A British Medical Association Lecture ON THE PATHOLOGY OF GASTRIC ULCER.

DELIVERED TO THE DERBY DIVISION, MAY 18TH, 1923,

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PART I.—THE ETIOLOGY OF PEPTIC ULCER.

It is now generally believed, on strong clinical and pathological evidence (Bolton, 1913¹), that all chronic gastric ulcers arise in and from acute ulcers—that is, that all ulcers are rapidly formed in the first instance, a chronic ulcer being merely one which has been in existence for a certain length of time. Two etiological problems are thus presented—(A) the cause or causes of acute ulcer, and (B) the factors which lead to the persistence or non-healing of such an ulcer.

A. ETIOLOGY OF ACUTE ULCER.

The various factors, clinical and experimental, concerned in the production of acute ulcers fall into two categories: (1) those which act by producing injury (malnutrition, devitalization, etc.) of the gastric mucosa, and (2) the digestive action of the gastric juice.

1. Causes which Act by Damaging the Mucosa.

Experimentally, injury to the mucosa of such a kind as to lead to ulcer may be brought about in a great variety of ways. Clinically, also, many possible causes have to be taken into account. Whatever the agent, the most frequent mechanism appears to be by the production of a focus of necrosis, with or without a preceding focal haemorrhage, or the lesion starts as an inflammation of the lymphoid follicles.

(a) The theory of vascular blocking was one of the earliest to be put forward, and was a deduction by Virchow from the well known funnel-shaped character of many gastric ulcers. Such blocking might result from arterial embolism or venous thrombosis, with or without pre-existing disease of the vessel wall, but neither clinically nor experimentally is there any considerable body of evidence in support of this. The anastomotic connexions of the large and medium sized arteries of the stomach are so extensive and complete that it is practically impossible to produce ulcer experimentally by obstructing one or even several of them. It is possible, however, to produce typical acute ulcers by injecting into a gastric artery substances which will produce embolism in the small arteries of the mucosa and submucosa—for example, fat (Schridde, 1907²), or a suspension of lead chromate (Cohnheim, 1890³). Clinically it is not found that sources of sterile emboli are commonly present in cases of gastric ulcer, nor is venous thrombosis often met with except as a secondary or terminal event.

Vascular obstruction or stasis may also be brought about by spasm of the arteries or of the stomach itself. Durante (1916)⁴ produced ulcers by section of the vagus or sympathetic nerves, or both, and he attributed his results to arterial spasm, due, he believed, to excessive production of adrenaline, while the acute duodenal ulcers of experimental adrenaline intoxication (Friedman, 1915⁵) may have a similar explanation. There is no definite evidence that vasomotor spasm is a factor in the production of ulcer in man, although on clinical grounds there is much to be said for it. As Hurst (1922)⁶ points out, "something of this kind would alone explain the undoubted influence of sudden change of temperature in the production of relapses of gastric and especially of duodenal ulcer, and the frequent association of a poor peripheral circulation with gastric and duodenal ulcer."

Spasmodic contraction of the stomach itself, on the other hand, is a well known and common accompaniment of chronic ulcer, and one which may well exert a vicious influence on the lesion. There is no proof, however, that it is a cause of ulcer in the first instance.

(b) General nutritional factors in the etiology of gastric ulcer are now largely discounted. Bolton emphasizes the fact that there is no reliable evidence to show that chlorosis is etiologically related to ulcer as was once thought, "neither is there any evidence to show that an acute ulcer spreads more readily in anaemic patients." The terminal acute ulcers occasionally met with in cachectic subjects can be much better accounted for by a terminal infective hypothesis.

(c) Trauma by chemical or by physical agents is an undoubted cause of gastric ulcer, but from its supposed infrequency is generally regarded as of little clinical importance. The swallowing of caustic substances—strong mineral acids, silver nitrate, and the like—may be followed by ulcer, and Bolton has emphasized the possible importance in this connexion of the dietetic use of vinegar, acetic acid being a powerful protoplasmic poison even in dilute solution (2 per cent.). Mechanical trauma, whether from within or from blows on the abdomen, is even less important. It is well known that the stomach will tolerate in a quite remarkable way the presence in its interior of hard foreign bodies, such as knives and nails, without becoming ulcerated. From time to time cases are reported—for example, the recent case of H. E. Griffiths (1922)⁷—in which there is apparently a very close connexion between a blow on the abdomen and the development of gastric ulcer, and one has seen lesions of the stomach (focal haemorrhages and lacerations) in cases of traumatic death which might well have been the starting point of ulcer had the patient survived.

Thermal trauma, scorching or scalding from hot food and drink, has had much importance attached to it by some writers. Decker (1887)⁸ produced gastric ulcer in two dogs by feeding them on gruel at 62° C., while Heiser (1922)⁹ found that in 108 gastric ulcer patients there were only four who were not notorious for insisting on their food and beverages being served very hot, or they were very rapid eaters, or both.

(d) Bacterial infection and intoxication is, however, undoubtedly the most important direct cause of acute gastric and duodenal ulcer in man, as it is the method by which, particularly in the hands of Rosenow, some of the most remarkable experimental results have been obtained. It has long been known that acute ulcer might occur during the course of acute bacterial infections, as well as in other forms of toxæmia, but it is only within recent years that the importance of this connexion has been fully established (Gandy, 1899,¹⁰ and Bolton, 1913¹).

I have analysed a series of 53 cases of acute gastric and duodenal ulceration met with in the course of 1,500 consecutive autopsies. In 2 cases only were the ulcers the proximate cause of death—one a man of 42 years of age who died of mesogastric and mediastinal cellulitis due to three acute linear ulcers near the cardiac orifice, the other an infant of 4 months who died of haemorrhage from multiple duodenal ulcers. In half the cases (27 out of 53) acute septic disease was present; peritonitis from various causes 14, bronchopneumonia 6, empyema 3, pyelonephritis 2, and pericarditis and meningitis one each. The principal causes of death in the remainder were cancer (6), cardio-vascular disease (6), tubercle (2), corrosive poisoning (2), and syphilis (1).

Many writers have stressed the importance of less serious, localized forms of infection, both in relation to the etiology of acute ulcer and as a cause of acute exacerbations in chronic ulcer. Dental and tonsillar infections, appendicitis and cholecystitis in particular, have been incriminated on strong clinical evidence.

The clinical connexion between non-bacterial forms of intoxication and ulcer is much less clear, although in animals positive results have been obtained by the injection of a large variety of substances (arsenious acid, chloroform, snake venom, bile salts, gastrototoxic serum, etc.). There is, however, one form of ulcer in man which probably belongs to this class—that which follows extensive burns.

In a series of 6,800 autopsies there were 115 subjects dead of burns, of whom 57 were 20 years of age or over. In this group 2 cases only showed ulceration of the stomach or duodenum. In a child of 5 who died thirty-three days after extensive burns of the trunk and limbs there was a small acute ulcer in the pyloric region of the stomach. In a man

of 50 who died thirteen days after very extensive burns of the trunk and limbs there were multiple acute ulcers in the duodenum.

A possible etiological connexion between burns and ulcer of the stomach and duodenum has long been recognized. The association, however, is rare; Bolton suggests once in every 25 or 30 cases of burns. A perusal of the literature suggests that in former years the combination was more common than now, possibly because burns more frequently became septic.

Experimentally, the work of Rosenow in particular goes far to establish the importance of bacterial infection in the etiology of gastric ulcer. So long ago as 1857 it was shown by Lebert¹¹ that acute gastric ulcers could be produced, as part of a general pyaemia, by the intravenous injection of pus. Later Letulle (1888),¹² Chantemesse and Vidal (1888),¹³ Charrin and Ruffer (1889),¹⁴ and others produced a similar result by the injection of a variety of bacterial cultures or their filtrates (staphylococci and streptococci, pneumococci, *Bacillus pyocyaneus*, dysentery and colon bacilli, etc.). The presence of bacteria has been frequently demonstrated in the margins and floors of both spontaneous and experimental ulcers, but the possibility of these being secondary invaders has always to be borne in mind.

In 1913 Rosenow¹⁵ reported a series of experiments in which the intravenous injection of streptococci of sufficiently low virulence not to cause a general infection was followed in a certain number of cases by ulcer of the stomach and duodenum. The ulcers were usually single and deep, with marked tendency to haemorrhage and perforation, and in many respects resembled gastric ulcer in man. The streptococci were obtained from various sources, but especially from infected tonsils, and it was shown that the ulceration was the result of a localized infection, with secondary digestion.

Later, Rosenow and Sanford (1915)¹⁶ showed the almost constant presence of streptococci, often in pure culture, in the depths of chronic gastric and duodenal ulcers in man. The organisms isolated were of a relatively low grade of virulence, but tended to localize in the mucous membrane of the stomach and duodenum, producing circumscribed areas of infection, with haemorrhage and ulceration, in a high percentage of the animals inoculated.

In subsequent papers Rosenow (1915,¹⁷ 1916,¹⁸ 1921¹⁹) showed the remarkable specificity of these and other streptococci, which tended, in general, to reproduce similar lesions to those from which they had originally been recovered. To this phenomenon he applied the term "elective localization." He also demonstrated that streptococci from cases of appendicitis, cholecystitis, endocarditis, tonsillitis, and dental apical infection were specially liable to localize in the stomach and duodenum, with production of haemorrhagic areas and ulcers.

In a recent paper Rosenow (1923)²⁰ goes on to show that as in man, so in animals, spontaneous ulcer of the stomach is associated with the presence therein of electively localizing streptococci, which reproduced gastric lesions—ulcer, haemorrhage, and infiltration—in no less than 86 per cent. of the rabbits and dogs injected.

2. The Action of the Gastric Juice.

The strict limitation of peptic ulcer to the stomach, first part of the duodenum, jejunum (following gastro-jejunosomy), and, rarely, the lower part of the oesophagus, at once suggests that the gastric juice plays an important part in the etiology of this disease. Normally the living gastric mucosa possesses complete immunity to the digestive action of the gastric juice, but immediately a portion of it becomes devitalized, whatever the cause, then the dead or damaged part becomes acted upon by the gastric secretion, and is gradually removed by peptic digestion, an acute ulcer resulting.

The pathology of the process has been studied and the importance of the gastric juice clearly demonstrated by Bolton. By the intraperitoneal injection of a non-lethal dose of gastrototoxic serum—that is, the serum of an animal, of different species, which has been immunized against the gastric mucosal cells of the first—he was able to produce within twenty-four hours or less patchy necrosis of

the stomach wall. After about forty-eight hours this necrosed tissue disappeared, leaving sharply punched out ulcers with clean bases, exactly comparable in distribution and appearance to the acute gastric ulcers of infective origin in man. If, however, the gastric juice was put out of action while the poison was acting, by the introduction into the stomach of a solution, over 1 per cent., of sodium bicarbonate no lesion of the stomach developed, even microscopical examination failing to reveal any pathological changes. Bolton has also shown, by experiment, that acute ulcer is much more easily produced in the digesting than in the resting stomach, and that in the former it is much more extensive in character. Moreover, ulceration produced in the presence of hyperacid stomach contents is much more extensive than that produced in a stomach whose contents are of normal acidity.

Recent experimental work by Mann, Kawamura, and Williamson (1922,²¹ 1923²²) has an important bearing on the relationship between acid stomach contents and the development of duodenal ulcer. By diverting the secretions which normally neutralize the gastric juice as it leaves the stomach to another portion of the intestine remote from the point of emergence of the acid, they were able to produce in dogs in a high percentage of cases typical sub-acute or chronic peptic ulcers in the intestinal (duodenal or jejunal) mucosa. These were quite comparable pathologically to the ulcers found in man.

It is obvious from these findings that while hyperchlorhydria, in man, will render conditions more favourable for the development of gastric or duodenal ulcer, yet it is by no means a necessary or essential factor. Gastric juice which possesses only the normal content of hydrochloric acid is quite able to play its part in the pathological process, although, as already shown, hyperacid juice has a much more powerful effect.

Examination of the stomach contents by the fractional method of Rehfuess shows that while hyperchlorhydria or a high normal figure is very commonly met with in cases of duodenal ulcer in man, it occurs in less than half the cases of gastric ulcer. Thus Moynihan (1923)²³ found that 73 per cent. of his cases of duodenal ulcer had a high hydrochloric acid content and only 21 per cent. of gastric ulcer cases. Bell's figures (1922),²⁴ at Guy's Hospital and New Lodge Clinic, are appreciably higher, especially in the case of gastric ulcer—79.4 and 45.8 per cent. respectively. About one-third of all cases of gastric ulcer are hypochlorhydric or achlorhydric, and about 10 to 12 per cent. of duodenal ulcer cases. It is perhaps worthy of note in this connexion that out of 150 cases of carcinoma of the stomach occurring in the present series of 6,800 autopsies, only 2 showed any evidence of simple ulceration at a distance from the growth, while in a series of nearly 40 cases of pernicious anaemia—one of the few diseases in which achlorhydria is constant—peptic ulcer, whether gastric or duodenal, was not once met with.

The importance of what he terms the "hypersthenic gastric diathesis" in the etiology of duodenal ulcer is strongly emphasized by Hurst (1922).⁶ He points out that a certain proportion of healthy persons are hyperchlorhydric (10 per cent. of the healthy medical students examined by Bennett and Ryle, 1921²⁵), and that some of them at any rate have also hypertonic stomachs. Such individuals, more often men than women, have an inborn variation from the average normal which manifests itself in hypertonus of the stomach with active peristalsis and rapid evacuation, and hyperchlorhydria with hypersecretion. In such people the "duodenal cap," by far the commonest site for chronic duodenal ulcer, is exposed, for several hours of each day, to an undiluted gastric juice of unusual acidity, and it only requires the intervention of one of the other factors already mentioned (especially bacterial localization) for a duodenal ulcer to develop. Hurst goes further than this: he believes that a duodenal ulcer cannot develop in anybody who has not this "duodenal diathesis."

Excessive smoking, which stimulates both the secretory and the motor functions of the stomach, is regarded by both Moynihan and Hurst as an important contributory cause of ulcer.

B. ETIOLOGY OF CHRONIC ULCER.

The opinion has already been expressed that a chronic ulcer is merely an acute ulcer which has lasted a certain length of time. What, then, are the factors which prevent an acute ulcer from healing? In most of the experimental work which has been done on this subject the acute ulcers have healed with great readiness and in quite a short time (two or three weeks), and the difficulty has been, not to get them to heal, but to devise means to prevent them from healing—that is, to convert them into chronic ulcers, comparable to those met with in man.

The effect of diet has been studied experimentally by Bolton. He found that in cats a meat diet appreciably delayed the healing of acute gastrototoxic ulcers as compared with a control series of milk-fed animals. He attributes this to two factors: (a) the prolonged retention of meat food in the stomach, and (b) the more copious secretion of gastric juice induced by a meat diet.

In his next experiments Bolton first produced mechanical constriction of the duodenum in cats, and followed this up with the production of acute gastrototoxic ulcers, as before. In 10 out of 16 cats which survived these procedures, the effect was to cause a definite delay in the healing of the ulcers, which might amount to thrice the time taken for normal healing to occur. In no case, however, did a chronic ulcer result; healing was merely retarded to this quite moderate extent. Both Rosenow, and Mann and Williamson, on the other hand, have definitely succeeded in producing chronic ulcer by the methods already described, the one by streptococcal inoculations, the others by stopping the normal neutralization of the gastric contents by the pancreatic and other duodenal secretions.

Does the experimentally demonstrated relationship between delayed emptying of the stomach and delayed healing of acute gastric ulcer apply also in man? There is a certain amount of evidence that it does. Ulcers of the pyloric portion of the stomach are very liable to be associated with some degree of reflex pyloric spasm, with resulting undue retention of acid contents. Bolton and Goodhart (1922)²⁶ have further shown that pylorospasm tends to interfere with the regurgitation of alkaline duodenal contents into the stomach, and so to delay the process of intragastric neutralization, which according to Boldeyreff (1915)²⁷ is the normal method of control of hyperacidity. Both pyloric spasm and the hyperacidity which often accompanies it tend to induce hypermotility, while the ulcer itself is frequently associated with a localized abiding spasm in its immediate neighbourhood. It is reasonable to suppose that these factors exert an unfavourable influence on the ulcer.

The clinical effects of diet in promoting or retarding the healing of gastric ulcer are generally admitted, although opinions vary as to the degree of importance to be attached to this factor. The disturbances of gastric function, motor and secretory, which follow dietetic faults are of a kind which must undoubtedly interfere with the healing of a gastric ulcer whether or no they play any part in the initiation of the lesion. The mechanical effects of badly masticated food and the chemical effects of protoplasmic poisons like vinegar (Bolton) may be mentioned in this connexion.

The distribution of chronic gastric ulcers as compared with acute would seem to have some bearing on the question. Acute ulcers are widespread in distribution, although most common in the pyloric half, and they are very frequently multiple; chronic ulcers are almost invariably single, and the great majority (90 per cent. of the present series) occur along the course of the original gastric tube—that is, on or near the lesser curvature. This would seem to suggest that the factors which lead to chronicity differ in some way from those which produce acute ulcer in the first instance. The comparative fixity of the lesser curvature, and the greater degree of trauma and friction from stomach contents to which the "Magenstrasse" is subjected may possibly explain, at least in part, why acute ulcers in this situation are more liable to become chronic than those in other parts of the organ. Radasch's (1923)²⁸ recent study of the distribution of the oxyntic cells of the

stomach fails to show any relationship to the distribution of either acute or chronic gastric ulcers.

In the case of the duodenum, the lodgement of highly acid juice for considerable periods of the day in the "duodenal cap" is probably an important factor in the conversion of acute into chronic ulcers. This would account for the preponderating localization of chronic ulcer in the first part of the duodenum in spite of the fact that acute duodenal ulcers are much more widely distributed.

[The references will be found at the end of Part II, to be published next week.]

The Bradshaw Lecture

ON

ANGINA PECTORIS: SOME POINTS IN PROGNOSIS.

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

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PROGNOSIS is one of the more fascinating aspects of medicine. It is a balancing of the probabilities and demands wide experience, intimate knowledge, and a keen sense of proportion combined with an instinctive capacity for weighing imponderables. Familial tendencies, the past history of the patient, the objective signs of actual disease, and those subtle but significant subjective discomforts pointing to depreciation of function must all be passed in review and their relative importance weighed before venturing on a verdict.

There are few conditions in which a clear statement as to the future is more anxiously demanded than where pain of an anginal nature has manifested itself. For the victim is conscious that in him "the unseen seat of life, and the target of death" is mortally attacked. There is with each attack an ominous trembling of the very foundations of a man's being, which leaves behind it a shaken and apprehensive soul.

The problem of assessing the expectation of life under these conditions is most difficult, and even after careful consideration of all the facts and an attempt to view the symptoms in their correct perspective, an accurate opinion is not easily attained, and where so much is uncertain we must seek for any solid ground on which to base our opinion.

I have recently reviewed the records of 309 patients in whom the dominant feature was pain of an anginal type, in an attempt to formulate the results of my personal experience, and have dealt with them more particularly in relation to prognosis.

CAUSE OF ANGINAL PAIN.

It is not my intention to enter either the debatable ground of the essential nature of angina or of the special pathological changes which are said by some to be causally inevitable. We are now dealing not so much with the interpretation of the pain in angina as with the mortality.

It will be generally conceded that anginal pain is the resultant of two factors: (1) afferent stimuli passing from the heart and aorta, and (2) the sensitiveness of the receiving apparatus—in other words, of those levels of the central nervous system associated with the heart and aorta; and it is to Sir James Mackenzie that we are more particularly indebted for the full appreciation of the importance of this latter factor.

From the interaction of these two we have pain, and the accuracy of prognosis will depend on a careful consideration of both, and a decision as to which of the two is dominant. The more exalted the sensitiveness of the segments involved, the more susceptible to stimulation, then the less ominous the outlook and the greater the ground for hope of a satisfactory response to treatment. On the other hand, the second essential matter for investigation is the reserve power of the heart, the health of the aorta, arteries, and myocardium, and also the permanent load on the heart of