STOMACH, 16 DAYS AFTER PRODUCTION. IT WAS INITIALLY 4 mm. IN DIAMETER. x 6.
FIG. 31. HEALED ULCER, INITIALLY 4 mm. DIAMETER, IN RABBIT STOMACH 15 DAYS AFTER PRODUCTION. THERE IS A PROMINENT NODULE OF HYPERPLASTIC EPITHELium. x 8.
acute ulcers and erosions because it protects the ulcer floor.

Except for a narrow zone in the deepest part of the stomach wall, including the serosa, cauterization produces necrosis of the whole thickness of stomach wall. An acute inflammatory reaction immediately follows in the surviving tissues around the necrotic lesion and is especially marked for 4 or 5 days. Vascular hyperaemia is associated with oedema and a brisk polymorphonuclear leucocytosis, so that, macroscopically, there is swelling and redness of the affected part. Many of the polymorphs migrate into the necrotic central part and become phagocytic, but most of the necrotic material disappears — though often surprisingly slowly — by the concomitant processes of peptic digestion and sloughing. As the polymorphs become fewer, there is an increasing infiltration with large mononuclear phagocytes and, later, by small numbers of cells of lymphocytic type. Little fibroblastic activity is seen until the 4th, 5th, or 6th days, when there is a sudden burst of activity and, as would be expected, this is conspicuous in the connective tissue planes. When the ulcer is several days old, reticulin and collagen fibres are formed in an orderly manner, lying parallel to the surface of the stomach between rows of fibroblasts. By the 12th day, a well-defined fibrous layer occupies the ulcer floor, replacing the damaged portion of stomach wall; during its formation, the surface of/
of this layer has been progressively covered by the thin epithelial layer which differentiates into glands. At first, the glands consist only of a few simple tubules but later they increase in number; finally the surface of the healed ulcer consists of a fairly thick mucosa of pyloric type, though usually thinner than normal. After 3 months, some chief and parietal cells may be identified in the new mucosa. Generally, the latter is fairly uniform in thickness but it may present a slightly papillary irregularity; cystic dilatation of a few glands is occasionally present. Commonly, the mucous membrane immediately around the ulcer, for a few to several millimetres, is thickened, to a slight or moderate extent, because of hyperplastic epithelial proliferation in the superficial part of the mucosa; the necks of the glands are usually elongated and may be widened; this hyperplastic change is seen particularly well in the rabbit and appears to the naked eye as a boss of tissue. As the ulcer heals, the fibrous floor becomes progressively less cellular and may eventually become hyaline. In a few animals the ulcer floor contains adipose as well as fibrous tissue. Fibrous adhesions are formed on the peritoneal surface of the ulcer.

Phases in the normal healing process are illustrated in figs. 32 to 42.

In many of the experiments to be described, ulcers
of various size were produced by the method described in groups of 10 to 30 animals. In most of the experiments, the ulcer site was usually the middle of the posterior wall of the body ("fundus" in the American nomenclature), midway between the curvatures, but in one of the earliest experiments the possible influence of the ulcer site itself on healing was investigated and this experiment will now be described:—

SITE OF ULCER AND HEALING TIME

An investigation into this relationship was undertaken in the guinea-pig. Ulcers 4 mm. in diameter were produced in the stomachs of 3 groups, each containing 12 animals. In the first group, the ulcer was at the oesophago-gastric junction, in the second it was on the middle of the lesser curve; and in the third group it was at the gastroduodenal junction. The animals were killed on the seventeenth day.

Results: The ulcers at the oesophago-gastric junction and on the middle of the lesser curve had healed completely. Eight lesions at the gastroduodenal junction had healed completely. The remaining four were almost, but not entirely, healed.

Dragstedt (1917) reported that acute ulcers 1.0 to 1.5 cm. diameter in the mucosa of a Pavlov pouch in dogs healed/
FIG. 32. HEALING ULCERS IN GUINEA-PIG STOMACH.

(A) 4th DAY. H. and E. x 135.
(B) 6th DAY. H. and E. x 80.
(C) 9th DAY. H. and E. x 50.
FIG. 33. HEALING ULCER IN GUINEA-PIG STOMACH. 7th DAY.
THE GROWING EPITHELIUM IS CLEARLY SEEN AND ITS PARTIAL
DETACHMENT IS AN ARTEFACT. H. and E. x 275.
FIG. 34. HEALING ULCER IN GUINEA-PIG STOMACH ON THE 13th DAY. H. and E. x 40.

FIG. 35. HEALING ULCER IN GUINEA-PIG STOMACH ON THE 15th DAY. H. and E. x 40.

FIG. 36. HEALING ULCER IN GUINEA-PIG STOMACH ON THE 15th DAY. NOTE THE DEVELOPMENT OF NEW GLANDS. H. and E. x 112.
FIG. 37. HEALING ULCER IN GUINEA-PIG STOMACH ON THE 17th DAY. H. and E. x 90.

FIG. 38. HEALED ULCER IN GUINEA-PIG STOMACH ON THE 23rd DAY. NOTE THE DEVELOPMENT OF GLANDS OF PYLORIC TYPE. H. and E. x 40.
FIG. 39. HEALED ULCER IN GUINEA-PIG STOMACH ON THE 25th DAY. H. and E. x 75.

FIG. 40. HEALING ULCER IN GUINEA-PIG STOMACH ON THE 14th DAY. TWO UNUSUAL FEATURES ARE SEEN: (1) A POLYPOIDAL DEVELOPMENT OF REGENERATED EPITHELIUM, (2) THE DEVELOPMENT OF ADIPOSE TISSUE IN THE FLOOR. H. and E. x 60.
FIG. 41. HEALED ULCER IN STOMACH OF RABBIT ON 25th DAY. 
THE RECONSTITUTED MUCOSA (PYLORIC IN TYPE) ON THE LEFT 
IS THICKER THAN THE NORMAL (BODY TYPE) MUCOSA ON THE 
RIGHT. H. and E. x 30.

FIG. 42. HEALED ULCER IN RAT STOMACH ON 60th DAY. 
THE RECONSTITUTED MUCOSA IS PYLORIC IN TYPE. 
H. and E. x 75.
FIG. 43. SECTION OF HUMAN EMBRYO STOMACH AT 12 WEEKS.
H. and E. x 40.

FIG. 44. SECTION OF HUMAN EMBRYO STOMACH AT 25 WEEKS.
H. and E. x 40.

(FIGS. 43 and 44 are to be compared with the previous illustrations of healing and healed gastric ulcers)
healed in 5 - 15 days, while ulcers of similar size in
the duodenum healed in 20 days. Ivy (1920) observed
that, in dogs, ulcers of this size healed in 9 - 13 days
in the body mucosa, in 12 - 18 days in the pyloric mucosa
and in 16 - 24 days in the duodenum. Morton (1927) ob-
served in the dog that defects made in the body, pyloric
and duodenal mucosa healed in 2 weeks; and he stated
that, under adverse conditions, ulcers on the lesser curve
healed more slowly than those on the greater curve.

Yano (1925), using rabbits, found that ulcers made
with a hot iron healed more rapidly when made in the body
of the stomach than along the lesser curve. Walker (1931),
however, found that excision ulcers in the rabbit stomach
healed more rapidly in the pylorus than in the body.

Nicolaysen (1920) observed that in the vagotomized
rabbit an excision ulcer on the anterior wall healed while
a chronic ulcer formed on the lesser curve.

McIlroy (1927) observed in the cat that defects made
in the pyloric mucosa healed more slowly than ulcers made
elsewhere in the stomach. Bolton (1913) found no differ-
ence in the rate of healing of ulcers produced in various
parts of the stomach in this animal.

The largest evidence thus indicates some delay in the
healing of gastric ulcers as the pyloric portion is approach-
ed. It has been suggested (Ivy, Grossman and Bachrach,
1951) that this gradient of healing potential is inversely
proportional to the gradient of susceptibility to acid
injury/
injury; furthermore, this suggestion, if correct, would explain why chronic gastric ulcers are usually found in the distal portion of the stomach.

As far as the guinea-pig is concerned, my experiments do not indicate any delay in the healing of acute ulcers on the lesser curve and throw no light on the mysterious cause of the vulnerability of the lesser curve to chronic ulceration in humans. It is worth mentioning, however, that none of the factors invoked in the pathogenesis of human chronic ulcers on the lesser curve, such as undue susceptibility of the "magenstrasse" to trauma or paucity of its blood supply, can be held responsible. The detailed observations of Barlow, Bentley and Walder (1951) give no support to the contention that there is a deficiency of blood vessels in this region; moreover, radiographic evidence (Neilson and Christiansen, 1932; Gianturco, 1934) indicates that there is, in fact, very little traffic, if any, along the "magenstrasse", which appears to be more of a hypothetical pathway suggested by the anatomical appearances.

ULCER SIZE AND HEALING TIME

In man and animals, surgical wounds generally heal in 2 - 3 weeks. Lumière (1917, 1918) states that the rate of healing of a wound \( V \) is \( V = L/T \), where \( L \) is the initial/

initial breadth of the wound and T the time required for complete healing. Hence \( T = \frac{L}{V} \). V is obtained from the slope of the healing curve.

Studies on the wound healing have mostly concerned skin wounds. Young, Fisher and Young (1941), in a careful study of healing "under a scab" in rabbits, found that large wounds heal at a greater rate than smaller ones and that, in general terms, the rate of closure is directly proportional to the area of the wound. Arey (1936) stated that internal wounds of mucous surfaces differed in no fundamental way from those of external surfaces. He noted, moreover, that epithelialization ceased if, after contraction of the wound, the area remaining to be covered exceeded 2.5 cm.

Under ordinary conditions, acute ulcers of the stomach and duodenum of experimental animals heal rapidly and no essential difference has been found between the healing of an acute peptic ulcer in man and that found in animals. Most studies on the rate of healing of acute peptic ulcers in experimental animals have been on the dog and in this animal Morton (1927) observed that defects in the gastric or duodenal mucosa, 2 cm. in diameter, healed in 2 weeks.

Using groups of 10 to 30 animals for each experiment, ulcers of various sizes were made on the posterior wall of the body of the stomach, midway between the curvatures, in rabbits, guinea-pigs and rats. The animals were killed/
killed at intervals and the degree of healing is indicated in the following tables:

RESULTS

KEY:

C denotes complete healing.

N denotes nearly-complete healing (defect pin-head in size, or less).

U denotes unhealed ulcer (defect larger than pin-head size).

TABLE 2. ULCERS INITIALLY 18 mm. IN DIAMETER

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>DAY 40</th>
<th>DAY 30</th>
<th>DAY 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUINEA-PIG</td>
<td>5 C</td>
<td>1 C 4 N</td>
<td>3 N 2 U</td>
</tr>
<tr>
<td>RABBIT</td>
<td>5 C</td>
<td>4 C 1 N</td>
<td>4 N 1 U</td>
</tr>
</tbody>
</table>

TABLE 3. ULCERS INITIALLY 12 mm. IN DIAMETER

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>DAY 30</th>
<th>DAY 25</th>
<th>DAY 20</th>
<th>DAY 15</th>
<th>DAY 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUINEA-PIG</td>
<td>5 C</td>
<td>4 C 1 N</td>
<td>1 C 3 N</td>
<td>2 N 3 U</td>
<td>5 U</td>
</tr>
<tr>
<td>RABBIT</td>
<td>5 C</td>
<td>4 C 1 N</td>
<td>2 C 2 N</td>
<td>3 N 2 U</td>
<td>5 U</td>
</tr>
</tbody>
</table>
**Table 4. Ulcers Initially 4 mm in Diameter**

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>DAY 20</th>
<th>DAY 18</th>
<th>DAY 17</th>
<th>DAY 16</th>
<th>DAY 15</th>
<th>DAY 14</th>
<th>DAY 13</th>
<th>DAY 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUINEA-PIG</td>
<td>-</td>
<td>5C</td>
<td>5C</td>
<td>4C</td>
<td>4C</td>
<td>3C</td>
<td>1C</td>
<td>5N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1N</td>
<td>1N</td>
<td>2N</td>
<td>4N</td>
<td>4N</td>
<td>2N</td>
<td>5N</td>
</tr>
<tr>
<td>RABBIT</td>
<td>-</td>
<td>-</td>
<td>5C</td>
<td>4C</td>
<td>3C</td>
<td>2C</td>
<td>1C</td>
<td>3N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1N</td>
<td>2N</td>
<td>3N</td>
<td>4N</td>
<td>2N</td>
<td>2U</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>DAY 60</th>
<th>DAY 50</th>
<th>DAY 40</th>
<th>DAY 30</th>
<th>DAY 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAT</td>
<td>5U</td>
<td>2C</td>
<td>2N</td>
<td>1N</td>
<td>5U</td>
</tr>
<tr>
<td></td>
<td>1N</td>
<td>3N</td>
<td>4U</td>
<td>5U</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 5. ULCERS INITIALLY 1 mm. IN DIAMETER

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>DAY 20</th>
<th>DAY 18</th>
<th>DAY 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAT</td>
<td>5 C</td>
<td>3 C</td>
<td>5 N</td>
</tr>
</tbody>
</table>

In summary, these experiments have shown that in guinea-pigs and rabbits 4 mm. ulcers in the body of the stomach, midway between the curvatures, healed completely in 13 - 17 days; ulcers 2.5 mm. in diameter healed in the same time as the 4 mm. lesions, while ulcers 12 mm. and 18 mm. in diameter healed completely in 15 - 30 and 25 - 40 days respectively. In rats, 4 mm. ulcers in the stomach required 40 - 60 days for complete healing, though 1 mm. ulcers healed in 18 - 20 days; the prolonged healing time for the larger ulcer is possibly related to the proximity of the 4 mm. burn to the main arterial supply of the glandular stomach in this animal (Berg, 1949).

The results of these experiments support the contention that the rate of closure of wounds is proportional to the area and they also agree with Arey's recognition of the essential similarity between internal and external wounds. Unfortunately, the size of the animal used precluded an attempt to confirm his interesting observation of the importance of wound size in limiting healing. It might be noted, however, that although it is possible that some/
some instance of gastric ulcer in humans fail to heal because of the large size of the lesions, the majority of chronic gastric ulcers have a diameter of 1.5 cm. or less and yet remain unhealed. In man, it appears that acute peptic ulcers 1.0 - 1.5 cm. in diameter usually heal in 3 - 4 weeks and the best available evidence indicates that chronic gastric or duodenal ulcers heal in 14 - 100 days (average 40 days) under strict medical management (Ivy, Grossman and Bachrach, 1951).
REFERENCES


NEILSON/


SYSTEMIC DISORDERS AND LOCAL HEALING

It is believed that disorders which influence the body generally, such as sepsis, nutritional disturbances and anaemia, may have an important influence on the local healing of wounds. Carrell (1924) and Kiaer (1927-3) stressed the importance of sepsis in any part of the body as a retarding factor in the healing of wounds and there are many other reports suggesting that wound healing is adversely influenced by general factors; unfortunately, many of these reports are not supported by a sufficient number of controlled experiments. As for chronic peptic ulcers, no single systemic disturbance has ever been incriminated as of paramount importance in the pathogenesis, nevertheless, the possibility remains that some such disturbance exists, though so far undiscovered. The subject is of considerable biological interest and offers a wide range of experimental approaches. Here, only 2 experiments are described and these are concerned with the possible retarding influence of a second surgical operation on the healing of a gastric ulcer.

EXPERIMENT 1. A medium-sized ulcer (4 mm. diameter) was cauterized in the middle of the posterior wall of the body portion of stomach in 12 guinea-pigs which had undergone laparotomy. Six days later, the animals were re-anaesthetized with ether and a long, deep incision made into the skin and muscle of the anterior abdominal wall and lower limb on the right side, extending from the costal margin/
margin to the knee. This incision was afterwards closed with interrupted linen sutures and the animals were killed 17 days later, viz. healing of a 4 mm. ulcer is complete in normal animals.

Result: No retardation of healing in any animal.

**FIG. 45.**

**EXPERIMENT 2.** This was the same as that described in Experiment 1 except that the second operation was that of a right nephrectomy, performed on the 3rd day following the original laparotomy.

Result: No retardation of healing in any animals.
Comment: Cuthbertson (1932) described the brisk catabolic phase following operation which, after a few days, changes rather abruptly to a less intense but longer period of anabolism. It is at this stage, too, that wound healing begins in earnest. Moore (1953) believes that the early catabolism is due to hormones and points out that its cessation is marked by features - diuresis and a transient eosinophilia - that are observed on withdrawal of cortisone administration. It seemed possible, therefore, that a second operation might retard the healing of a primary wound, i.e. a gastric ulcer, but the results of the experiments described show that healing of the gastric ulcers occurred/
occurred normally despite the severity of the second surgical operation. Theoretically, however, it is still possible that local healing can be retarded if the organism is subjected to secondary stress of sufficient intensity and duration as has been suggested by the experimental observations of Selye (1951).

HEALING OF "SECONDARY" GASTRIC ULCERS

Lorin-Epstein (1927) observed that repeated simple fractures of bone heal better than primary wounds. Secondary skin wounds are also stated to heal more rapidly than do primary ones. Young, Fisher and Young (1941), in a careful study of healing "under a scab" in rabbits found that secondary skin wounds heal more rapidly than do primary wounds and they deduced from these results that some accessory accelerating factor must operate in the closure of secondary wounds, which is lacking in the primary ones. They concluded that the healing of a wound is not exclusively a local phenomenon but depends to some extent on general or constitutional factors. The healing of "secondary" gastric ulcers was investigated in the following experiment:--

EXPERIMENT (See fig. 47) In 24 guinea-pigs, a large ulcer (12 mm. diameter) was cauterized on the posterior wall of the body of stomach, midway between the curvatures. The site was marked by 4 symmetrical India ink tattoo marks/
marks made on the perimeter. Six weeks later, a "secondary" medium-sized (4 mm. diameter) ulcer was cauterized on the scarred site of the healed primary ulcer and the animals were killed after 17 days.

Result. (See fig. 47) In the 16 survivors, there was a marked retardation of healing in 6 animals, slight retardation of healing in a further 6 animals and complete healing in 4 animals. Fig. 48 illustrates some of the microscopic features seen in the unhealed secondary ulcers.

Comment: The results differ from those concerning secondary wounds reported in other parts of the body, especially in the skin and may have special significance in relation to the chronicity of human gastric ulcers. The floor of these secondary experimental ulcers closely resembles the floor of chronic gastric ulcers in humans in consisting of thick fibrous tissue and it is possible that this dense and relatively/
relatively avascular tissue may be the major cause of the unhealed character of the lesions. It is possible that regenerated epithelium cannot grow normally over such scar tissue and fails to adhere to it. An alternative explanation of the failure to heal may lie in the character of the mucosa immediately around the "secondary" ulcer; this mucosa is part of the healed primary ulcer and is, therefore, not the mucosa normally found in this part of the stomach; in other words, instead of the normal body mucosa, there is a thin mucosa of pyloric type, which might not regenerate so readily as the normal mucosa and might be more susceptible to injury. This latter hypothesis seems an inadequate explanation, however, and the failure to heal is probably closely related to the dense fibrous floor, which is such a striking feature.
Fig. 48. Unhealed "secondary" ulcers on 17th day. In (c) bone-formation is seen around a cystic gland in the floor. H. and E. x 60.
REFERENCE


In skin wounds, mild mechanical irritation facilitates healing, apparently by increasing the rate of formation of connective tissue. Irritation just short of destruction is alleged to produce exuberant granulation tissue or "proud flesh", while excessive irritation or infection delays healing, apparently because fibroblasts are destroyed.

The effect of mechanical trauma on healing was studied by Ivy (1933) on gastric ulcers 1.0 to 1.3 cm. in diameter produced by the intragastric injection of silver nitrate in a pylorostomy pouch in dogs. The ulcer was manipulated three daily/
LOCAL IRRITANTS AND THE STOMACH

PHYSICAL IRRITANTS

That mechanical pressure, e.g. rubbing, can produce erosions of the gastric mucosa, particularly if the latter is hyperaemic, is a well-attested fact. The association has been described vividly by Wolf and Wolff (1943) in their human experimental subject "Tom" who had a gastric fistula. The widespread prescription of "bland" diets for patients with chronic peptic ulcer is the consequence of the popular, traditional view that the chronicity of peptic ulcers depends to some extent on mechanical irritation. Many clinical impressions support this theory and there are some experimental results in its favour but there is also clinical and radiological evidence to the contrary, e.g. Doll and Pygott (1952) produced reliable evidence to indicate that the form of diet makes no difference to the healing rate of human chronic peptic ulcers.

In skin wounds, mild mechanical irritation facilitates healing, apparently by increasing the rate of formation of connective tissue. Irritation just short of destruction is alleged to produce exuberant granulation tissue or "proud flesh", while excessive irritation or infection delays healing, apparently because fibroblasts are destroyed.

The effect of mechanical trauma on healing was studied by Ivy (1920) on gastric ulcers 1.0 to 1.5 cm. in diameter produced by the submucosal injection of silver nitrate in a pyloric pouch in dogs. The ulcer was manipulated twice daily/
daily with bread crumbs, dry cotton or the fingers for 10 to 15 minutes until marked congestion or some bleeding occurred. The healing time was increased from 15 - 20 days (10 control ulcers) to 30 - 52 days (11 test ulcers).

Ferguson (1928; 1929-30) reported the production of chronicity in excision ulcers in the gastric mucosa of rabbits by a technique which left silk sutures in the base of the lesion. A similar result was reported by Fanley and Ivy (1930), who assumed that the proliferation of connective tissue in response to a suture (foreign body) is the chief factor in predisposing to retarded healing of a gastric ulcer in the rabbit; they also concluded from their experiments that healing occurred more rapidly on a "soft diet" of bread, milk and cooked pureed carrots than on the usual "rough diet". These experiments, together with the knowledge that some instances of "anastomotic" ulcers in humans are regarded as partly caused by the presence of suture material, prompted the following experiment in guinea-pigs:

**EXPERIMENTS WITH SUTURE MATERIAL**

Silk suture material was placed in the stomach wall of 12 guinea-pigs, about the middle of the posterior wall of the body, then a 4 mm. diameter ulcer was cauterized in the mucosa at this site. The animals were killed 17 days later.

Result: (See figs. 49 and 50) An inflammatory and granulomatous reaction was present around the suture material and there/
FIG. 49. "SUTURE ULCERS" ON 17th DAY. NAT. SIZE.

FIG. 50. SECTION OF ONE OF THE ULCERS IN FIG. 49. H. and E. x 45.
there was a slight to moderate excess of fibrous tissue in
the wound. The surface, however, was completely covered
by regenerated mucosa except where suture material protruded
from the surface.

It was concluded that no notable interference with
wound healing in the guinea-pig stomach was produced by
the presence of silk suture material and a similar experi-
ment, in which linen sutures were used, gave a similar re-
sult.

EXPERIMENTS WITH SAND, TALC AND GRAPHITE

In one series of experiments with 12 guinea-pigs, in
which the healing of a 4 mm. cautery burn was studied,
sand, talc and graphite, or mixtures thereof, were rubbed
into the floor of the ulcer immediately after its produc-
tion but it was found that no notable interference with
healing was apparent 17 days later. In another series of
6 guinea-pigs, where a suspension of talc and graphite in
normal saline was injected into the stomach wall prior to
the production of a 4 mm. cautery ulcer, the result at the
end of 17 days was similar.

CHEMICAL IRRITANTS

Many chemical substances are known to be capable of
injuring the stomach when brought into direct contact with
the gastric mucosa. Alcohol and hydrochloric acid will be
mentioned later in separate sections because of their special
importance. Despite the widespread nature of the belief
that/
that dietary ingredients commonly cause acute erosions and even ulcers of the stomach, the true incidence and importance of the relationship is not known, e.g. although red pepper in the diet is said to account for the frequent occurrence of gastric ulcer in Abyssinia (Bergsma, 1931) and parts of India (McCarrison, 1931), there is, strictly, no proof that this association is a true one; vitamin and protein deficiencies in the diet could equally be causative factors and it is of interest that although native diets are eaten from early childhood onwards, ulcers apparently do not develop until adolescence at the earliest.

Various therapeutic drugs are also alleged to be capable of producing gastric erosions and ulcers when swallowed. Drugs such as cinchophen can certainly produce such lesions, though the mechanism may be an indirect one. In the case of other therapeutic substances, such as acetyl-salicylic acid and iron haematinics, opinion is divided regarding their possible damaging effect on the stomach.

Oral ferrous sulphate is very widely used therapeutically and although it may cause nausea, colicky pain and diarrhoea in some patients, it is generally regarded as innocuous and intolerance to iron preparations, in the usual therapeutic dosages, is regarded mainly as psychological in origin (Kerr and Davidson, 1958). During an investigation of a small series of anaemic patients by gastric biopsy, small deposits were found in 2 females who had been treated orally with ferrous sulphate. The histological findings in both patients were similar and a brief description of one of/
of the cases is given below:

CASE-REPORT

A female patient, aged 42, with marked iron deficiency anaemia, was given 2 tablets of a well-known haematinic (each tablet containing ferrous sulphate, gr. 3) 3 times daily by mouth. One week after she had commenced treatment, gastric biopsy was performed using a modified Australian instrument. In the biopsy material, one minute area of healed superficial erosion was seen, associated with small amorphous deposits of iron material and a slight inflammatory reaction, mainly histiocytic, in the uppermost part of the mucosa.

There is no doubt that a sufficient dosage of iron salts can severely damage the mucosa. (Quincke 1875, 1882) injected ferric chloride solutions into the gastric submucosa of animals, thereby producing sloughing and ulcers and several authors, e.g. Forbes (1947), have described marked haemorrhage and areas of necrosis in the human stomach following the accidental swallowing of ferrous sulphate tablets. I have personally examined the stomach of a female infant of 16 months who died from ferrous sulphate poisoning. She was found by her mother to be "playing with some green tablets" (these were tablets of ferrous sulphate prescribed by the doctor for the mother). She took a fit and later vomited blood and collapsed. Death occurred after 3 hours and at post-mortem, most of the interior of the stomach was ulcerated and haemorrhagic.

Forbes/
Forbes (1947) described gastric haemorrhages, erosions and ulcers in the stomachs of guinea-pigs and cats given oral ferrous sulphate and I made a similar investigation in guinea-pigs:

**EXPERIMENT**

A crushed tablet of ferrous sulphate (gr. 3) was administered orally to each of 3 large adult guinea-pigs which were on a normal diet. When the animals were killed 36 hours later, several small areas of haemorrhage and haemorrhagic erosion were seen in the gastric mucosa. Microscopically (figs. 51 and 52), the affected portion of tissue presented signs of largely healed, superficial and haemorrhagic erosion, associated with the deposition and inclusion of small deposits of ferrous and ferric iron salts.

In another experiment in guinea-pigs, the possible local influence of ferrous sulphate on the healing of a gastric ulcer was investigated:

**EXPERIMENT**

In 10 adult guinea-pigs laparotomy was performed and the anterior wall of the stomach opened. Then 0.2 ml. of 1% aqueous ferrous sulphate solution was injected into the stomach wall, at a site on the middle of the body. Immediately afterwards, a medium-sized (4 mm. diameter) cautery ulcer was produced at the same site. The animals were killed 17 days later.

**Result:** In 4 guinea-pigs, healing of the gastric ulcer was/
FIG. 51. SUPERFICIAL EROSION IN GUINEA-PIG STOMACH FOLLOWING THE INGESTION OF FERROUS SULPHATE. H. and E. x 40.

FIG. 52. DETAIL OF FIG. 51 TO SHOW THE EROSION, IRON DEPOSITS AND GLANDULAR DEGENERATION x 95.
FIG. 53. UNHEALED "FERROUS SULPHATE" ULCERS. DAY 17 x 6.5.
The presence of indigestible material such as silk or linen sutures, or even, talc or charcoal, in the floor of gastric ulcers does not impair the healing process.
was incomplete (fig. 53) and microscopically (fig. 54) the fibrous floor of the ulcer was seen to contain numerous siderocytes and was covered by a thin layer of granulation tissue and purulent exudate which protruded slightly on the surface. In the other animals, healing was complete and only a few siderocytes were present in the fibrous part of the healed lesion.

CONCLUSIONS

1. The presence of unabsorbable material such as silk or linen sutures, or sand, talc or charcoal, in the floor of gastric ulcers does not impede the healing time in guinea-pigs.

2. The oral administration of ferrous sulphate in humans or guinea-pigs may produce mucosal injury in the stomach.
REFERENCES


"RING" BURNS AND THE HEALING OF GASTRIC ULCERS

In 2 series of original experiments in guinea-pigs an attempt was made to delay the healing of gastric ulcers by producing a circular burn in the stomach wall around an ulcer and a few millimetres from it. The experiments were as follows:-

**EXPERIMENT 1.**

**RING BURN AROUND MEDIUM-SIZED ULCER POSTERIOR WALL OF STOMACH**

Fig. 55. Ring burn around medium-sized ulcer on posterior wall of stomach.

In 8 guinea-pigs, a medium-sized (4 mm. diameter) ulcer was cauterized on the posterior wall of the body of the stomach and, immediately afterwards a circular burn (12 mm. diameter and 2 mm. in breadth) was cauterized by means of a brass cylinder, around the ulcerated area. The animals were/
were killed 17 days later.
Result: The ulcers were completely healed in all the animals.

EXPERIMENT 2.

This was the same as Experiment 1 except that the circular burn was produced on the outer surface of the stomach.
Result: In all 8 animals there was a lack of healing in the ulcers; this was marked in 5 animals, while in the other 3 it was moderately retarded. Unhealed ulcers are illustrated in fig. 56. Microscopically, (fig. 57) the ulcer floor was densely fibrous and there was an obvious lack of an epithelial covering.

Interpretation of Experimental Results

The interference with healing which occurred with external ring burns and the absence of retardation with internal ring burns suggest that the former is related to the vascular – presumably the blood-supply of the stomach. As the large blood vessels are mostly in the external part of the stomach wall – the arteries entering and the veins leaving from the subserosa – it is reasonable to assume that external circular burns retard the healing of an ulcer within their perimeter by virtually cutting off the major blood-supply, whereas with internal circular burns the blood-supply to the contained ulcer is sufficient to permit normal healing.

Comments on the Vascular Factor in Gastric Ulceration

Ivy/
FIG. 56. (A & B). UNHEALED ULCERS AFTER "OUTSIDE" BURN. DAY 17. x 6.

FIG. 57. SECTION OF THE ULCER IN FIG. 56 (B). H. and E. x 45.
Ivy, Grossman and Bachrach (1951) have reviewed the factors known to produce acute peptic erosions and ulcers and they have also discussed the factors which may retard healing and produce chronicity in peptic ulcers. Although the literature abounds with contradictory evidence concerning the importance of the blood-supply of the stomach in relation to peptic ulceration, there seems no reasonable doubt that it plays an important part in the initiation of acute erosions and ulcers and it might even be correct to state that it plays an essential role. These authors state that the best way to account for the circumscribed nature of the acute lesions caused by acid or any other ulcerogenic agent is by assuming a local disturbance of the blood-supply and in doing so echo an opinion expressed by Virchow as long ago as 1853 that a local vascular disturbance is responsible for a locus minoris resistentiae. Such a local disturbance of the blood-supply may follow very many different causes such as local physical or chemical trauma, infections, nervous disorders, shock or the administration of drugs such as histamine, pilocarpine, caffeine or adrenaline. Penner and Bernheim (1939) from a study of human autopsy material, were convinced that certain peculiar gastro-intestinal ulcerations in shocked subjects resulted from vasomotor changes and they injected adrenaline intraperitoneally in dogs, cats, guinea-pigs and rabbits and produced gastro-intestinal lesions, ranging from petechiae to large ulcers. There was prolonged vasoconstriction which led to tissue necrosis. Microscopically,
Microscopically, changes in the rabbit and guinea-pig first appeared in the submucosa (as commonly happens in man) but in the mucosa of cats and dogs. Recently, the author examined the body of a 17-year-old male student who developed acute appendicitis, with rupture and peritonitis. Laparotomy and appendicectomy were performed but the patient remained very ill, with considerable shock, despite noradrenaline infusion, and died 7 days later. At autopsy, there were most extensive necrotic and ulcerative lesions in the oesophagus, stomach and jejunum. The lesions resembled those described in "necrotizing enteritis", which has frequently been reported during the last few years, where an infective aetiology has been suspected but rarely satisfactory proven (see Koch, 1948 and Rudolph and Sage, 1948). Although in these cases, the lesions are so widespread, they have a special interest and importance and would appear to arise from a disturbed blood-supply. The ischaemic lesions are essentially like those seen in ordinary acute peptic ulcers and erosions and suggest that the latter may also have a vascular origin.

The nature of the base of an ulcer is usually regarded as a major limiting factor in delaying healing, since epithelial cells will only grow over healthy granulation tissue and will not cover avascular, dense fibrous connective tissue (Ivy, Grossman and Bachrach, 1951). It is clear that the vascular channels in healing tissue bring an abundant supply of oxygen and nutriments to support the large number of metabolically active and dividing cells that/
that are present in it. A decreased blood-supply to the base of a calloused ulcer could account for the slow healing of gastric ulcers. Unfortunately, most of the reported experimental attempts to study the effect of blood-supply on the healing of an acute gastric ulcer have given negative results, e.g. when the blood vessels along the lesser curvature are ligated there is no delay in healing of an acute gastric ulcer, but these attempts have had no regard for the normal rich anastomotic blood-supply of the stomach. The external ring burns that have been described resulted in delayed healing of an ulcer apparently because there was an effective interference with the blood-supply to the ulcer base.
REFERENCES


(Loeb, 1897; Raviv, 1899), the epithelial cells manifesting an inherent tendency to cover surfaces and migrating or sliding from all sides across the defect. It is believed that chemical agents are concerned in the stimulus to epithelial growth but little is known about it. Wigglesworth (1897), from experiments on insect epidermis, suggested that migration is due to an activating substance liberated by wounding and he assumed that such a substance was thermolabile since, as stated, no epithelial migration occurs after heat injury. This last statement certainly is not true of the animal experiments described here.

There are, indeed, many unsolved problems in wound healing. One puzzling feature is the co-ordinated connection of growth in epithelium and connective tissue in the last stages of wound healing. The causes of the adherence of the overlaying epithelium to the underlying granulation tissue is also unknown. Until the epithelium becomes firmly adherent to the wound edge, it is easily detached, and various factors, both within the tissue that epithelium calls to cover to other forms upon the floor and the floor in its usual place, appear to influence this process (as in the "callus" process).
FURTHER ATTEMPTS TO DELAY HEALING IN GASTRIC ULCERS

There are 2 essential components in the healing of ulcers: (a) epithelial regeneration and (b) the formation of granulation tissue. Epithelial regeneration is perhaps the most active in the body and gastric epithelium regenerates at the rate of approximately 2 mm. a week (Cameron, 1952). This regeneration commences within one hour (Loeb, 1897; Ranvier, 1898), the epithelial cells manifesting an inherent tendency to cover surfaces and migrating or sliding from all sides across the defect. It is believed that chemical agents are concerned in the stimulus to epithelial growth but little is known about it. Wigglesworth (1937), from experiments on insect epidermis, suggested that migration is due to an activating substance liberated by wounding and he assumed that such a substance was thermolabile since, he stated, no epithelial migration occurs after heat wounds; this last statement certainly is not true of the mammalian experiments described here.

There are, indeed, many unsolved problems in wound healing. One puzzling feature is the co-ordinated cessation of growth in epithelium and connective tissue in the last stages of wound healing. The cause of the adherence of the outgrowing epithelium to the underlying granulation tissue is also unknown. Until the epithelium becomes firmly adherent to the substrate, it is easily detached. Examination of ulcers in humans suggests that epithelium fails to cover an ulcer floor when the floor is composed of dense, avascular fibrous tissue (as in the "callous" ulcer/
ulcer) or when the floor is covered by loose purulent or necrotic material. There have, however, been few or no animal experiments to confirm these impressions.

The cause of the production of granulation tissue in wounds is also largely speculative (Cameron, 1952). Altered metabolism, especially oxygen lack, has been suggested as a prime factor and released products of cell destruction are believed to be essential. Such growth-promoting substances were described by Marchand (1901) and were later referred to as "wound hormones" (Haberlandt, 1921) or "trephones" (Carrel, 1924). Embryonic tissue contains such substances and serum possesses a growth-inhibiting substance which increases with age.

In the experiments now to be described, attempts were made to alter the normal healing process in the floor of an acute gastric ulcer and particular attention was paid to the interrelation of the epithelium and subepithelial layers. These investigations fall into 2 groups:

1. The **local** injection of oily and colloidal materials, also of tubercle bacilli, into the ulcer floor.

2. The **parenteral** injection of trypan blue and hormones.

---

**HEALING AFTER LOCAL INJECTIONS**

In the course of a separate experimental investigation into immunity reactions in the stomach, Freund's adjuvant was injected into the stomach wall. This mixture, which acts/
acts in an unexplained way, as an enhancer of antibody-production (Freund, 1947), has 3 components: a light mineral oil ("Bayol F"), an absorption base derived from lanolin ("Falba") and dried, killed mycobacterium tuberculosis. The addition of the latter greatly increases the adjuvant effect, apparently by the participation of a lipopolysaccharide contained in the bacillus. The adjuvant is composed of a homogenized mixture of:

2 parts Bayol F, containing 1 mg/ml. dried, killed mycobacterium tuberculosis, and 1 part Falba.

The nature and intensity of the inflammatory reaction that was produced were so striking that it occurred to me that the adjuvant might be usefully employed in studies on the healing of acute gastric ulcers. It was used for this purpose and the results were of such interest that the studies were extended to include the effects of individual components of the adjuvant as well as other agents.

**EXPERIMENT 1. EFFECT OF MINERAL OIL ALONE**

In 12 guinea-pigs, laparotomy and gastrostomy were performed, then 0.5 ml. of the light paraffin oil "Bayol F" was injected into the stomach wall from the mucosal aspect, using a tuberculin syringe and a fine needle. Immediately afterwards, 1 large (12 mm. diameter) cautery ulcer was produced over the site of injection and the ulcer site marked with 4 small India ink "tattoo" marks. The stomach and abdominal wounds were then sutured and the animals were killed/
killed 30 days later.

**Result:** Of the 9 surviving animals, complete healing was present in 7. Microscopically, (fig. 58) the scar was a thin one. The regenerated mucosa was well-formed and rested on a substrate composed of a small amount of fibrous connective tissue which contained some prominent oil spaces; the latter were associated with a mild histiocytic reaction. In the remaining 2 animals, healing of the ulcer was complete except for a minute central area where there was some dense fibrous tissue, accompanied by a foreign body reaction and an absence of epithelial covering.

**EXPERIMENT 2. EFFECT OF A MIXTURE OF MINERAL OIL AND EMULSIFYING AGENT**

This experiment was the same as Experiment 1 except that 0.5 ml. of a mixture of 2 parts of light mineral oil ("Bayol F") and 1 part of emulsifying agent ("Falba") was used instead of the mineral oil alone.

**Result:** In the 7 animals which survived the duration of the experiment and which were killed on the 30th day, there was complete healing of the large gastric ulcer. The histological appearances (fig. 59) resembled those seen after the injection of mineral oil alone, but the histiocytic reaction and the degree of fibrosis were slightly greater.

**EXPERIMENT 3. EFFECT OF A MIXTURE OF MINERAL OIL, EMULSIFYING AGENT AND KILLED TUBERCLE BACILLI (FREUND'S ADJUVANT)**

This experiment resembled the 2 experiments just described except/
FIG. 58. HEALED LARGE ULCER IN WHICH BAYOL F HAD BEEN INJECTED. H. and E. x 45.

FIG. 59. HEALED ULCER IN WHICH BAYOL–FALBA HAD BEEN INJECTED. H. and E. x 45.
except that the injected material was the complete mixture
constituting Freund's adjuvant, viz. a mixture of mineral
oil, emulsifying agent and tubercle bacilli.

Result: All the ulcers were unhealed in the 8 surviving
guinea-pigs killed on the 30th day of the experiment
(fig. 60). The ulcer base (fig. 61) was composed of
loose granulation tissue containing numerous vacuolated
and granular histiocytes, lesser numbers of polymorpho-
nuclear leucocytes and some oil spaces. Acid-fast bacilli
were also present, both extracellularly and also within
some histiocytes. Only a few large, multinucleate histio-
cytes were seen and most of these were around food parti-
cles. The ulcer floor was thick, in contrast to the floor
of the ulcer floor in the previous 2 experiments, but the
amount of fibrous tissue was relatively slight. In all
the ulcers there was some epithelial covering but in only
2 of them was it nearly complete. In all the ulcers, the
new epithelium, which was cubical or columnar and degenerate-
looking, was very loosely attached to the underlying in-
flammatory tissue and was easily swept away.

It is well-known that the injection of turpentine
into tissues leads to an acute inflammatory reaction, with
a brisk polymorphonuclear leucocytosis and, often, abscess-
formation. The following experiment was therefore, under-
taken to see whether this substance could also hinder the
healing/
FIG. 60 (A, B & C). UNHEALED GASTRIC ULCERS AFTER INJECTION OF FREUND'S ADJUVANT. DAY 30. X 8.
EXPERIMENT 4, EFFECT OF TURPENTINE ON HEALING

The form of experiment was identical with that of the preceding experiments but the material injected consisted of 0.5 ml. of the following mixture:

Light Paraffin Oil ("Oval F") . . 3 parts.
Salicylic Acid Agent ("Salbe"), . . 1 part.
Turpentine Oil . . . . . . . . . . . . 4 parts.

The injected material thus resembled Freund's adjuvant.

FIG. 61. PART OF AN UNHEALED 12 mm. GASTRIC ULCER INJECTED WITH FREUND'S ADJUVANT. H. and E. x 45
healing reaction of an acute gastric ulcer.

**EXPERIMENT 4. EFFECT OF TURPENTINE ON HEALING**

The form of experiment was identical with that of the 3 preceding experiments but the material injected consisted of 0.5 ml. of the following mixture:

- Light Paraffin Oil ("Bayol F") . 2 parts.
- Emulsifying Agent ("Falba") . . . 1 part.
- Turpentine Oil . . . . . . . . . 4 parts.

The injected material thus resembled Freund's adjuvant but included turpentine oil instead of dried, killed tubercle bacilli.

**Result:** There were 6 animals which survived the 30 days of the experiment. In all of these, the ulcers were unhealed. Microscopically (fig. 62-64), the appearances were very similar to those in Experiment 3, where Freund's adjuvant was injected; they differed in 2 respects: (1) in the absence of any dead tubercle bacilli, and (2) in the production of rather more fibrous tissue, especially in the deeper part of the ulcer floor. In 4 of the 6 animals, epithelial covering of the ulcer floor was far advanced in area but the attachment was loose and insecure.

In another group of experiments, the possible influence of live bacillus Calmette-Guerin (B.C.G.) and of Tuberculin on the healing of acute gastric ulcers in guinea-pigs/
FIG. 62. UNHEALED 12 mm. GASTRIC ULCER 30 DAYS AFTER THE INJECTION OF FREUND'S ADJUVANT + TURPENTINE. H. and E. 45.
FIG. 63. DETAIL OF PART OF FIG. 62 SHOWING THE NATURE OF THE ULCER FLOOR. H. and E. x 135.
FIG. 64. ALMOST HEALED 12 mm. GASTRIC ULCER 30 DAYS AFTER THE INJECTION OF FRIED'S ADJUVANT + TURPENTINE.
guinea-pigs was studied:

**EXPERIMENT 5. EFFECT OF B.C.G. ALONE**

Following laparotomy and gastrostomy, 0.2 ml. of B.C.G. vaccine was injected into the stomach wall of 12 guinea-pigs, about the middle of the posterior wall, the site being marked with India ink. Six weeks later, the stomach was re-opened through an incision in the anterior wall and a medium-sized (4 mm. diameter) cauterized ulcer produced. The stomach and abdominal incisions were then sutured and the animals were killed 17 days later.

**Result:** There were 8 survivors. In all the animals, the injected site in the stomach presented a granulomatous reaction, with numerous large mononuclear cells and smaller numbers of polymorphonuclear leucocytes, many acid-fast bacilli and a variable, but generally slight, amount of fibrosis. Necrosis was not a feature and the very few multinucleate giant cells that were present were usually associated with food particles included in the tissue. In 2 animals, a defect remained on the mucosal site, uncovered by epithelium (figs. 65 and 66) but in the other 6 animals there was complete covering by epithelium (fig. 67); moreover, in these 6 animals, the epithelial covering appeared to be firmly adherent to the underlying granulation tissue, which was, however, less in amount than in the 2 uncovered ulcers.

**EXPERIMENT 6. EFFECT OF TUBERCULIN ON HEALING**
FIG. 65. UNHEALED GASTRIC ULCER 17 DAYS AFTER THE LOCAL INJECTION OF B.C.G. IN A SENSITIZED GUINEA-PIG. H. and E. x 45.
FIG. 66. DETAIL OF PART OF FIG. 65 TO SHOW THE NATURE OF THE ULCER FLOOR. H. and E. x 135.
Normal healing occurred in sensitized (2 sensitizations for:
acute gastric ulcers in 2 groups of 6 guinea-pigs each
0.5 ml. 1:100 or undiluted Old Tuberculin (Kemps
Vaccines & Co.) respectively having been injected into the
stomach wall immediately prior to the production of the
ulcer.

EXPERIMENT 2. EFFECT OF LOCAL INJECTION OF B. C. G.
or 0.2 ml. 1:1000 Old Tuberculin was injected into the
hind limb of 6 guinea-pigs.

FIG. 67. HEALED GASTRIC ULCER 17 DAYS AFTER THE LOCAL
INJECTION OF B.C.G. IN A SENSITIZED GUINEA-PIG.
H. and E. x 135.
Normal healing occurred in medium-sized (4 mm. diameter) acute gastric ulcers in 2 groups of 8 guinea-pigs in which 0.5 ml. 1:100 or undiluted Old Tuberculin (Burroughs Wellcome & Co.) respectively had been injected into the stomach wall immediately prior to the production of the ulcer.

**EXPERIMENT 7. EFFECT OF B.C.G. AND TUBERCULIN**

0.2 ml. B.C.G. vaccine was injected intramuscularly into the hind limb of 6 guinea-pigs. Six weeks later, 0.2 ml. 1:1000 Old Tuberculin was injected intradermally. A positive sensitivity reaction was obtained. Laparotomy and gastrostomy were then performed and 0.4 ml. 1:1000 Old Tuberculin injected into the stomach wall in the middle of the posterior wall, then a 4 mm. cautery ulcer was made at the site of injection. The animals were killed 17 days later.

**Result:** In all the animals, the gastric ulcers showed complete healing, with no abnormal features.

Tuberculous or sarcoid involvement of the human stomach is very rare. A case of the latter was, however, recently encountered and brief mention will be made of it because of its relation to the healing processes just considered:

**CASE REPORT - SARCOID LESIONS IN THE STOMACH**

In August 1956, a female aged 36 was admitted to hospital with/
with haematemesis and melaena. Previous similar episodes had occurred in 1954 and 1952, while in 1955 a perforated gastric ulcer was performed. Radiological examination gave an indefinite suggestion of a gastric ulcer on the lesser curve. Partial gastrectomy was performed. No ulcer was seen in the resected specimen but in several random sections from the stomach many sarcoid lesions were irregularly scattered in the mucosa and submucosa (fig. 68).

In addition, many areas of mucosa presented features suggestive of healed erosion. It is interesting to note that erosions are capable of healing over such 'granulomatous' lesions. (c.f. Experiment 5, where healing occurred over B.C.G. lesions in the guinea-pig stomach).

The relationship of the original gastric ulcer to the sarcoidosis is conjectural but may be merely coincidental.

Subsequent biopsy in this patient revealed sarcoid lesions in the liver.

---

CARRAGEENIN AND GASTRIC HEALING

Carrageenin is a sulphated polygalactose derived from Irish moss, which, injected subcutaneously into guinea-pigs, produces a granuloma rich in collagen. Williams (1957) has described the histological sequence of events in experimental lesions. He found that when carrageenin is injected subcutaneously, it soon becomes invaded by polymorphs and mononuclear cells which ingest the polysaccharide. By the 5th day/
SARCOID LESIONS IN MUCOSA AND SUBMUCOSA OF STOMACH. PARTIAL GASTRECTOMY SPECIMEN. H. and E. x 40.
day, granulation tissue, with active fibroblasts and histiocytes, begins to invade the carrageenin mass. By the 10th day, most of the carrageenin has been ingested, leaving a highly cellular tissue interlaced with reticulin fibres which rapidly mature to collagen. But, as fibrosis over-takes the centre of the original carrageenin deposit, the recently formed peripheral collagen simultaneously disappears and, within 6 weeks of the onset, the whole injection site consists largely of adipose tissue. This speeding-up process of collagen-formation, and its subsequent loss, was not found when other macromolecular substances such as methylcellulose and dextran were used instead and Williams suggested that the high degree of sulphation of carrageenin (about 30%) may account for its specific biological effect. This degree of sulphation gives it considerable anticoagulant power, which may account for the complete absence of fibrin or fibrinoid material from the lesions, as judged by conventional histological methods.

I have been able to confirm that Williams’ description of the histological events following the injection of carrageenin subcutaneously applies also to injection of the substance into the stomach wall. Fig. 69 illustrates the histological appearances in the stomach wall of the guinea-pig on the 7th day after the injection of carrageenin. Furthermore, I tested the effect of another mucilage, namely tragacanth, and obtained similar results.

It seemed desirable to investigate the possible influence that/
FIG. 69. REACTION IN STOMACH WALL OF GUINEA-PIG 7 DAYS AFTER THE INJECTION OF 1% CARRAGEENIN. H. and E. x 45.

FIG. 70. PART OF COMPLETELY HEALED 12 mm. ULCER 35 DAYS AFTER THE LOCAL INJECTION OF 1% CARRAGEENIN. H. and E. x 45.
that carrageenin might produce on the healing of an acute
gastric ulcer. Consequently, the following experiment
was performed:

**EXPERIMENT 7. EFFECT OF INJECTION OF CARRAGEENIN**

A large (12 mm. diameter) cautery ulcer was produced
on the posterior wall of the middle of the body of the sto-
mach in 8 guinea-pigs, immediately following the injection
of 0.5 ml. 1% carrageenin (in normal saline) into the sto-
mach wall at the same site. The animals were killed 30
days later.

Result: There was complete healing of the ulcer (fig. 70).
The regenerated mucosa was well-formed and contained glands
of pyloric type; it rested on a base which consisted not of
dense fibrous tissue but of rather finely-textured fibro-
fatty connective tissue.

**HEALING AFTER PARENTERAL INJECTION**

Histological examination of human chronic gastric ul-
cers reveals that in some subjects the ulcers have a very
dense fibrous floor, whereas in other subjects the floor
has a thinner, less fibrous and more delicate structure.
This finding suggests that the degree of fibroplasia may be
related to systemic factors such as hormones. A series of
experiments was, therefore, undertaken to see whether the
fibrous floor of an ulcer could be modified by systemic
agents/
agents and for this purpose groups of female animals were injected parenterally with trypan blue, oestradiol and cortisone respectively.

EFFECT OF TRYPSIN BLUE

Two or three decades ago there was much discussion about "reticulo-endothelial blockade" in immunological circles. By this term was meant a saturation of the reticulo-endothelial system with vital dyes or particulate material with the intention of retarding antibody production. The subject has been well reviewed by Cannon and his colleagues (1929). The results of such blockade have shown no notable effects on the production of immune bodies, although some temporary retarding influence on antibody production is caused and several observers have reported a marked decrease in resistance to infection (Rindani, 1953). The interpretation of blockade experiments is further complicated by the fact that many of the substances employed are toxic and the results obtained may accordingly be of a non-specific origin.

During a preliminary investigation in which trypan blue was injected intraperitoneally into a rabbit in which an acute gastric ulcer had been produced 7 days earlier, the author was so impressed by the striking phagocytosis of the dye in the ulcer floor (figs. 71 and 72) by cells of both histiocyte and fibroblastic type, that it was considered desirable to see whether this substance could retard the healing of experimental gastric ulcers. Consequently, experiments/
FIG. 71. GASTRIC ULCER AT 4 DAYS IN RABBIT INJECTED 7 DAYS PREVIOUSLY WITH TRYPAN BLUE. H. and E. x 80.

FIG. 72. DETAIL OF FIG. 71. SHOWING PHAGOCYTES AND FIBROBLASTS IN THE ULCER FLOOR. H. and E. x 500.
Experiments were undertaken in rabbits (1.5 to 2.0 kg. in weight) and guinea-pigs (average weight 300 g.). Female animals, in groups of 6 - 18, were used. The experiments were as follows:

**EXPERIMENT 1.**

Laparotomy and gastrostomy were performed and a medium-sized (4 mm. diameter) cautery ulcer was produced in the middle of the posterior wall of the stomach. After the stomach and abdominal wall were sutured, trypan blue (0.5 g./kilo) was injected in a 1% solution (in normal saline) intraperitoneally. The animals were killed 17 days later.

**EXPERIMENT 2.**

Resembled Experiment 1 except that a large ulcer (12 mm. diameter) was made and the animals were killed on the 30th day.

**EXPERIMENT 3.**

Resembled Experiment 1 except that the injected dose of trypan blue was 0.25 g./kilo.

**EXPERIMENT 4.**

Resembled Experiment 3 except that the ulcer produced was a large one (12 mm. diameter) and the animals were killed on the 30th day.

Result: The amount of fibrous tissue formed in the ulcer was less/
less than normal but not markedly so. Epithelial regeneration was not altered.

EXPERIMENT 5.

In this experiment daily intraperitoneal injections of 1% trypan blue (0.01 g./kilo) were given for 17 days to rabbits and guinea-pigs. A medium-sized (4 mm. diameter) cautery ulcer was first produced on the posterior wall of the body of the stomach and the first injection of the dye was given immediately after the operation was completed. The animals were killed on the 17th day.

Result: These were not different to those seen in the earlier experiments where only a single dose of the dye was injected. (See fig. 73).

EFFECT OF OESTRADIOL

Oestrogens are alleged to have a general inhibitory effect on the formation of granulation tissue. The following experiments were therefore undertaken to determine whether the administration of oestrogen-administration altered the healing of acute gastric ulcers in experimental animals:

EXPERIMENT 1.

Oestradiol (2.5 mg/kilo) was injected intramuscularly each day into rabbits. Five days after the first injection, a medium-sized (4 mm. diameter) cautery ulcer was produced on/
FIG. 73. HEALED "TRYPAN BLUE" ULCER IN GUINEA-PIG STOMACH. DAY 17. H. and E. x 70.
on the middle of the posterior wall of the stomach. The injections were continued for 17 days after operation, when the animals were killed.

Result: The amount of fibrous tissue in the ulcer floor was less than normal but not markedly so. No other abnormality was seen.

**EXPERIMENT 2.**

An exactly comparable experiment was repeated but on this occasion in guinea-pigs.

Result: These were essentially the same as in the rabbit experiment.

**EFFECT OF CORTISONE**

Howes et al. (1950) observed in man and in laboratory animals that cortisone retarded the formation of granulation tissue but did not stop epithelial proliferation.

Plotz et al. (1950) studied the effect of A.C.T.H. and cortisone on the healing of incised wounds of the skin and stomach of various animal species and reported a delayed formation of connective tissue in all wounds. In 1954, the author wrote a short preliminary report on the effect of cortisone on the healing of experimental gastric ulcer in rabbits, guinea-pigs and rats. An outline of the experimental procedure and the results is given here:-

**EXPERIMENT 1.**

Female/
Female rabbits (1.5 to 2.0 kg.) guinea-pigs (300 - 400 g.) and rats (average weight 200 g.) were used. In each animal laparotomy and gastrostomy were performed and a 4 mm. diameter cautery ulcer produced on the posterior wall of the stomach.

Beginning on the day of operation, test animals were injected daily intramuscularly with cortisone acetate (Merck), while control animals were injected intramuscularly each day with an equal volume of "cortisone vehicle".

Eight rabbits were given daily intramuscular injections of cortisone (1.0 mg/100 g. body weight); 2 were killed on the 10th day and 6 on the 15th day. Eighteen guinea-pigs were injected each day with 5.0 mg. cortisone acetate per 100 g. body weight; 6 were killed on the 10th day, and 12 on the 15th day. Eighteen rats were injected with 1.5 mg. cortisone per 100 g. body weight each day; 6 were killed on the 21st day, 6 on the 31st day, and 6 on the 60th day.

**EXPERIMENT 2.**

The general procedure was the same as in Experiment 1 but higher doses of cortisone were given to 6 rabbits, 6 guinea-pigs and 6 rats in which a gastric ulcer had been produced as described. The daily injections were, however, begun 3 days before operation. The doses of cortisone were 2.0 mg/100 g. body weight in the rabbit, 12.5 mg/100 g. body weight in the guinea-pig, and 3.0 mg/100 g. body weight in the rat. Two animals of each species were killed on the/
the 5th day and 4 on the 10th day after operation.

Result: Macroscopically, there was no difference in the appearance of the stomach lesions in the test and control animals of each species at the same time after operation.

Microscopically, it was observed that formation of granulation tissue and fibrous tissue was imperfect in the cortisone-treated animals. This abnormality was best seen in the rat, less well-seen in the rabbit and least noticeable in the guinea-pig. In the test animals of each species, reticulin and collagen were formed but in subnormal amounts. Fibroblasts, though still fairly plentiful, were less numerous than normal and these cells, and their associated fibrils, tended to be arranged in a less orderly manner than the same elements in the wounds of the control animals.

In the test animals, there was no abnormality of epithelial regeneration. The ulcer bed was covered by epithelium as quickly in the test animals as in the controls, but the fibrous tissue was less well formed.

Higher doses of cortisone showed a greater inhibitory effect on fibroplasia, especially in the rat. In all 3 species, the acute inflammatory response was not suppressed.
SUMMARY AND MAIN CONCLUSIONS

(1) Complete healing of a gastric ulcer depends on the co-ordinated growth of surface epithelium and its connective tissue substrate.

(2) The explanation of such growth, and of associated phenomena such as the adhesion of the epithelium to the substrate, is very incomplete but can be related to both local and general factors.

(3) Where the substrate is composed of abundant, loose inflammatory tissue, such as in seen after the injection of Freund's adjuvant or a similar mixture containing turpentine oil instead of killed tubercle bacilli, the regenerated epithelial layer is very loosely attached and incomplete.

(4) Where the substrate is composed of firmer granulation tissue, epithelial adhesion is possible and is observable even after the local injection of live B.C.G.

(5) The local injection of the mucilage carrageenin does not impede the healing of gastric ulcers.

(6) The parenteral administration of trypan blue, oestradiol or cortisone produces some impediment of fibroplasia in healing gastric ulcers but this is not a gross effect. The way in which this effect is produced is not clear, but presumably the final effect is on the fibroblast. It has been suggested that cortisone reduces the amount and quality of granulation tissue by subduing the initial inflammatory reaction in wounds but there is still uncertainty/
uncertainty about this (Sevitt, 1957); more general factors may be involved, e.g. protein synthesis (Gubner, 1951) and pituitary growth hormone. (Bangham, 1951).
REFERENCES


The excessive consumption of drinks containing ethyl alcohol is generally believed to induce acute or chronic gastritis, the latter often being described as "atrophic"; moreover, many clinicians attribute the dyspeptic manifestations of alcoholism to such inflammation. Theoretically, gastritis is a reasonable expectation and there is reliable evidence that it occurs in alcoholics. However, in a recent personal histological study of gastric mucosa from a series of alcoholics (Wynn Williams, 1956) inflammatory lesions were notably slight or entirely absent, even in some inveterate spirit drinkers. This observation, together with the conflicting observations of opinions concerning the effects of alcoholic excess on the stomach of humans and the paucity of histological data referring to the effects of alcohol on the gastric mucosa, suggested the need for a re-evaluation of current opinion on a subject that is obviously of practical importance.

The published reports of animal experiments concerned with the effects of alcohol on the stomach are relatively few. The impression gained from these is that serious damage to the gastric mucosa is rare or absent but the experimental conditions have been so variable that final deductions cannot be drawn with confidence. Ivy et al. (1950) mention that Quincke (1875) utilised the local application of alcohol to the gastric mucosa as a method of producing acute ulceration in experimental animals.
Grant (1945) also described acute superficial erosion following the application of 50% alcohol to the gastric mucosa of cats; she was impressed by the rapidity of healing which was found to be faster than that observed in the skin. Sternberg (1907, 1908) observed gastric ulcers in guinea-pigs following the introduction of 96% alcohol into the stomach, but Greggio (1916) reported an absence of ulceration in 26 rabbits given various amounts of 16% alcohol or Marsala wine by stomach tube for periods up to 50 days; and Friedenwald (1905) who administered alcohol to 120 rabbits in doses of 5 to 8 ml. for several months to over 4 years found chronic ulcers in only 2 cases and scars of healed ulcers in 4 others. Layne and Carey (1943) gave 75 ml. 20% ethyl alcohol daily by stomach tube to 4 dogs for periods of 336, 394, 799 and 906 days respectively and found no haemorrhages, erosions or ulcerations at autopsy. Finally Ivy et al. (1950) refer to the unpublished work of Wigodsky in their laboratory: he gave 12 dogs cheap bonded whisky for up to one year in amounts which would correspond to a litre daily for a 70 kilo man and found no gastric erosions or ulcers.

A description is given herewith of animal experiments which were undertaken to assess the effects of ethyl alcohol in graded doses and concentrations on the stomachs of fasting and non-fasting guinea-pigs. These have furnished information on a variety of subjects, including the role of alcohol in the production of gastric erosions and ulcers and its influence/
influence on the healing of gastric ulcers. This is followed by a brief account of the histological findings in the gastric mucosa of a series of 25 alcoholic subjects.

EXPERIMENTAL INVESTIGATIONS

Adult guinea-pigs, mostly 300 - 400 g. in weight, were used. A length of polythene tubing, with a bore of 0.86 mm. diameter and a wall 0.57 mm. thick was passed orally into the stomach and alcohol solutions administered with the aid of a 10 or 20 ml. Record syringe. At the completion of an experiment, animals were killed by chloroform anaesthesia. Immediately after death, the abdomen was opened and ligatures placed at the cardia and pylorus; then 20 ml. 10% formol-saline were injected into the stomach cavity. Afterwards, the stomach was removed, immersed in 10% formol-saline for at least 24 hours then opened and the mucosa washed under a gentle stream of water. This technique permitted examination of a well-fixed stomach wall, free of excessive folds. Finally, representative blocks of stomach wall were taken and paraffin sections of these were stained routinely with haematoxylin and eosin, Southgate's mucicarmine, Motteram's trichrome stain for gastric mucosa and Masson's trichrome stain.

CONCENTRATION OF ALCOHOL

The effect of variations in the concentration of alcohol on the gastric mucosa was studied in 6 groups of non-fasting guinea-pigs, each group containing 6 animals. The dose/
dose (5 ml.) was constant but the concentration (volume for volume) increased in arithmetic progression from 10% in the first group to 60% in the last. The animals were killed 24 hours later. No notable changes were seen in the animals given 10%, 20% or 30% alcohol, but those given 40% or more had multiple erosions and ulcers in the stomach and also showed loss of body weight and fatty change in the liver, especially in the periphery of the lobules. The gastric lesions were situated mostly in the upper two-thirds of the stomach; they varied in size from a pin-point to nearly 1 sq. cm. and many of the larger ones appeared to have been formed from the confluence of smaller ones; the majority were irregular in shape but some were oval, round or linear; they were frequently haemorrhagic. These erosions and ulcers were frequently deep and microscopy often revealed almost complete penetration of the stomach wall by large ulcers. In the sections, brisk acute inflammatory signs, including hyperaemia, oedema and polymorphonuclear leucocytosis, were prominent. Similar lesions were observed in 10 guinea-pigs given 5 ml. of reputable brands of undiluted Scotch or Irish Whisky or Gin, the alcohol concentration of which is approximately 40%. Examples of such ulcers are illustrated in figs. 74-77.

VOLUME OF ALCOHOLIC SOLUTIONS

The effect of increasing the volume of the lower concentrations of alcohol was studied in non-fasting animals. Ten/
FIG. 74. ULCERS IN GUINEA-PIG STOMACH 24 HOURS AFTER THE ADMINISTRATION OF 'NEAT' GIN. x 9.
FIG. 75. ULCERS IN STOMACH OF GUINEA-PIG 3 DAYS AFTER THE ADMINISTRATION OF 'NEAT' GIN. x 9.
FIG. 76. ULCERATED PORTION OF STOMACH IN GUINEA-PIG GIVEN 60% ALCOHOL 48 HOURS PREVIOUSLY. H. and E. x 60.

FIG. 77. SEVERE ULCERATION IN GUINEA-PIG STOMACH. THE ANIMAL WAS GIVEN 60% ALCOHOL. H. and E. x 60.
Ten ml. of 10% alcohol was administered to each of 6 guinea-pigs, the same volume of 20% alcohol to a second group of 6 animals and 10 ml. 30% alcohol to a third group of 6 animals. All the animals were killed 24 hours later. A few small erosions and ulcers were observed in the stomachs of animals which had been given 20% alcohol, while more numerous and larger erosions and ulcers were seen in animals given 30%; in both these groups, there was some slight loss in body weight and slight fatty change in the liver; moreover, the stomachs contained a copious volume of watery fluid, with little or no free HCl and less pepsin than normal; in cultures of gastric contents, Gram-negative intestinal coliform organisms and heat-resistant streptococci were constantly found and Clostridium sporogenes was isolated from 3 animals. This experiment was repeated using twice (i.e. 20 ml.) the volume of alcohol but concentrations of 10% and 20% only. After 24 hours, the gastric findings were essentially the same as those observed after the administration of the smaller volume of alcohol.

From all the experiments so far described, it is concluded that the concentration of alcohol is the prime factor in producing gastric erosions and ulcers, but the volume administered may be of some importance when less concentrated solutions (e.g. 20%) are administered.
INFLUENCE OF FASTING

The effect of fasting was studied in 3 groups of guinea-pigs, each group containing 6 animals. The animals were allowed water ad lib. but were deprived of food for 24 hours by being kept in a stocks, this being necessary because hungry guinea-pigs always eat their faeces if no food is available. Ten ml. alcohol was then administered to each of the animals, those in the first group receiving 10% alcoholic solution, those in the second 20% and those in the third 30%. They were killed 24 hours later. In the animals given 20% and 30% alcohol the appearances in the stomach resembled those seen in non-fasting animals given the same volume and concentration of alcohol but the lesions were slightly more severe.

SPEED OF ONSET OF EROSIONS AND ULCERS

This was studied in 6 large guinea-pigs (average weight approximately 650 g.) which were deprived of food overnight and then given 8 ml. of 60% alcohol by stomach tube. One animal was killed after $\frac{1}{2}$ hour, the next after 1 hour and the remainder after 2, 4, 6 and 8 hours respectively. Some of the results are illustrated in fig. 78 also in fig. 80.

After $\frac{1}{2}$ hour, no mucosal lesions were present but one hour after the administration of alcohol small scattered erosions, some haemorrhagic, were evident, almost entirely in the upper two-thirds of the stomach; after 2 hours, many
FIG. 78.  SPEED OF ONSET OF EROSIONS AND ULCERS IN GUINEA-PIG STOMACH FOLLOWING THE ADMINISTRATION OF 60% ALCOHOL.
FIG. 79. NORMAL MUCOSA FROM BODY OF GUINEA-PIG STOMACH. H. and E. x 60.

FIG. 80. NECROTIC FOCUS IN BODY MUCOSA OF GUINEA-PIG STOMACH 2 HOURS AFTER THE ADMINISTRATION OF 60% ALCOHOL. H. and E. x 60.
of the erosions appeared to have coalesced, while after 4 hours the lesions were still more extensive in area and also in depth.

The focal character of early erosions (see fig. 80) appears, to the author, to constitute presumptive evidence of a vascular origin for these lesions and it would seem that a disturbed blood supply, rather than a direct toxic effect alone, is responsible for the gastric erosions and ulcers. Comparable lesions were observed by Bishton (1950) in the stomachs of guinea-pigs after the parenteral injection of pilocarpine; he noted ischaemic lesions 20 minutes after the injection and demonstrated the role of the blood-vessels by injecting these with colloidal silver iodine and then exposing the tissues to a photographic developer.

SOME LATE EFFECTS OF ALCOHOL, INCLUDING ITS INFLUENCE ON THE HEALING OF GASTRIC ULCER.

In experiments already described, it was demonstrated that a "cautery" ulcer 4 mm. in diameter heals by the 17th day in the stomach of healthy guinea-pigs. The effect of administering 4 ml. 60% alcohol by stomach tube each day to guinea-pigs for 17 days after the production of such an ulcer was studied in one experiment. Because of the anticipated effect of concentrated alcohol solutions in producing multiple gastric erosions and ulcers, the perimeter of the ulcer was "tattooed" with Indian ink at 4 symmetrically-placed points, thereby facilitating identification of the site/
site. Only 12 out of 30 animals survived the full 17 days of the experiment; these were emaciated and had lost a quarter to a third of their body weight at the commencement of the experiment: the body fat was small in amount and a dull yellow-brown colour; the large intestine was distended with firm, dry, brown, scybalous faeces; the adrenals were enlarged and the thickened cortex was dark brown in colour; the liver was about normal size or a little smaller than normal and dark brown in colour, and it showed, microscopically, slight fatty change only.

In all the survivors there were many erosions and ulcers in the stomach. Microscopically, these presented acute or subacute inflammatory features, often severe, but no notable chronic inflammatory signs; figs. 76 and 77 are characteristic of many of these lesions. Variable degrees of glandular degeneration, atrophy and disappearance, associated with changes in the surface epithelium suggestive of healed erosion, were present in other parts of the stomach mucosa (figs. 81 and 82); in the most severely affected parts (fig. 83) there was a marked paucity of glands with, in some instances, chronic inflammatory signs, the appearances resembling those seen in human cases of gastric atrophy or chronic atrophic gastritis.

The "cautery" ulcer had healed completely in 4 animals (figs. 84 and 85); in 2 more animals healing was complete except for a minute central area; in 6 animals, however, there was an unhealed area, approximately 1.5 to 2.0 mm. in diameter. The unhealed part presented the microscopic/
FIG. 81. DEGENERATED AND ATROPHIC MUCOSA IN STOMACH OF GUINEA-PIG GIVEN 'NEAT' GIN DAILY FOR 5 DAYS. H. and E. x 90.

FIG. 82. ATROPHIC GASTRIC MUCOSA IN GUINEA-PIG GIVEN 60% ALCOHOL DAILY FOR 14 DAYS. H. and E. x 60.

FIG. 83. MARKEDLY ATROPHIC GASTRIC MUCOSA IN GUINEA-PIG GIVEN 60% ALCOHOL DAILY FOR 17 DAYS. H. and E. x 40.
FIG. 84. PART OF LINING OF STOMACH OF GUINEA-PIG GIVEN 60% ALCOHOL FOR 17 DAYS SHOWING (a) A LARGE ACUTE 'ALCOHOL' ULCER ON THE LEFT AND (b) A HEALED 'CAUTERY' ULCER ON THE RIGHT (MARKED BY ARROW). x 9.

FIG. 85. HEALED 'CAUTERY' ULCER IN STOMACH OF GUINEA-PIG GIVEN 60% ALCOHOL DAILY FOR 17 DAYS. H. and E. x 60.
microscopic appearances of subacute ulceration, while in the immediately surrounding mucosa erosion and inflammation were present to a variable extent.

**SUMMARY AND COMMENT**

The result of the animal experiments described indicate that erosive lesions, often haemorrhagic, are found in the guinea-pig stomach following the administration of alcoholic solutions by stomach tube in concentrations of 20% or more. The greater the concentration of alcohol, the more severe are the lesions. Furthermore, increasing the volume of alcohol and fasting tend to increase the severity of the gastric lesions. Repeated daily administrations of 60% alcohol produce mucosal degeneration and atrophy as well as multiple erosions and ulcers; these repeated doses of alcohol tend to interfere with the healing of "cautery" ulcers in the guinea-pig stomach. It seems probable that a disturbed blood supply is the important factor determining erosion or ulcer following the administration of alcohol. This is not to deny a direct toxic effect by alcohol on the gastric mucosa but, in this respect, the undoubted healing of "cautery" ulcers and the preservation of gastric mucosa that are seen in stomachs followed the repeated administration of concentrated alcoholic solutions indicate that gastric epithelium has considerable resistance to direct injury or else has considerable power to regenerate. The possible/
possible influence of hydrochloric acid-pepsin in the pathogenesis of the alcohol-induced erosions and ulcers has not been investigated in detail but it was observed that the administration of alcohol in these experiments was frequently followed by marked hypochlorhydria or achlorhydria and very low pepsin values, and it therefore seems doubtful whether the "acid-pepsin" factor plays an important role in the development of the lesions.

The mode of production of the glandular atrophy following repeated daily doses of alcohol is uncertain. A direct toxic action on the epithelium may be the explanation, in part at least, but repeated surface erosion may be equally or more important. In the affected portions of gastric mucosa, the surface epithelium presents irregularities which are highly suggestive of the appearances seen in healed superficial erosions and minute areas of acute erosion may also be seen. Grant (1945) observed that the rate of healing of gastric erosions produced by alcohol is very rapid. Reference has already been made to the similarity in the histological appearance of the gastric mucosa where there was marked glandular atrophy and disappearance in the guinea-pig and gastric atrophy or chronic atrophic gastritis in humans.

It is again mentioned that complete healing of a "cautery" ulcer did occur in 4 of the 12 guinea-pigs given 60% alcohol for 17 days. It would appear that interference with the normal healing process in the remaining 8 animals was dependent on the co-existence of alcohol-induced erosions and/
and/or ulcers which involved the superficial and marginal part of the healing ulcer. Other factors, e.g. disturbed blood supply or a poor nutritional state of the body generally, may also be involved.

EFFECTS OF ALCOHOL ON THE HUMAN STOMACH

Spirits, like whisky and gin, have an alcohol concentration of about 40%; fortified wines such as port or sherry a concentration of about 20%, while beer and cider have a concentration of 5 - 10%. Although the amounts of alcohol administered to the guinea-pigs were relatively very large compared with those consumed by most human subjects, it is reasonable to expect that the consumption of large quantities of the more concentrated alcoholic drinks in humans may lead to lesions of the stomach such as erosions and ulcers, especially if the drinks are taken on an empty stomach. Moreover, it would seem probable that drinks such as beer, which contain only a small amount of alcohol, would be well tolerated even when taken in excess for many years. What, in fact, is the influence of alcohol on the stomach of human subjects? Opinions in the medical literature vary considerably and there are too few well-established and agreed facts. Beaumant's published studies (1833) on the appearance of erythema, simple erosions ("aphthous patches") and a cloudy viscid secretion in the stomach of the celebrated Alexis St. Martin following alcoholic sprees remain prominent in the history of gastroenterology. It is perhaps unfortunate that more was assumed/
assumed from such dramatic findings than the complete picture of alcohol-intake warrants, for the conviction that alcoholism inevitably leads to acute or chronic gastritis became firmly established in the minds of most people, including medical practitioners. Theoretically, gastritis is a reasonable expectation and there is some reliable evidence that it does occur in some cases of alcoholism but there seems no doubt that its incidence has been greatly exaggerated. In an attempt to establish the histological appearances of the stomach in alcoholics, the author made a special study of the gastric mucosa in a series of 25 cases (Wynn Williams, 1956). In 16 patients, who were admitted to hospital for full investigation of vague symptoms apparently related to alcoholism, gastric biopsy was performed, using a modified Australian flexible tube (Coghill and Wynn Williams, 1955; see figs. 86 and 87). Six alcoholic subjects came to necropsy and in these the stomach had been fixed with formal saline within 1 hour of death. The remaining 3 cases were alcoholics who underwent partial gastrectomy for chronic gastric or duodenal ulcer. Briefly the findings were as follows:

Normal gastric mucosa was present in 9 subjects, mild to moderately severe chronic inflammatory changes, mostly mild, were present in the gastric mucosa in 7 subjects and chronic atrophic gastritis was seen in 6 patients, 3 of whom had a chronic gastric ulcer and one a chronic duodenal ulcer. A few small mucosal haemorrhages and erosions were present/
FIG. 86. PROXIMAL AND DISTAL PORTIONS OF THE MODIFIED AUSTRALIAN INSTRUMENT USED IN GASTRIC BIOPSY. A KNUCKLE OF MUCOSA IS SUCKED INTO A SMALL TUBE AND CUT OFF BY A KNIFE.

FIG. 87. GASTROSCOPY PAINTING OF BIOPSY SITE.
present in the gastric mucosa of 6 of the patients. Three patients had one chronic gastric ulcer and one patient 2 acute gastric ulcers; in 2 other patients one chronic and one subacute ulcer, respectively, was found in the duodenum.

The haemorrhages, erosions and ulcers may have been caused, directly or indirectly, by excess of alcohol, but definite proof is lacking. The same may be said of the inflammatory changes in the gastric mucosa; moreover, in assessing the significance of such changes, the general trend towards an increasing incidence and severity of chronic gastritis with increasing age (Wynn Williams, 1950) must be remembered and may well apply in this series. The findings do not suggest that alcoholism must be indicted as a prominent cause of gastric lesions in the human. The following examples will indicate this remarkable negative correlation as regards severe lesions:—

**Male, aged 20** with a history of heavy drinking for 6 months and intermittent epigastric discomfort. Radiographic appearances, gastric juice and gastric biopsy all normal.

**Woman, aged 48** with delirium tremens and a history of heavy drinking in the past 14 years. Liver and spleen enlarged. Gastric biopsy: normal.

**A bar-tender, aged 35,** drank an average of 70 bottles of beer and 2 bottles of gin a week and complained of morning sickness and occasional vomiting for 8 months. Gastric biopsy: an excess of chronic inflammatory small round cells was/
was present in the superficial part of the mucosa; in addition, the appearances of the superficial epithelium suggested regenerative change following superficial erosion.

A ship's steward, aged 33, who had been drinking heavily, including 5 bottles of rum a week, for 4 weeks and died with severe weakness, cyanosis, burning epigastric discomfort, and haematemesis of 2 days' duration. Necropsy findings were sarcoidosis and fatty liver, kidneys and heart. The stomach mucosa was normal except for multiple small haemorrhages and erosions which could have been agon-al.

Male, aged 67, chronically addicted to whisky, died with carcinoma of pancreas, obstructive jaundice and terminal haematemesis. Stomach: mucosa normal except for a few small haemorrhages in the body and antrum, apparently agon-al.

Comparison of the findings in this series of 25 alcoholics with the results of the animal experiments clearly illustrates the frequent difficulty of reliable deduction from clinical material and the comparative ease of obtaining accurate information from animal investigations. Although it is clear that many alcoholics show no histological abnormality in their stomach, the available information does not refute the possibility that alcohol may be an important cause of gastritis, erosion and ulceration in individual cases. Attention has already been drawn to the/
the similar appearances between the human examples of gastric atrophy or chronic atrophic gastritis and the severe atrophic appearances in the gastric mucosa of the guinea-pig after the repeated administration of concentrated alcohol. That these lesions are not commoner in chronic alcoholics may be due to many factors associated with drinking and eating habits. It is customary to prohibit alcoholic drinks in the treatment of peptic ulcers because they are believed to impede healing by stimulating gastric secretion and also, possibly, by direct irritation of the ulcer. Ivy et al. (1956), however, state that there is no proof to support the clinical impression of impaired healing. They add, moreover, that alcohol is important in the pathogenesis of peptic ulceration. In the light of the experimental work described, however, it would seem prudent to continue the current practice of avoiding strong alcoholic drinks in patients with peptic ulcer.
REFERENCES


HYDROCHLORIC ACID AND GASTRIC ULCER

In a recent review of the pathogenesis of peptic ulcer (Kirsner et al., 1956) the following conclusion is drawn:

"The permanent and complete elimination of HCl would eliminate the problem of peptic ulcer, regardless of dietetic, psychogenic, neurogenic, vascular, hormonal and other aetiologic considerations".

Not everyone would agree with this statement, but the acid factor stands so high in the list of preferred theories of the causation of chronic gastric or duodenal ulcers that it might at first seem absurd to question its paramount importance. Nevertheless, strict proof, as against circumstantial supportive evidence, of the major role of HCl in the pathogenesis of these chronic ulcers is lacking. Moreover, there are several facts which suggest strongly that HCl may be only one of a complex of factors involved in the development of a chronic ulcer, particularly as far as the stomach is concerned. These will be considered under the following headings:

(1) Acidity levels in human cases of chronic gastric ulcer.
(2) The focal character of chronic gastric ulcer.
(3) The structure of the floor in chronic gastric ulcers.
(4) Experiments involving hyperchlorhydria.
Morphologically, chronic gastric and duodenal ulcers have many similar features, but it does not follow that they are the outcome of the same disease process. In cases of duodenal ulcer, the gastric juice is characteristically of large volume and acidity, whereas in cases of gastric ulcer is varies considerably and is often found to be normal or even subnormal both in amount and reaction (Illingworth, 1953). According to Johnson (1957), patients with gastric ulcer do not, on the average, secrete so much hydrochloric acid as do healthy people, and many of them have no free HCl in their gastric contents. This author has, however, proposed the theory that gastric ulcers arise from the local effect of recently secreted HCl, which is more concentrated than that present in the main gastric content; he refers to the latter as the "sump". He suggests that in the sagging J-shaped stomach commonly found in patients with chronic gastric ulcer, the innocuous contents of the sump cannot readily come in contact with the upper reaches of the gastric body and what is trickling down the walls of this position is a mixture of acid parietal juice mixed only with mucus and lacking alkaline antral juice (fig. 88). He adds that the lesser curve is obviously the area least accessible to antral juice and that anything which encourages the formation of a "puddle" of acid juice, lacking alkaline antral juice, must cause an unusually potent/
FIG. 88. EXTREME FORMS OF STOMACH: (A) LONG, NARROW, POORLY MIXING, ASSOCIATED WITH GASTRIC ULCER; (B) STEER-HORN, HYPERTONIC, WELL-MIXING, ASSOCIATED WITH DUODENAL ULCER.

(Hatching, acid parietal-cell juice; stippling, alkaline antral juice).
potent acid attack locally. Such a situation arises when
the stomach is divided into two loculi by an hour-glass
deformity, by folding or by the narrowing commonly seen in
the middle of a long hypotonic stomach. When pyloric
stenosis develops in a duodenal ulcer patient, acid gastric
juice is retained in the stomach and a gastric ulcer not
infrequently appears as a complication. Gastric ulcers de-
velop, too, after ligature of the pylorus in rats (Shay et
al., 1945) and after vagotomy in rabbits (Beazell and
Ivy, 1936). These, too, could all be regarded as "retention-
type" gastric ulcers.

If Johnson's theory is correct, the healing of acute
gastric ulcers in experimental animals would be hindered
by procedures causing retention of gastric juice. The
following experiments were, therefore, undertaken to test
its validity:

**EXPERIMENT 1.**

Laparotomy was performed in 12 guinea-pigs and a
"wasp-waist" narrowing of the mid-portion of stomach pro-
duced by tying a linen ligature, which was partially thread-
ed through the wall (fig. 89). An incision was then made
in the anterior wall of the upper compartment and a 4 mm.
diameter cautery ulcer produced on the posterior wall just
proximal to the stenosed segment. The gastrostomy and
abdominal wall incisions were then sutured. The animals
were killed 17 days later.

**Result:** The ulcers healed normally in the 10 animals which
survived the duration of the experiment.
FIG. 89. PRODUCTION OF GAUERY ULCER IN GUINEA-PIG STOMACH JUST PROXIMAL TO A STENOSED SEGMENT.

FIG. 90. PRODUCTION OF GAUERY ULCER IN A POUCH OF GUINEA-PIG STOMACH.
EXPERIMENT 2.

This resembled the first experiment, but instead of a "wasp-waist" narrowing of the stomach a small pouch, in which a 4 mm. diameter ulcer had just been made, was made by partially isolating a segment of stomach about the middle of the greater curve, using a linen ligature (fig. 90).

Result: There were 8 animals which survived the duration of the experiment and in these the ulcer had healed normally.

In a third experiment, an attempt was made to study the healing of a 4 mm. diameter cautery ulcer, produced on the middle of the posterior wall of the stomach after the pylorus had been partially stenosed by the application of a linen ligature. All the animals, however, died within 48 hours, 8 from uncertain cause and 4 from perforation of the ulcer and peritonitis. Whether the perforation was due to digestion by gastric juice or to raised intra-gastric pressure, or both, is uncertain.

(2) THE FOCAL CHARACTER OF CHRONIC GASTRIC ULCER

A chronic gastric ulcer in humans is a very well-defined lesion, usually solitary and round or oval. Even assuming HCl is an important agent in the pathogenesis, it seems essential that some other factor or factors, acting locally, must/
must account for the focal character of the lesion. In other words, if HCl were the one and only cause of ulceration, then diffuse involvement of tissue or, at least, many focal lesions would be expected.

These observations apply also to human peptic ulcers in sites other than the stomach, e.g. in the duodenum or jejunum, and also to peptic ulcers produced in experimental animals by almost any method.

(3) THE STRUCTURE OF THE FLOOR IN CHRONIC GASTRIC ULCERS

The observation of Pavy (1863) that the removal of a patch of gastric mucosa in the dog is followed by complete healing has been confirmed many times. There is a gradual formation first of granulation tissue and then of fibrous tissue in the ulcer, while the inner surface becomes covered by a layer of new epithelium from which simple glands develop. The amount and density of fibrous tissue, however, are relatively small, in marked contrast to the usual appearances in a chronic gastric ulcer.

The concentration of HCl-pepsin in normal gastric juice is sufficient to cause severe destruction of skin and other tissues and may even tarnish metals or rot fabrics. Price and Lee (1946), in extensive experiments, proved that normal gastric juice digests all living tissues except the stomach mucosa but including fibrous connective tissue.
tissue and skin. In an attempt to demonstrate this destructive effect of normal gastric juice, the following experiment was performed:

**EXPERIMENT**

Laparotomy was performed in 6 guinea-pigs and an incision about 1.5 cm. long was made in the anterior wall of the stomach, at right angles to the curvatures. The margins of this stomach wound were then stitched, with linen sutures, to the peritoneal surface of the anterior abdominal wall just to the left of the midline; the line of union formed a circle roughly 1 cm. in diameter (fig. 91). The laparotomy incision was then closed in 2 layers and the animals returned to their cage, where they had access to normal food and water.

**Result:** Four animals died within 48 hours from peritonitis but the remaining 2 survived the 21 days of the experiment, when they were killed. In one animal 2 unhealed chronic ulcers (approximately 2.0 x 0.5 x 0.2 cm. and 0.5 x 0.3 x 0.2 cm. respectively) were present at the site where the stomach was adherent to the abdominal wall; moreover, very thick and dense fibrous tissue occupied most of the abdominal wall beneath the ulcerated site and formed part of the floor. No fistula or skin ulceration were seen in this animal. In the second guinea-pig, 2 small orifices (each approximately 3 mm. diameter) were seen at the site of adhesion of the stomach to the abdominal wall. One orifice/
FIG. 91. STITCHING OF GASTROSTOMY WOUND TO ANTERIOR ABDOMINAL WALL.
orifice was a small, unhealed chronic ulcer with a densely fibrous base, while the other continued into a funnel-shaped fistula which led to a very large (approximately 5 cm. diameter) chronic ulcer in the skin of the anterior abdominal wall. The fistula was surrounded by dense fibrous tissue.

The pH of strongly acid gastric juice (0.1N HCl) is 1. The isoelectric point (i.e. the pH at which proteins become least soluble) of cellular proteins approximates the pH at which strong acids produce death of muscle cells and fibroblasts (the latter do not grow in tissue culture when the acidity is more than pH 5.0 (Fischer, 1921)). Thus, when "free acid" (pH lower than 4.0) is present in the gastric contents the muscle cells and fibroblasts exposed by acute ulceration could be destroyed unless protected by some mechanism. In other words, one would expect that an acute ulcer - either in humans or animals - would penetrate rapidly to the serosa and would not heal so long as cells in the ulcer are exposed to "free HCl". Since such ulcers rarely penetrate and usually heal, factors must operate which prevent them from being affected by "free acid". How this protection is brought about is unknown but the following explanations have been suggested:-

i. The slow rate of penetration by acid

ii. Buffering of acid by mucus and food (at the surface) and by plasma transudates (in the tissues).

Fibroblasts/
Fibroblasts begin to proliferate in several hours and their exposed surface may be renewed. The outer layer of fibroblasts may be killed, which would provide protection for the underlying fibroblasts.

When the free acid is absent, being buffered by food and mucus, the fibroblasts would not be injured. Between meals, the secretion normally is low in volume and the acid which actually comes into contact with the base and margins of the ulcer can be buffered by transudate and the outer film of cellular detritus. Either such factors operate to protect the fibroblasts, or fibroblasts growing in vivo are more resistant to acid than those growing in vitro, because we know that acute ulcers usually heal in 3 or 4 weeks although free acid can be found in the stomach at least during 16 hours out of the 24-hour period.

iii. The epithelial cells growing out from the margins to cover the granulation tissue must be resistant to acid solutions having a pH greater than 4.0. It might be noted, however, that the resistance of such proliferating cells to acid has not been studied by the method of tissue culture.

In an average human chronic gastric ulcer, one is impressed by the relatively small amount of necrosis that is present. Considering the destructive and digestive potential of the HCl-pepsin in gastric juice towards connective tissue, it is remarkable that only a narrow zone of necrosis is present in the superficial part of the ulcer. Beneath this there is a layer of granulation tissue, then a/
a thick layer of dense fibrous tissue. In operation specimens, it is not uncommon to see viable polymorphs very close to, or even on, the surface. Clearly, there must be mechanisms in operation which protect from acid injury, as we have just considered in relation to the healing of acute ulcers. Why, then, do chronic ulcers tend to remain unhealed? Possibly the answer lies more in the nature of the floor which, in some way, prevents an epithelial covering.

EXPERIMENTS INVOLVING HYPERCHLORHYDRIA

(a) Acute Lesions.

All the evidence indicates that HCl formed by the parietal cell has a concentration of 0.58% (or a pH of 0.83 and a normality of 0.159). Thus the cells lining the gland tubule are not damaged by 0.58% HCl solution.

Matthew (1893) showed that HCl in physiological concentration would not harm the stomach mucosa but produced superficial necrosis in the jejunum when perfused through a loop of the latter. Many later investigations have confirmed these observations and have demonstrated a gradient of susceptibility of acid injury in the gastro-intestinal tract: the further the mucosa is from the source of acid formation, the less resistance of the surface epithelium to acid injury.

It has been reported, however, that 0.4% HCl introduced into the stomach of cats and dogs results in the production/
production of acute ulcers within 3 days. If this is true, it means that either the surface epithelium is more susceptible than the gland epithelium or the acid, as it is formed, is rapidly discharged or, as another alternative, the glands alternate between secretion and non-secretion.

HCl solutions more concentrated than physiological solutions may, however, produce gastric lesions. There have been many reports of this effect, e.g. Puhl (1932) introduced 0.4 - 0.6% HCl into the stomach of dogs and observed degenerative and erosive changes in the stomach and duodenum, while Gotschlich (1930) observed minute gastric erosions after the introduction of 15-20 cc. 0.8 - 1.5% HCl by stomach tube. It is, however, difficult to determine from such reports precisely what is the nature of the earliest mucosal damage caused by the HCl.

The following experiments were undertaken to study the effect of N/10 and N/2 HCl on the gastric mucosa. The solutions also contained 2% pepsin, simply because acid gastric juice always contains pepsin. This enzyme facilitates the digestion of cells only after the latter have been injured by any means.

**EXPERIMENT 1.**

3 guinea-pigs were anaesthetized with Nembutal and a minimal amount of ether, then laparotomy was performed. The stomach was brought outside the abdominal cavity and opened by an incision in the middle of the anterior wall, at/
at right-angles to the curvatures. The margins of the incision were then retracted with tissue forceps and the posterior wall of the stomach pushed forward through the aperture and kept in position by small gauze packs. Then N/10 HCl - 2% pepsin (in normal saline) was dropped on to the exposed mucosa from a burette, the tip of which was placed 2 inches above the mucosa, at the rate of 6 drops per minute for 3 hours, when the animals were killed. Paraffin sections were prepared from the stomach after formalin fixation.

Result: The mucosa became very slightly hyperaemic and an inconspicuous, thin grey film of mucus formed on its surface. Microscopically, there were no notable changes; in particular, signs of cellular damage were absent.

EXPERIMENT 2.

This resembled the first experiment but instead of N/10 HCl - 2% pepsin, N/2 HCl - 2% pepsin was dropped on to the exposed gastric mucosa.

Result: The gastric mucosa became hyperaemic, covered by a thin, grey film of mucus and progressively swollen. After approximately 10 minutes, several minute haemorrhagic foci appeared in the mucosa, at the site of impact of the drops, and during the succeeding 3 hours these increased in number and size and many became confluent. Microscopically, necrotic areas were seen in the mucosa after 3 hours' exposure to the solution; these areas involved/
involved the superficial part of else the whole thickness of mucosa and were frequently haemorrhagic; often the superficial part of the necrotic area was missing, viz. an erosion was present. The mucosal and submucosal arteries, veins and capillaries were congested with blood and an early leucocytosis was seen. Oedema was also present, especially in the submucosa.

Comment: The necrotic changes which appear in gastric mucosa when the latter is exposed to concentrated acid solution are focal and appear to be primarily vascular in origin.

When the second experiment was repeated, using 2 guinea-pigs, killed at the end of 1 hour instead of 3 hours, other changes of a less destructive nature were observed microscopically in sections, apart from those lesions described above. These changes were, first, a partial shedding of the outer portion of the surface epithelial cells also of some entire cells of this kind; secondly shrinkage and some hyperchromatism of the glandular epithelium, with slight to moderate dilatation of the lumen.

(b) Chronic Lesions.

Numerous investigations and experiments have been performed in an effort to prove that HCl, especially when present in abnormal concentration, can cause chronic peptic ulceration. Although the experimental evidence regarding intestinal "peptic" ulcers produced by exposure to gastric juice, e.g. by short-circuiting procedures (Mann and Bollmann, 1932)/
leaves no doubt about the importance of HCl in causing acute intestinal ulcers and, probably, chronic intestinal ulcers, the experimental results concerning the relationship between HCl and chronic gastric ulcers are not so clear-cut:

Schmidt and Fogelson (1937) introduced 300 cc. 0.36% HCl twice daily through an oesophageal fistula into the stomach of dogs which had been sham-fed for 50 days. After 10 days, the acid concentration was increased to 0.5% and continued up to 42 days. None of these animals developed erosions or ulcers. Overgaard (1931) gave 350-400 cc. of 0.5% HCl once or twice daily to dogs for 5 weeks to 42 months but no ulceration was seen. A similar experiment was undertaken by Gage et al. (1936), using 1% HCl for 55 days without producing any chronic ulcer.

Subacute chronic ulcers were reported in dogs by Mann and Bollman (1932) after instilling 0.4% HCl into the stomach via a gastric fistula for 4 weeks. The acid was introduced for 8 hours daily at a rate of less than 1 cc. per minute. These results could not be duplicated by Friesen et al. (1944) who were unable to produce gastric ulceration in dogs by perfusing 82-108 cc. per hour 0.4% HCl 6 1/2 - 7 hours daily for 15 - 26 days. Finally, Howes et al. (1936) reported that the healing of excision ulcers of the stomach in cats was not affected by perfusion with HCl of pH 1.1 but was delayed by acid of pH 0.9/
pH 0.9. Even with the latter concentration, however, chronicity could not be induced.

The problem of the relationship between HCl and chronic gastric ulcer has also been studied in animals by the use of histamine injections. The maximal secretory rate of HCl secretion evoked by histamine is about 8 cc. per kilogram body weight per hour and this secretion contains an average of 0.14 N HCl (Hanson et al., 1948).

Two frequently quoted reports claiming the induction of chronicity in gastric ulcer by the administration of histamine injections are those of McIlroy (1927-28), using cats and Flood and Howes (1934), using cats and dogs. These investigators produced an excision ulcer of the stomach and afterwards administered daily injections of aqueous histamine. Their results are, however, unconvincing, which is hardly surprising considering their use of a short-acting (aqueous) preparation of histamine and the short duration of the experiments.

Following the discovery of Code and Varco (1940) that a long-acting (at least 24 hours) preparation of histamine could be prepared by suspending the drug in a mixture of beeswax and mineral oil, many investigators (e.g. Hay et al., 1942) were able to produce acute peptic ulcers in many animal species. Although there are claims to the contrary, there is no convincing evidence that the continued administration of histamine can produce chronic peptic/
peptic ulcers. As was described in the early part of this work, a 4 mm. diameter acute cautery ulcer in the stomach of the guinea-pig heals in 17 days. The layers of the stomach in this animal are so thin and well-defined that both the normal healing processes in a gastric ulcer and any slight alteration of these processes are readily observable. Moreover, the guinea-pig is notoriously responsive to histamine. For these reasons, the following experiment was undertaken to determine whether injections or a long-acting histamine preparation would delay the healing of acute gastric ulcers.

**EXPERIMENT**

24 adult guinea-pigs were used. Following laparotomy under ether anaesthesia, the anterior wall of the stomach was incised and a 4 mm. diameter cautery burn produced in the middle of the posterior wall, the site being marked with Indian Ink. The stomach incision and the abdominal wall were afterwards sutured, then the animals were given a subcutaneous injection of histamine dihydrochloride in a mixture of beeswax and mineral oil. A single injection of this preparation is known to produce an augmentation of gastric HCl for at least 24 hours. (Code and Varco, 1940). The preparation was heated to 45°C so that it melted and it was injected from a warm syringe through a broad needle. The dose was 1.0 mg. histamine base. On subsequent days, subcutaneous injections of the preparation were given morning and/
and evening, each dose on the second day of the experiment being 1.5 mg. histamine base, 2.0 mg. on the third day, 2.5 gm. on the fourth day and 3.0 mg. on the fifth day and subsequent days. On the 17th day, the animals were killed, the abdomen opened and the stomach carefully examined after being first filled and fixed with 10% formal saline.

Result: Two animals died on the first day, one on the 2nd, 3rd, 4th and 5th days respectively, 2 on the 6th, 3 on the 7th and 2 on the 13th days. Eleven animals survived the 17 days of the experiment and in all of these the cautery ulcers had healed. Macroscopically, a small pale scar was seen, while microscopically, there was no abnormality in the healing process.

Except for some slight to moderate increase in the size of the ulcer during the first 3 or 4 days, no abnormality was generally seen in the earlier days of the experiment. One ulcer, however, had nearly perforated.

In every stomach an area of unhealed ulceration was present in the anterior wall, at the site where the wall was originally incised and then sutured. Such ulcers have been seen very frequently in this type of operative procedure (see figs. 114-116); they are frequently fairly large and heal slowly and they develop the histological characters of a subacute or chronic gastric ulcer. It was considered that the absence of signs of excessive digestion in the cautery ulcers might possibly, though improbably/
improbably, be due to some heat-induced alteration of the necrotic cells which rendered them more resistant to digestion. However, it was observed that the healing process of the 'gastrostomy' ulcers showed only slight alteration from those in guinea-pigs not given histamine: in the first few days there was slightly more necrosis at the site; later there was only a slight and inconstant increase in the depth of the superficial necrotic zone in the ulcer floor.

Apart from the changes just described, some acute 'histamine' erosions or ulcers were seen in the stomach, also areas of subacute or healed erosions of the same character. Minute recent or older infarcts were also seen in the liver.
SUMMARY

Whereas HCl-pepsin may be regarded as an important factor in the pathogenesis of acute peptic erosions and ulcers, the evidence that this factor is responsible for the chronicity of gastric ulcers does not constitute proof. The available evidence suggests, indeed, that other factors are at least equally responsible. These factors, which are, at present unknown, are ultimately concerned with the co-ordinated growth and adhesion of epithelium and connective tissue.
REFERENCES


ILLINGWORTH, C.F.W. Peptic Ulcer, Livinstone Ltd., Edinburgh, 1953.


Histamine (beta-iminazolyl-ethylamine) occurs in most tissues, mostly in combined form, and is liberated under certain physiological and pathological conditions. One of the best known of its effects is on gastric secretion: it is the most effective stimulant of acid juice. It can also stimulate smooth muscle. Finally, it may induce a shock-like state in many animals.

Because of the dramatic effect of histamine on the output of hydrochloric acid in the stomach, it has often been used in animal experiments in an attempt to produce ulcers. Some of the experimental results so impressed many investigators that high hope of a complete solution of the peptic ulcer problem was raised. In reality, the problem seems much more complex and it is even doubtful whether gastric acidity is the critical factor in the pathogenesis of chronic peptic ulcer. Nevertheless, the investigations into the effects of histamine on the stomach and intestine have been, and continue to be, of considerable value in increasing our understanding of basic problems in the pathology of peptic ulcer. A few years ago, the author made a special study of acute lesions of the stomach produced by single injections of histamine (see J.Path.Bact., 1951, 62, 465); this experimental study has recently been amplified and also supplemented by experiments in which an attempt was made to impede the healing of gastric erosions and ulcers by continuous histamine action.
A parenteral injection of an aqueous solution of histamine rapidly produces effects which are of short duration. Repeated injections of such a solution have been given in an attempt to produce gastric ulcers in laboratory animals but almost all the results have been negative, e.g. Overgaard (1931) and Orndorff et al. (1935), using dogs, and O'Shaughnessy (1931) and Heinkin and Kastrup (1937-38), using cats. Buchner and Molloy (1927) and Burckle-de la Camp (1929), however, had some success with rats - an unexpected and peculiar finding, since rats are regarded as relatively resistant to histamine.

Code and Varco (1940) discovered, however, that when beeswax is used as a base for the parenteral administration of histamine, there is slow absorption of the latter; large doses of the drug may safely be administered and the effects persist over 24 hours or more. The discovery of this preparation provided an effective, reliable method for the production of peptic erosions and ulcers. The technique was elaborated by Hay and his associates (1942), by mixing dry histamine powder with beeswax and mineral oil. The final mixture is semi-solid at room temperature and is prepared as follows:

Batches of 600 mg. histamine dihydrochloride are ground/
ground to a fine powder in a dry, hot mortar and 0.8 cc.
melted beeswax added. These are mixed until homogeneous,
when 2.8 cc. hot mineral oil is added. The contents
of the mortar are again mixed until homogeneous. When
still molten, this mixture is drawn into 1 cc. tuberculin
syringes which have been lubricated with hot mineral oil;
it is then injected through broad (20 gauge) needles.

As prescribed, each cc. of the mixture contains 100 mg.
histamine base. It is injected daily, either subcutaneous-
ly or intramuscularly, in doses that vary with the animal
species, e.g. 5 mg. for adult guinea-pigs and 30 mg. for
dogs. Since absorption is slow, there is no severe gen-
eralised histamine effect but a large volume of a highly
acid gastric juice is poured out, e.g. Code and Varco
(1942) in 24 hours collected 675 cc. juice, with an acid-
ity of almost 150 clinical units, from the Heidenhain
pouch of a dog, compared with only 15 cc. in a control
animal.

Hay et al. (1942), employing this preparation have
regularly produced acute erosions and ulcers in the stomach
and duodenum of several animal species, including monkeys,
dogs, cats, rabbits and guinea-pigs, but they used repeat-
ed daily histamine injections. Olovson (1950), however,
claimed positive results after only one injection and
concluded that ulceration may be apparent in less than 24
hours. The following experiment was undertaken in an
attempt to confirm his findings:-

EXPERIMENT 1.
40 male guinea-pigs (average weight 450 g.), on a normal diet, were given a single intramuscular injection of a suspension of histamine-acid-phosphate in 4.5 per cent (weight/volume) white beeswax-in-arachis oil, this preparation having a long-acting effect similar to that of the original Code and Varco preparation already described. The dose varied between 2.5 and 12.0 mg. histamine base. The animals were killed 15 hours later. In addition, 20 control animals were injected intramuscularly with 2 ml. base only and killed 24 hours later. In all the animals, the stomach was filled with 30 ml. 10% formol-saline and allowed to fix in a large volume of the same fixative for 24 hours before being opened, washed gently and carefully examined. Blocks were taken of some of the lesions and paraffin sections prepared.

RESULTS.

These are summarized in table 6; they resemble those of Olovson (1950) except that in his experiments, duodenal lesions were more frequent than gastric ones.

Erosive lesions were present in 28 of the 40 test animals; they were present in the stomach alone in 17 animals, in both stomach and duodenum in 6 animals and in the duodenum alone in 5 animals. In 2 stomachs, the erosive lesions had proceeded to perforated ulcers. Mucosal haemorrhages only were present in 7 stomachs.

The erosions or ulcers were usually multiple, haemorrhagic or non-haemorrhagic and usually not more than about 5 mm. in/
FIG. 92. ACUTE EROSIONS IN GUINEA-PIG STOMACH - FOLLOWING THE INJECTION OF HISTAMINE - CLEARLY VISIBLE THROUGH THE SEROUS SURFACE.
## Table 6. Incidence of Stomach and Duodenal Lesions Following Histamine Injections.

<table>
<thead>
<tr>
<th>Dose of Histamine (mg.)</th>
<th>Animals</th>
<th>Animals with Gastric Lesions Only</th>
<th>Animals with Duodenal Lesions Only</th>
<th>Animals with Gastric and Duodenal Lesions</th>
<th>Animals without Gastric or Duodenal Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>3 (haemorrhages only)</td>
<td>1 (erosions)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>7 (erosions in 5; haemorrhages in 2)</td>
<td>2 (erosions)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>5 (erosions in 3; haemorrhages in 2)</td>
<td>2 (erosions)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>5 (erosions in 3; perforated ulcer in 2)</td>
<td>1 (erosions)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>4 (erosions)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### "Test" Animals

### "Control" Animals

20 (Single small erosion in one animal; 3 small erosions in the other animal)
in length or diameter. Many were irregular in shape but some were round or oval. They occurred in any part of the gastric mucosa but most commonly in the body or antrum. In the unopened stomach, they were clearly visible through the serosa (fig. 92). The duodenal erosions appeared as small round foci or streaks, either pale and ill-defined or else brown, "scorched-looking", or bile-stained lesions, extending for a variable distance, up to 2 cm., from the pylorus and most prominent on the posterior wall.

Histologically, the erosive lesions consisted of deficiencies in the mucosa of variable depth. Often, only the superficial part of the mucosa was affected; in other instances, the underlying submucosa or deeper layers were exposed, viz., true ulcers were present. Signs of haemorrhage were often present in the floor, which had a superficial thin covering of necrotic material. Inflammatory cells, mostly polymorphonuclear leucocytes, were usually only few in number. Submucosal oedema was prominent as a rule. Apart from some degeneration and shrinkage of glandular epithelium and/or congestion with blood and oedema in its superficial part, there was no abnormality in the mucosa immediately around the erosions. Examples of these histamine-induced lesions are illustrated in figs. 93 - 99.

How are the erosions and ulcers formed? Olovson (1950) noted that they may appear very quickly and I have confirmed this observation, e.g. in animals given histamine, gastric/
FIG. 93. ACUTE HISTAMINE EROSIONS AND ULCERS IN GUINEA-PIG STOMACH.

FIG. 94. DETAIL OF FIG. 93. SHOWING THE ACUTE LESIONS.
FIG. 95. ACUTE HISTAMINE EROSIONS AND ULCERS IN GUINEA-PIG STOMACH.

FIG. 96. DETAIL OF FIG. 95 SHOWING THE ACUTE LESIONS.
FIG. 97. ACUTE HISTAMINE EROSION IN GUINEA-PIG STOMACH.
H. and E. x 80.

FIG. 98. ACUTE HISTAMINE ULCER IN GUINEA-PIG STOMACH.
THERE IS PARTIAL DESTRUCTION OF THE MUSCULARIS MUCOSA.
H. and E. x 80.
FIG. 99. ULCERATED PART OF GUINEA-PIG STOMACH 2 DAYS AFTER AN INJECTION OF HISTAMINE. H. and E. x 80.

FIG. 100. INFARCT OF LIVER IN GUINEA-PIG FOLLOWING HISTAMINE INJECTION 2 DAYS PREVIOUSLY. H. and E. x 80.
gastric erosions have been seen 4 hours later. It has been assumed that these lesions are the consequence of direct damage of the mucosa by acid gastric juice. If, however, the excessive secretion of highly acid gastric juice were entirely responsible for the lesions, one would expect to find diffuse instead of focal erosion of the mucosal surface. It is more likely that the lesions have a vascular (ischaemic) basis: their scattered distribution, the early appearance of haemorrhage and the healthy intervening mucosa all suggest such a mechanism. Similar lesions have been noted in experimental animals following the administration of drugs such as pilocarpine, morphine and caffeine. Twenty minutes after the parenteral administration of pilocarpine to guinea-pigs, Brinston (1950) was able to demonstrate ischaemic lesions in the mucosa by injecting the blood vessels with colloidal silver iodide and then exposing the blood vessels to a photographic developer; he regarded such lesions as forerunners of erosions. Once the surface epithelium is destroyed, gastric juice is free to increase the destruction. Crane (1954) has demonstrated similar ischaemic lesions in the rabbit stomach, following the administration of pilocarpine. Further evidence of the influence on blood vessels is seen in minute subcapsular infarcts found in the liver of many of the test animals. (fig. 100).

HEALING OF ACUTE GASTRIC EROSIONS CAUSED BY HISTAMINE

The acute gastric erosions produced by the single injection/
injection of histamine in beeswax and oil have a natural tendency to heal completely in a few days. This was demonstrated in the following experiment:

**EXPERIMENT 1.**

Twelve adult female guinea-pigs (average weight 400 g.) were injected intramuscularly with histamine dihydrochloride in beeswax mineral oil, the dose being 15 mg. histamine base per kg. body weight. Twenty hours after the injection, laparotomy was performed. Gastric erosions were present in 10 animals and their position and shape were recognisable on the serosal aspect of the viscus. These measured up to 1 cm. in length but no more than 3 mm. in breadth. The site of 2 of the largest lesions in each animal was marked with 2 Indian ink spots and a record was made of the size and shape. The abdominal wall was then sutured and the animals returned to their cages, where they were allowed a normal diet.

Result: When they were killed 17 days later, healing was complete.

The above experiment was repeated, using 8 animals instead of 12 and killing them on the 8th day instead of the 14th. Again, the erosions were completely healed.

If the theory is correct that chronicity in peptic ulcers is due to the action of HCl-pepsin in preventing healing/
healing, one would expect repeated injections of histamine preparations with a prolonged effect to produce chronic peptic ulcers. Although there have been many claims that chronic peptic ulcers have been produced in various experimental animals under the continuous influence of histamine, no true imitation of the human chronic ulcer has been produced, certainly not in the stomach. This is remarkable when one considers the highly acid secretion of the large volume of gastric juice poured out after the injection of slow-acting histamine preparations, e.g. Code and Varco (1940) found that in a dog with a Heidenhain pouch, the 24 hour secretion was over 675 cc., with an acidity of almost 150 clinical units.

This important relationship has been tested in 2 experiments that are now described, and are continued in the next section.

**EXPERIMENT 2.**

In 15 adult female guinea-pigs (average weight 450 g.), a single intramuscular injection of histamine dihydrochloride in histamine beeswax mineral oil was given: dose 1.5 mg. histamine base per kilo. Twenty hours later, laparotomy was performed. Gastric erosions were observed in 11 animals; these were easily observable on the serosal aspect and the size and shape of 2 of the largest in each stomach were recorded and the site marked with Indian ink. The abdomen was then sutured and the animals returned to their cage/
FIG. 101. ACUTE AND HEALED EROSIONS IN GASTRIC MUCOSA OF GUINEA-PIG GIVEN TWICE DAILY INJECTIONS OF HISTAMINE FOR 12 DAYS. NOTE THE THINNESS AND PAUCITY OF GLANDS IN THE HEALED AREAS OF MUCOSA - FEATURES SEEN IN "GASTRIC ATROPHY" AND "CHRONIC ATROPHIC GASTRITIS" H. and E. x 80.
cage, where they were allowed a normal diet. Beginning 4 hours after operation, the histamine injections were repeated twice daily and the animals were killed 12 days later, viz. on the 14th day of the experiment.

**Result:** One animal died on the 3rd day after operation, viz. on the 5th day of the experiment with acute peritonitis which was due to a perforation of one of the two marked gastric erosions. The remaining 10 animals showed complete healing of their 'marked' gastric erosions but multiple acute gastric erosions, also multiple areas of healed erosions. (figs. 101 and 102).

**CONCLUSION:** It is simple to assume that the perforation of one of the marked gastric erosions was due entirely to the progressive destruction of the floor. This may indeed be the true explanation, but another must be considered, e.g. the initial ischaemic lesion may have involved almost the whole thickness of stomach wall, so that only a relatively slight mechanical or chemical (acid-pepsin) stress would result in rupture. It seems highly significant that erosions of comparable size and, probably, depth healed in the other animals. Unfortunately, the exact depth of the lesions originally seen at laparotomy cannot be ascertained. In order, therefore, to test the effect of repeated histamine injections on an acute ulcer of known size the following additional experiment was performed.

**EXPERIMENT 3.**
FIG. 102. HEALED EROSIONS IN GASTRIC MUCOSA OF GUINEA-PIG GIVEN TWICE DAILY INJECTIONS OF HISTAMINE FOR 12 DAYS. H. and E. x 80.

FIG. 103. PART OF "GASTROTOMY" ULCER IN GUINEA-PIG GIVEN TWICE DAILY INJECTIONS OF HISTAMINE FOR 12 DAYS. THE NECROTIC SURFACE ZONE IS SLIGHTLY THICKER THAN IN CONTROL ANIMALS. (c.f. fig.115). H. and E. x 80.
Ten adult female guinea-pigs were given intramuscular injections of histamine dihydrochloride in beeswax (1.5 mg. histamine base per kg. beeswax) twice a day. Twenty-four hours previously, these animals underwent laparotomy and after the anterior wall of the stomach had been opened and a 2 mm. cautery ulcer produced in the middle of the mucosal surface of the posterior wall. In these lesions, there is destruction of the stomach wall as far as the serosa. Twelve days later the animals were killed.

Result: There was complete healing of the small ulcer but acute histamine erosions were seen in the stomach, also multiple areas of healed erosions. (figs. 101 and 102).

In any guinea-pig operated upon in the manner described an ulcer usually develops at the gastrostomy site and it heals slowly whether histamine is given or not. In animals given daily doses of histamine the only difference is that there is slightly more necrosis at the surface than in the corresponding lesions in control animals (fig. 103: compare with fig.115).
SUMMARY

1. A description is given of acute gastric lesions produced by histamine injections.

2. Acute histamine erosions probably have an ischaemic origin and have a natural tendency to heal quickly.

3. Repeated injections of long-acting histamine preparations fail to impede the healing of acute gastric erosions and ulcers in guinea-pigs.

4. The experimental evidence, although not conclusive, suggests that the role of HCl in the pathogenesis of chronic gastric ulcer has been exaggerated.

REFERENCES

REFERENCES


TWO ORIGINAL METHODS OF PRODUCING GASTRIC ULCERS

To understand fully the pathogenesis of chronic gastric ulcers it is necessary to consider first the development of acute erosions and ulcers and, secondly, the factors, which impair the healing of these lesions. This view is an echo from one of Aschoff's celebrated "Lectures on Pathology" delivered in the U.S.A. in 1924 and is so self-evident that it needs no further emphasis. Although acute gastric erosions and ulcers are well-recognised both clinically and experimentally and are produced under the influence of many widely different agents, there is evidence of a final common pathway in the pathogenesis in many, probably most, instances. The fact remains, however, that we are remarkably ignorant of the underlying mechanisms responsible for most of the acute lesions in humans; moreover, the reasons for the failure of healing of such lesions is at least equally baffling and, according to the author, is not to be equated merely with the destructive effect of gastric juice. Because of these serious deficiencies in our knowledge, any new information is welcome as a possible help to our understanding and, for this reason, some original observations in experimental animals — one concerning acute gastric lesions and the other relating to chronic gastric ulcers — are now mentioned.
ACUTE "ANURIC" EROSIONS AND ULCERS IN
EXPERIMENTAL ANIMALS

During an investigation by Dr. R.C. Nairn into the effects of renal extracts, given intravenously, on the distribution of body water in nephrectomised rabbits, post-mortem examination of one animal revealed the presence of acute peritonitis associated with perforation of an acute duodenal ulcer. This change observation prompted a special study by Nairn and Wynn Williams, part of which was published in 1955. It was confirmed that gastro-duodenal erosions occurred invariably in nephrectomised rabbits given intravenous injections of renal extracts. Subsequent experiments showed that similar lesions developed after bilateral nephrectomy alone, or after ligation of the ureters in rabbits. Moreover, guinea-pigs and rats responded to these procedures in a similar manner. The findings implicated anuria as the dominant factor in the production of these lesions and the injection of organ extracts appeared to have an intensifying effect, which could be simulated by the injection of histamine. Experiments designed to determine the mechanism whereby the anuria produced the lesions were not conclusive but suggested that disturbance of water and electrolyte metabolism might play an important part in the pathogenesis.

METHODS

The behaviour of 90 rabbits, usually about 2 kg. in weight/
weight, as well as 16 adult guinea-pigs and 12 adult rats, was studied in the following circumstances:

A. **Bilateral nephrectomy combined with the intravenous injection of extracts of kidney and liver.**

B. **Experiments designed to investigate the role of anuria.**

These included (i) bilateral nephrectomy or bilateral ureteric ligation in rabbits; (ii) the injection of extracts into rabbits with intact kidneys; (iii) control operations in rabbits, namely unilateral nephrectomy, mock nephrectomy, hysterectomy and splenectomy, sometimes performed alone, sometimes in combination; (iv) bilateral nephrectomy and control experiments in guinea-pigs and rats.

C. **Experiments on the comparative effects of histamine and tissue extracts.**

During experiments, all the animals were fed on food pellets (M.R.C. diet 18) and allowed water ad lib. Metabolism cages were used for the observation of urinary output in certain control experiments. All operations were performed with sterile precautions under nembutal and ether anaesthesia. After the various operative procedures the animals were observed for 2 - 4 days and were then killed by air embolism. The stomach and duodenum were immediately filled with 10% formol-acetate and allowed to lie for 2 - 3 hours before opening. A special note was made of the presence of petechial haemorrhages, erosions or ulcers. Histological/
Histological examination of the gastro-intestinal tract was made routinely, and other organs were examined microscopically when this seemed indicated.

RESULTS

The gastro-duodenal lesions following anuria in the rabbit.

Macroscopic appearances: The lesions (figs. 104-106) were present in the stomach or duodenum or both. They comprised (a) petechial haemorrhages, (b) erosions, and (c) ulcers, i.e. lesions extending beyond the muscularis mucosae; in two animals a large perforated duodenal ulcer was found. Erosion and ulcers were frequently haemorrhagic, particularly in the stomach; duodenal erosions were often bile-stained. True ulcers were less common than the other lesions and were rarely multiple. On the other hand, although petechiae and erosions did occur singly, they were usually multiple and were often present in large numbers.

The petechiae were found anywhere in the gastric or duodenal mucosa but were most conspicuous in the proximal half of the stomach, possibly because they were least frequently obscured by the other lesions. In the stomach the erosions and ulcers occurred mainly in the antrum or pylorus, where they were most severe, but occasionally they appeared elsewhere. In the duodenum they were most frequent in the proximal 2 cm. and, in particular, close to the biliary orifice. The erosions and ulcers varied considerably in shape and their diameter ranged from 1 to 15 mm.; there/
FIG. 104. PERFORATED DUODENAL ULCER IN A RABBIT 2 DAYS AFTER BILATERAL NEPHRECTOMY. x 3.5.

FIG. 105. PERFORATED DUODENAL ULCER AND A LARGE PREPYLORIC EROSION IN A RABBIT 3 DAYS AFTER BILATERAL NEPHRECTOMY.
FIG. 106. LARGE PREPYLORIC ULCERS AND EROSIONS IN A RABBIT 3 DAYS AFTER BILATERAL NEPHRECTOMY. x 3.5.

FIG. 107. SUPERFICIAL EROSION IN BODY MUCOSA OF RABBIT STOMACH 3 DAYS AFTER NEPHRECTOMY. H. and E. x 40.
there was much variation in depth.

**Microscopic appearance:** The petechiae were found in all parts of the stomach wall but were most common in the mucosa, particularly near the lumen. Sometimes the haemorrhages in the superficial part of the mucosa formed eosinophilic, relatively structureless foci in which the individual red cells were difficult to identify. The erosions (figs. 107 - 108) ranged in depth from shallow depressions with necrotic margins to craters extending to the muscularis mucosae. Haemorrhage in and around the erosions was a common though not invariable finding and a brisk polymorphonuclear leucocytosis was frequently present. In most cases no special changes were seen in the blood-vessels around the erosions, though occasionally ante-mortem thrombus was found. A fibrinous exudate was often seen in the floor of the erosions and in the neighbouring part of the mucosa. In some instances small superficial parts of the mucosa were necrotic but still in situ. Sometimes more extensive mural necrosis was a notable feature. The ulcers resembled the erosions histologically except that they extended more deeply into the wall (figs. 109-111). Significant invasion of the bowel wall by bacteria was not a feature of the lesions as judged by the examination of Gram-stained sections. A few scattered Gram-positive cocci were often seen in the debris on the surface of the erosions and ulcers and sometimes in the necrotic floor of the lesions, but Gram-negative and Gram-positive bacilli were very scanty, being identified in only 25 per cent of the lesions examined.

Organisms/
FIG. 108. DUODENAL EROSION IN A RABBIT 3 DAYS AFTER BILATERAL NEPHRECTOMY. H. and E. x 50.

FIG. 109. PREPYLORIC ULCER IN A RABBIT 3 DAYS AFTER BILATERAL NEPHRECTOMY. H. and E. x 50.
FIG. 110. DUODENAL ULCERATION IN A RABBIT 3 DAYS AFTER BILATERAL NEPHRECTOMY. H. and E. x 50.

FIG. 111. PREPYLORIC ULCER IN A RABBIT 3 DAYS AFTER BILATERAL NEPHRECTOMY. H. and E. x 30.
Organisms were not found in the viable tissue at the periphery of the lesions. Rabbits are coprophagic and this habit may have been responsible for the minor bacterial contamination found.

Other intestinal lesions.

These were rare. In a few rabbits in which large numbers of erosions were present in the duodenum, similar lesions were found in the upper part of the jejunum. Erosions and ulcers were never encountered in the ileum and petechiae were very infrequent. In the colon no lesions were found, with the single exception that one rabbit had a solitary shallow ulcer of the ascending part. It was noted that the stools were commonly loose and watery, though not overtly mucoid or haemorrhagic.

**EXPERIMENTAL INVESTIGATIONS**

Bilateral nephrectomy combined with the intravenous injection of extracts.

Fourteen rabbits, divided into 4 groups, were given extract of (a) rabbit kidney, (b) human kidney, (c) rabbit liver and (d) human liver respectively. The extract was injected intravenously in a dose of 2 ml. twice daily for 2 - 4 days. Post-mortem, all the animals had petechiae and erosions in either the stomach or duodenum or both; in 7 of the 14, true ulceration was found. There was no recognisable difference in the type of distribution of the lesions according to the extract administered and no further distinction/
distinction will be made between the different extracts. The incidence and distribution of the lesions are given in table 7.

The only other lesions found in the gastro-intestinal tract were erosions in the upper part of the jejunum in 4 rabbits and a few petechial haemorrhages in the ileum of 2 rabbits.

In considering the mode of production of these gastro-duodenal lesions, the anuric state of the rabbits seemed to be a factor of major importance and the following groups of experiments were therefore performed to test this hypothesis.

**TABLE 7.**

Incidence of gastro-duodenal lesions in 14 nephrectomised rabbits given extracts of kidney or liver

<table>
<thead>
<tr>
<th>No. of rabbits with</th>
<th>no lesions</th>
<th>petechiae</th>
<th>erosions</th>
<th>ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0</td>
<td>13</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Duodenum</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>4 *</td>
</tr>
</tbody>
</table>

* Two with perforation

The role of anurie.

(i) **Bilateral nephrectomy or ureteric ligation in rabbits.**

Fourteen/
Fourteen rabbits were used. Bilateral nephrectomy was carried out in 11 and bilateral ureteric ligation in 3. All these rabbits developed gastro-duodenal lesions similar in kind to those seen in the first series of experiments but the lesions were less numerous and less severe, and no perforation occurred. In one rabbit erosions were also found in the upper part of the jejunum. The results were indistinguishable, whether nephrectomy or ureteric ligation was performed, and therefore these 2 groups are considered together. (table 8).

### TABLE 8.
Incidence of gastro-duodenal lesions in 14 anuric rabbits.

<table>
<thead>
<tr>
<th>No. of rabbits with</th>
<th>no lesions</th>
<th>petechiae</th>
<th>erosions</th>
<th>ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>2</td>
<td>9</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Duodenum</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

(ii) The injection of the extracts into rabbits with intact kidneys. The above findings made it clear that the extracts used in the first series of experiments are not essential for the production of the gastro-duodenal lesions. Furthermore direct experiment has shown that they/
they do not cause significant lesions in rabbits with functioning kidneys. Extracts were injected in the same dosage as before into 6 normal rabbits and into 2 rabbits after unilateral nephrectomy: only a few gastric and duodenal petechiae were found post-mortem in 4 of the animals.

(iii) Control operations in rabbits. It now appeared to be necessary to consider the possibility that the lesions following nephrectomy or ureteric ligation were non-specific in character, i.e. that they might have developed after any operative procedure of similar magnitude. Therefore a series of control operations in 3 groups of rabbits was performed: (a) hysterectomy (3 rabbits); (b) hysterectomy and splenectomy (3 rabbits); (c) "mock" nephrectomy (5 rabbits). Post-mortem, one animal from group (b) had a single duodenal erosion; in the other 10 animals no lesions were found.

In a second control series of 9 rabbits, unilateral nephrectomy was performed: in 3 of these, splenectomy was also carried out to simulate more closely the degree of surgical trauma that had been inflicted on the test animals. Post-mortem, 3 of the animals in which unilateral nephrectomy alone was performed had respectively: (a) a few haemorrhagic and bile-stained erosions in the stomach and duodenum; (b) 4 small superficial duodenal erosions just visible to the naked eye; (c) a single petechial haemorrhage in the stomach and in the duodenum. It is noteworthy that rabbit (a) passed no urine during the 3 days between the operation/
operation and the post-mortem. The cause of the anuria was not clear, but the gastro-duodenal lesions that occurred might reasonably be attributed to it. Thus only 2 of the 8 control rabbits which continued to pass urine after unilateral nephrectomy had lesions post-mortem and these were minimal. The rabbits with combined unilateral nephrectomy and splenectomy showed no lesions.

(iv) Experiments in guinea-pigs and rats. To obtain information about the effect of anuria in other animal species, the following experiments were performed.

GUINEA-PIGS. Bilateral nephrectomy was carried out in 5 guinea-pigs, which survived the operation for 2 - 3 days. Post-mortem, erosions were found in the stomach of 3 animals and petechiae in 1 animal; in 1 no lesions were present. No lesions were seen in the duodenum. A solitary petechial haemorrhage was present in the ileum of 1 animal.

In 5 control guinea-pigs in which "mock" nephrectomy had been performed 3 days previously no lesions were found in the stomach or duodenum.

In 2 other nephrectomised guinea-pigs, human kidney extract was injected intravenously in a dosage of 1 ml./kg. twice daily. The animals survived 2 days. Post-mortem, petechiae and erosions were present in the stomach of both animals; the duodenum showed no lesions. Three control guinea-pigs with intact kidneys were given similar doses of extract for 3 days; the only lesions found were gastric petechiae/
petechiae in 2 of them.

RATS: Bilateral nephrectomy was carried out in 6 rats which survived the operation for 2 - 3 days. Post mortem, erosions were found in the stomach in all the animals; no lesions were seen in the duodenum or elsewhere in the intestine. In 6 control rats in which "mock" nephrectomy had been performed 3 days previously, no lesions were found.

Thus nephrectomised guinea-pigs and rats showed much the same response, but somewhat different from that of rabbits in that the lesions were confined to the stomach.

The comparative effects of histamine and extracts.

The foregoing experiments have shown that operations producing total anuria caused gastro-duodenal lesions, whereas several other operations failed to do so. The extracts in the first series of experiments appeared to aggravate the lesions already present, not to initiate them. A possible explanation of this intensifying action might be that the extracts contained histamine or related compounds, or alternatively that their injection caused the liberation of such substances from the animal's own tissues. The following group of experiments gives some support to this hypothesis.

Histamine acid phosphate (0.25 mg./ml.) was given intravenously in dosage of 2 ml. twice daily for 2 or 3 days to 6 rabbits after bilateral nephrectomy. Post-mortem, gastro-duodenal/
gastro-duodenal erosions were found in all the animals; duodenal ulcers were found in 2, including one with erosions in the upper part of the jejunum. None had lesions in the ileum; one had a solitary shallow ulcer in the ascending colon. The lesions were more severe than those following nephrectomy alone and seemed to be of the same order of severity as those following nephrectomy and the administration of extracts.

The dose of histamine used here, like that of the extract, was the highest that could be given without killing the animals. It had been previously found by direct experiment that such a dose given for 3 days to 6 control rabbits with intact kidneys was following by no more than a solitary minute erosion in the stomach of 2 of the animals.

An attempt to obtain further information concerning the possible role of histamine by the use of an anti-histamine substance was abortive. The anti-histamine Antistin (2-phenyl-benzylaminomethyl imidazoline methane sulphonate) was given intravenously to 4 nephrectomised rabbits in the maximum dose tolerated (0.3 ml./kg.) 15 minutes before the administration of the extracts. Post-mortem, the gastro-duodenal lesions showed no essential difference from those in nephrectomised rabbits receiving extracts alone. However, Antistin was found to be equally ineffective in 3 nephrectomised rabbits given histamine instead of extracts. These findings are in accord with previous experimental work (reviewed by Ivy, Grossman and Bachrach, 1950) demonstrating that anti-histamine substances fail to prevent histamine-induced/
histamine-induced ulcers in guinea-pigs and dogs.

Possible factors concerned in the production of the lesions.

The experimental evidence so far favours anuria itself as the cause of the lesions in all 3 animal species but an enquiry into its mode of action has provided us with no more than a hint of the possible mechanism involved. The following seemed to be most worthy of investigation in the first instance.

(i) Acidity of the gastric juice following nephrectomy. An increase in acidity might in theory have been incriminated as a factor in the development of the lesions. However, in two nephrectomised rabbits with striking gastro-duodenal lesions, the pH of the gastric juice as measured with the glass-electrode was 0.9 in both, compared with a range of 0.9 - 1.6 in 4 control rabbits. Thus the acidity of the gastric juice in the nephrectomised rabbits was no greater than that of a control rabbit without lesions.

(ii) Alkalinity of the bile following nephrectomy. Reference has already been made to the frequent occurrence of erosions in the neighbourhood of the biliary orifice. A change in reaction of the bile might, in theory, have been responsible for these lesions but direct experiment did not support this view. The pH in 2 nephrectomised rabbits was 6.3 and 7.0 respectively, compared with a range of 6.0 - 7.5 in 4 control rabbits.

(iii) Elevation of the blood urea. As long ago as 1859 Treitz/
Treitz put forward the suggestion that the well-known intestinal lesions which occur in renal failure in man are the result of a local caustic effect by ammonium carbonate formed by bacterial action from urea. However, a similar mechanism cannot have been responsible for the gastroduodenal lesions in the present study since it has been shown in parts (i) and (ii) above that the reaction of the gastric juice was acid and that of the bile was either very slightly acid or neutral. Nevertheless it remained to be considered that a high urea level in the body-fluids might have caused the lesions in some other way. The experiments already described are complicated by the fact that the elevation of the urea occurred in animals with absent or damaged kidneys and it was therefore considered desirable to investigate the effects of an elevated blood urea in otherwise normal rabbits.

A high urea level was produced in 9 rabbits with intact kidneys, either by intravenous or by intraperitoneal infusion of concentrated urea solutions. The level of blood urea aimed at was between 100 and 400 mg./100 ml., the range within which lesions occurred in the nephrectomised animals. In 2 rabbits given 20 per cent aqueous urea solution intravenously three times a day for 2 or 3 days, a blood urea level of 450 mg./100 ml. was reached before death. The remaining 7 rabbits were given intraperitoneally, 7 per cent urea, either made up in water or in potassium-free mammalian Ringer solution, in amounts ranging/
ranging from 100 to 200 ml./mg./day for 2 - 3 days. The blood urea level that was reached before death in these animals ranged from 100 to 355 mg./100 ml. Post-mortem, in 8 of the 9 rabbits, it was found that these procedures had resulted in gastric petechiae; in 5 there were erosions, similar to though less severe and less numerous than those arising after nephrectomy (fig.112): the remaining animal had no lesions. Surprisingly, the duodenum was spared in all the rabbits. One showed intramural haemorrhage in a loop of the terminal ileum.

A complicating feature of these experiments was the fact that oliguria of varying degree developed in most of the rabbits; in one that had been given urea intravenously there was complete anuria the result of intravascular haemolysis. This animal and those with the most severe oliguria had the most conspicuous gastric lesions, suggesting that oliguria may have played a part in the development of the lesions. However, it could not have been the only factor concerned, since it has been found repeatedly in the present study that control operations may be followed by a poor urinary output without gastro-duodenal lesions developing. Nevertheless, the "artificial uraemia" experiments were inconclusive in incriminating excess of urea itself as a cause of the lesions; there was no correlation between the level of the blood urea and the severity of the lesions. The experiments did suggest another possibility - that water intoxication or other disturbance of electrolyte balance might be important, since the infused rabbits had poor renal function/
FIG. 112. PREPYLORIC EROSIONS IN A RABBIT WITH INTACT KIDNEYS GIVEN 500 mL. 20% GLUCOSE SOLUTION INTRAPERITONEALLY IN 1½ DAYS. x 3.5.

FIG. 113. ANTRAL EROSION IN A RABBIT WITH INTACT KIDNEYS GIVEN 200 mL. 7% UREA SOLUTION INTRAPERITONEALLY EACH DAY FOR 3 DAYS. H. and E. x 40.
function and were receiving large amounts of fluid.

To test this hypothesis, a further series of experiments was performed in which 4 rabbits were given intraperitoneal infusions in the same dose as before except that the urea was omitted from the infusion fluid, 20 per cent. glucose (which is approximately isotonic with 7 per cent urea solution) being substituted. In 2 rabbits aqueous solutions were used and in 2 the glucose was dissolved in potassium-free Ringer's solution. The first 2 animals survived less than 24 hours and, post-mortem, had gastric petechiae but no duodenal lesions. The other 2 animals survived 2 days and in each there were several petechiae and erosions in the stomach (fig.113), and one petechial haemorrhage in the duodenum.

The common factors in these infusion experiments include (a) the establishment of a positive water balance, and (b) gross interference with the electrolyte balance. Either or both of these might play an important part in the development of the lesions.

**DISCUSSION**

The experiments indicate that there is a causal relationship between anuria and gastro-duodenal haemorrhages, erosions and ulcers in the rabbit, rat and guinea-pig. The particular component of the anuric state responsible for the lesions has not been established but some evidence has been adduced that gross disturbance of water and electrolyte/
electrolyte balance may be important in the pathogenesis. The proximate mechanism whereby the lesions arise in the mucosa of the stomach and duodenum is also unknown. Histological studies have not provided any conclusive information. Ante-mortem thrombus was occasionally observed in the blood vessels in the immediate vicinity of erosions and ulcers, but the finding was so infrequent as to suggest that it was more probably an occasional result of the lesions than the cause. Other vascular abnormalities were sought in the stomach and intestines but no constant changes could be demonstrated. Bacterial clumps, often present in large numbers in the colonic ulcers from human cases of uraemia, were absent from the present gastro-duodenal lesions; only a few superficial contaminants were found. Because of the frequency of haemorrhages in the gastric and duodenal mucosa, it seems likely that the erosions and ulcers were sometimes derived from these. However, non-haemorrhagic areas of necrosis were also found in the mucosa immediately adjacent to the lumen, so that it seems probable that a proportion of erosions and ulcers arise by peptic digestion of these necrotic areas. The distribution of the lesions in the experimental animals does give a possible clue to their pathogenesis. They were practically confined to the stomach and duodenum, only very occasionally spreading into the upper jejunum. The usual stigmata of uraemia, such as widespread petechial haemorrhages on the serosa, were not seen, perhaps because of/
of the brief survival time. This observation indicates that the gastro-duodenal petechiae were not merely a manifestation of a general uraemic haemorrhagic state. The definite localisation of all the lesions to one part of the digestive tract implies some anatomical or physiological peculiarity of this part of the body. Alteration of the acidity of the gastric juice and of the alkalinity of the bile are local phenomena deserving of consideration here, but direct experiment showed that significant alterations did not occur. Moreover such chemical changes would be expected to produce diffuse lesions over the entire peptic area. For the development of isolated scattered lesions such as occurred in our animals, a localised peripheral vascular disturbance would seem to be a necessary factor. Such a disturbance would also explain the haemorrhagic nature of some of the lesions and the morphological resemblance of others to infarcts. It is of interest that Crane (1954) has produced similar lesions in the rabbit's stomach by the subcutaneous injection of pitressin: he showed by various techniques that ischaemia occurred in the area that ulcerated.

A relationship between uraemia and gastro-intestinal lesions has been appreciated for almost a century (Treitz, 1859; Fenwick, 1868, quoted by Konjetzny, 1928), but there have been few investigations to determine the nature of this relationship. Streicher (1928) attempted to reproduce uraemia in dogs by the intravenous injection of 10 or 20 per cent urea solutions, in a dose of 200 ml. three times
The animals developed signs analogous to those of clinical uraemia, with the intestinal manifestation of bloody diarrhoea. Post-mortem, the entire gastro-intestinal canal was found to be markedly hyperaemic but there was no sign of ulceration. The author described the condition of the bowel as enteritis but his illustration is more suggestive of patchy mucosal haemorrhages. In man, gastro-intestinal lesions associated with uraemia have been described in a few isolated case reports reviewed by Konjetzny. This author recorded the association of uraemia with acute gastritis, which was sometimes combined with acute ulcer formation. Hurst and Stewart (1929) also recorded the presence of acute peptic erosions in 4 cases of nephritis and a further case of multiple acute haemorrhagic erosions in the stomach of an adult man who died of acute ascending pyelonephritis. However, the only systematic study of gastro-intestinal lesions in a large series of cases of uraemia appears to be that of Jaffe and Laing (1934). They observed gastro-intestinal haemorrhages in 53 per cent of 136 uraemic autopsies; there were gastro-intestinal erosions and ulcers in 20 per cent, mostly in the large intestine and never in the duodenum. The authors observed that haemorrhage was a more notable feature of the uraemic erosions than of any other form of intestinal ulceration and concluded that they probably arose from mucosal haemorrhages. They could find/
find no correlation between blood urea level and the incidence of the lesions, which is in accord with our observations in the experimental animal. The incidence of ulceration in the stomach in their series was about 5 percent. In 25 personally studied fatal cases of uraemia from personal autopsy records erosions were found in one stomach and altered blood without visible ulceration in another at post-mortem examination. However, analysis of 50 "unselected" post-mortem cases from which there was no uraemia showed that erosions were present in 3 stomach, which suggests that the incidence of gastric erosions in uraemia may be the same as that in non-uraemic cases post-mortem. These figures were taken from records of routine post-mortems which may sometimes have omitted a description of minor gastro-intestinal lesions, and there is need for a controlled analysis of a further large series of cases giving special consideration to the incidence of these lesions.

The distribution of gastro-intestinal lesions in human cases of uraemia appears to be quite different from that observed in our rabbits, rats and guinea-pigs. In man, the colon is most severely affected and lesions in the stomach are relatively uncommon; in the rodents, lesions below the jejunum were extremely rare. The explanation of this species difference is not clear, but apart from possible anatomical differences it could conceivably be related to dietetic habit or differences in intestinal flora. The pathogenesis/
pathogenesis of the lesions in man is also unknown; the classical view that they arise from the caustic action of ammonia formed from the retained urea cannot account for gastric lesions when hydrochloric acid is present in the stomach. Further investigations into the pathogenesis in several animal species are required.

SUMMARY

Fourteen rabbits were given aqueous extracts of kidney or liver intravenously for 2 - 4 days after bilateral nephrectomy. Post-mortem, they all showed severe lesions in the stomach or duodenum, or both, including petechiae, erosions and ulcers; in 2 rabbits perforated duodenal ulcers were found.

In a second series of 14 anuric rabbits which had bilateral nephrectomy or bilateral ureteric ligation, extracts were withheld. These animals also developed lesions which, however, were less severe and less numerous than in the first series.

The extracts alone failed to cause lesions in 8 rabbits with functioning kidneys. They appeared to be merely potentiatators of lesions already present, possibly through a histamine-like effect. The administration of histamine acid phosphate intravenously to 6 nephrectomised rabbits resulted in lesions of the same order of severity as those found in the nephrectomised rabbits which had received extracts.

Nineteen rabbits had control operations which were not
not followed by anuria. These were designed to cause a similar degree of surgical trauma as bilateral nephrectomy, but they failed to produce significant gastro-duodenal lesions.

Nephrectomised guinea-pigs and rats developed similar lesions in the stomach but not in the duodenum; no lesions were found after control operations.

These experiments show that there is a causal relationship between anuria and the gastro-duodenal lesions, but the precise pathogenesis is not clear. The parenteral administration of large quantities of hypertonic fluids in rabbits with intact kidneys caused similar lesions, which perhaps implies that a disturbance of water and electrolyte metabolism may be important in their pathogenesis. The morphology and distribution of the lesions suggest that their development in the gastro-duodenal mucosa is the result of a peripheral vascular disturbance.

"GASTROSTOMY" ULCERS IN GUINEA-PIGS

As described on page 28, the technique which was employed in these studies for producing cautery ulcers in the stomach requires initial opening of the anterior wall of this organ. After the cautery ulcer has been produced on the posterior wall, the gastrostomy opening is closed by a sort of purse-string suture (see fig. 22). It was observed that an ulcer always develops at the gastrostomy site and its/
its appearances after about 2 weeks resemble those of a human chronic gastric ulcer very closely. In stomachs examined 17 days after operation (the commonest time of sacrificing the animals in these experiments) the ulcers are prominent lesions of variable size and shape. Some are round, with a diameter of at least 4 mm., while others are oval or pear-shaped and up to as much as 12 mm. in length; a small minority are irregular in shape. The ulcers are usually deep, with a floor which slopes sharply towards the centre and is covered by a thick purulent and necrotic layer. Often some suture material protrudes from the floor, but in some the suture has disappeared. Firm fibrous adhesion to the overlying liver is a common finding. The naked eye appearances of an ulcer are illustrated in fig.114. The ulcers heal slowly in 5 to 8 weeks. Microscopically, the various components of the floor are remarkably like those seen in human chronic gastric ulcers (figs. 115 and 116). At the surface, there is a purulent and necrotic layer and beneath this a layer of vascular connective tissue which merges in the depths of the ulcer floor into dense fibrous tissue, containing only few blood channels and no muscle bundles. The mucous membrane immediately around the ulcer shows signs of regeneration, another point of resemblance to the human counterpart.

It is of interest to consider the possible causation of these ulcers, particularly as this may have some relation to/
FIG. 114. A LARGE CHRONIC ULCER ON THE MUCOSAL SURFACE OF THE ANTERIOR WALL OF A GUINEA-PIG STOMACH, AT THE SITE WHERE THE ORGAN WAS INCISED AND SUTURED 23 DAYS PREVIOUSLY. NATURAL SIZE.

FIG. 115. SECTION OF THE ULCER IN FIG. 114. H. and E. x 20.
FIG. 116. DETAIL OF THE FLOOR OF THE CHRONIC "GASTROSTOMY" ULCER IN FIGS. 115 AND 114. H. and E. x 120.
to the pathogenesis of chronic peptic ulcers in the human. The first point to consider is that the initial trauma to the stomach is one which involves destruction of all the layers of the wall and this fact suggests that the depth of destruction of acute gastric ulcers may be important in determining the chronicity of the human chronic ulcer. Associated with this factor of depth, we must mention ectasia (Gk. ectasis, a stretching out), viz. a progressive dilatation of the periphery of the ulcer margin. This takes a few days to develop but appears to be a constant phenomenon. The surface of the ulcers is irregular in form and composed of soft purulent and necrotic material, this constituting an inferior base for the adhesion of the delicate epithelium which grows from the margins of the ulcer. Finally, another factor which may tend to maintain chronicity is firm fibrous adhesion of the ulcer and the surrounding serosal part of the stomach to the overlying liver, so that contraction of the ulcer is impeded or prevented.
REFERENCES


DISCUSSION

There is a consensus of opinion that two factors are concerned in the causation of chronic peptic ulcers: (1) the primary factor responsible for the initial trauma and (2) the secondary factor which interferes with the normal healing process. Beyond this simple statement, however, the medical literature abounds with conflicting ideas and it is obvious, even on clinical evidence alone, that there is still a great deal to be learned about the gastro-intestinal tract in this respect. At first glance, there appear to be overwhelming reasons why HCl-pepsin should be considered of prime aetiological importance: the fact that peptic ulcers occur only in those parts of the alimentary tract bathed by gastric juice; the fact that these ulcers are rarely encountered when achlorhydria is present; and, lastly, the fact that prolonged achlorhydria is associated with cure. However, while it can be admitted that some acute peptic erosions and ulcers may be intimately related to gastric juice, particularly in the intestine, there are many reasons why factors other than HCl-pepsin must be at least equally, if not more important, in the pathogenesis of chronic gastric ulcer: in many patients with this disease the acid secretion is subnormal and even close to achlorhydria; the lesions are focal and often solitary; acute gastric erosions and ulcers normally heal completely and quickly; experimental acute ulcers heal in spite/
spite of a sustained hyperchlorhydria; in both human and experimental chronic gastric ulcer, evidence of digestion of the ulcer floor is inconspicuous.

It would seem that in the past undue emphasis has been placed on the acid pepsin factor and too little attention focussed on protective factors; the latter have been studied much less and are little understood.

Doubt concerning the prime importance of acid in the aetiology of chronic peptic ulcers has already been expressed by a few investigators, e.g. Oliver (1947) and Appleby (1948). Moreover, James and Pickering (1949) believe that the acid factor is operative in duodenal ulcer but not in gastric ulcer. They made 24-hour observations on the gastric acidity in 20 cases of duodenal ulcer, 23 cases of gastric ulcer and 20 controls and they found that subjects with duodenal ulcer yielded more and subjects with gastric ulcer less HCl per hour than normal subjects. They deduced that gastric and duodenal ulcer are essentially distinct disorders and that the chief agent in their pathology is different, also that there is something other than intragastric acidity which is the essential agent in the pathogenesis of gastric ulcer.

The idea that peptic ulcer is probably not the result of any single group of aetiological factors has been expressed by Card (1952), Smith and Rivers (1953) and Dempster (1957). Card has written: "... it is most unlikely that peptic ulcer has a single universal cause...

There are likely to be multiple causes, any one of which
may be operating at one time or in one place; the cause of ulceration in the Southern Indian peasant is not necessarily the same as that of the London stockbroker; perhaps in searching for the cause of ulcer we should emphasize this by asking our question the other way 'Why do people not get ulcers?'

Most people agree that an area of devitalization of tissue precedes ulcer formation and some of our predecessors have recorded their observations and conceptions by using the term "locus minoris resistantiae", but such erudition has concealed their ignorance of the essential mechanisms involved. It certainly seems reasonable to assume that chronic peptic ulcers arise from acute ulcers or possibly erosions. Ivy, Grossman and Bachrach (1950) have aptly expressed the situation thus: "It is difficult to conceive, and no-one has explained adequately how a chronic ulcer could arise, like Minerva springing fully armed from the forehead of Jove, without it being an acute lesion of the mucosa."

Acute erosions are common lesions in the stomach and acute and subacute gastric ulcers are also well recognized. These lesions are caused by a wide variety of agents (Selye, 1951; Ivy, Grossman and Bachrach, 1950), some of which have already been mentioned earlier in this work. Normally, the lesions heal speedily but, for reasons that are not entirely clear, they develop into chronic ulcers in certain subjects. Since Virchow's time, vascular disease, including spasm, has been frequently proposed as the initial cause of erosions and ulcers and in this connection it is of interest that Schindler and/
and Baxmeier (1937) noted haemorrhagic erosions in the gastric mucosa of 44% patients with gastric ulcer as compared with only 5.6% without gastric ulcer; this observation lends support to the view that a localized vascular disorder, e.g. vasospasm, produces an acute erosion or ulcer which may progress to form a chronic ulcer. The writer has been impressed by the focal nature of acute gastric erosions and ulcers in many of the experiments described in this work and believes that the most probable explanation is a disturbed vascular supply, viz. ischaemia, whether produced by vascular spasm or by stasis of blood within vessels. Moreover, he has also noted the development of chronic gastric ulcers in guinea-pigs when the local blood supply was diminished, e.g. following external ring burns of the stomach wall.

While it can confidently be stated that there is very little evidence that gastritis is a cause of gastric ulcer, the roles of many other possible factors, such as endocrine or nervous, is still indeterminate.

Descriptions have already been given, however, of experiments in which chronic gastric ulcers developed in animals: (a) where a second cauterity ulcer was produced at the scarred site of a former, larger ulcer, (b) when an external ring burn was produced around a cauterity ulcer in the stomach, (c) following the local injection of "irritants" such as Freund's adjuvant and, finally, (d) at gastrostomy sites. In all these instances, there was a failure of the growing epithelium to cover and adhere to the ulcer floor which/
which was either densely fibrous or loose and irregular. It is deduced, therefore, that a special study of factors influencing the adherence of epithelium to underlying connective tissue is likely to prove of great value in our understanding of the peptic ulcer problem and, indeed, in other types of chronic ulcer.

Aschoff (1924) believed that chronic gastric ulcers developed from erosions if the latter were present on the lesser curve and he suggested that the reasons for this development were the lack of mucosal mobility and the discharge of chyme along the lesser curve and possibly also muscle spasm. No one has adequately explained the cause of the peculiar localization of chronic gastric ulcer to the lesser curve region. Possibly local anatomical factors are important; possibly, too, "diastasis", as apparently occurs in experimental ulcers at the gastrostomy site may be involved.
REFERENCES


