PAIN AND PEPTIC ULCER

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P A I N A N D P E P T I C U L C E R

A REVIEW OF THE LITERATURE

The origin of the characteristic pain of uncomplicated peptic ulceration has long been the subject of much speculation and discussion. Two main theories have been put forward: one that it is due to irritation of the ulcer base by the acid of the gastric juice; the other that it is due to the muscular activity, normal or abnormal, of the stomach or duodenum. A third view is that the inflammatory reaction round the ulcer with its oedema, congestion, and raised tissue tension is itself the cause of pain; the classical combination of rubor, tumor calor and dolor applying here as elsewhere in the body. Others have blamed irritation of the ulcer by coarse particles of food, distension of the stomach (Poulton, 1921) and traction on the mesentery by movement of the pylorus towards the midline (Alexis Thomson, 1909).

THE ACID THEORY

Hydrochloric acid is a highly irritant substance, which, when applied to the skin produces erythema, swelling and burning pain. It might seem self-evident that such a substance when present in the gastric juice in sufficient concentration would be bound to irritate the raw ulcer base and cause pain. There are a number of well known facts which would seem to support this view. The pain of an uncomplicated ulcer can generally be relieved by alkaline powders. Vomiting usually relieves pain and, similarly, pain is relieved by emptying the stomach and washing it out through a stomach tube. The common factor in each of these methods of relief is the neutralisation or removal of acid.

Many workers have sought to confirm the acid theory by showing that pain can be produced when hydrochloric acid is instilled into the /

the stomach through a Ryle's tube. Among the first was Talma, who, in 1884, was successful in producing pain by introducing 500 ml. of a solution of HCl 1:75 into the stomachs of two patients, one with a gastric carcinoma and the other with what was probably a peptic ulcer. A number of others have repeated the work with various concentrations of HCl, including Bonniger in 1908, and Heineke and Van Selms, also in 1908. The chief exponents of this method, and of the acid theory of pain, have been Palmer in the United States of America and Pickering in Britain. In 1926 Palmer reported a large series of 443 experiments on 109 patients with peptic ulceration. His technique was to inject 200 ml. of 0.5% HCl into the stomach and repeat the dose in half an hour if the first injection failed to produce pain. In 25 patients he failed entirely to produce pain in the course of 39 experiments. Thirty-five of these experiments were made in what he called distress free periods, that is to say the patient had had no spontaneous ulcer pain in the 24 hours preceding the experiment.

In 84 patients he was successful in producing pain in 324 experiments but even among these sensitive patients he did have failures - 70 failures in distress free periods and 10 failures actually in distress periods. Palmer admitted that 0.5% HCl was about twice the physiological concentration of acid in the gastric juice but he said he had been able to produce pain with concentrations of 0.1% and 0.2% HCl. In some experiments pain resulted when he reintroduced stomach contents which had been removed with relief during a pain period. There might be a latent period of as much as 1 hour or more between the introduction of the acid and the onset of pain, and again when the acid had been neutralised the pain occasionally took as long as 40 minutes to disappear. Distress could also be produced with 0.4% H_2SO_4, 3% acetic acid, and N/10 NaOH.

In a further series of experiments reported in 1927, Palmer investigated /

investigated the role of peristalsis and spasm in pain production, using an intraduodenal or intragastric balloon which was connected by a tube to a kymographic recording system. In addition he examined patients under the fluorescent screen after giving them barium made up in a solution of 0.5% HCl. He observed pain without contractions 198 times and pain synchronous with contractions only 19 times while recording motor activity on the kymograph. While screening his patients he noticed no phenomena during the presence of pain which were not present without it. Reviewing the position in 1934 Palmer concluded that ulcer pain arose at the site of the lesion, and that the usual stimulus was the free hydrochloric acid of the gastric juice, although it was possible that at times an adequate stimulus could be provided by peristaltic contractions or local spasm.

Bonney and Pickering, in 1946, confirmed Palmer's results. They found that 200 - 300 ml. of N/20 to N/10 HCl when injected into the stomach produced pain after a latency of about 10 minutes, the pain being relieved by emptying the stomach or by neutralising the gastric content with alkali. In the latter method there was a latent period of about 8 minutes before relief was obtained. When the stomach contents were sampled at half-hourly intervals during periods of spontaneous pain, it was found that pain occurred when the stomach contents became more acid, and disappeared when the acidity decreased. Pain never occurred in a given patient when the gastric acidity was less than a certain value for a given time. Some agreement was found between the levels of acidity producing pain following the injection of acid and those at which pain occurred spontaneously. Pickering thought that the latent period between the introduction of acid and the onset of pain could be explained by the time taken by the acid to penetrate the necrotic material in the ulcer crater before reaching sensitive nerve endings in its base.

Against this battery of evidence there is the fact that various reliable workers have failed to produce pain by injecting acid into the /

the stomach, including Hurst (1910), Schmidt (1909), Ginsburg, Tumpowsky, and Hamburger (1916), Carlson (1917) and many others. These authors have used concentrations of HCl ranging from 0.5% to 2% and even more. Another author, Boring (1915), failed to produce more than a feeling of hunger with 5% HCl. Hurst himself failed to produce pain in 6 cases of gastric ulcer when he introduced 4 ounces of 0.5% HCl into the stomach. Palmer of course used twice or four times that amount of acid in his experiments. Hurst was convinced that acid was not the direct cause of pain in peptic ulcer. In the hands of Ginsburg and his colleagues 70 ml. of 5% HCl produced a burning feeling and vomiting but no typical ulcer pain in patients with peptic ulcer. Wolf and Wolff (1943) in their wonderful series of observations on "Tom" found that a strong acid applied to the inflamed and even eroded mucosa was not painful, and there was no doubt that in their experiments the acid actually bathed the eroded area. On the other hand, pinching such an area did cause pain.

If there is argument about the ability of acid to produce pain to order, there is equally violent argument about the occurrence of pain in peptic ulcer in the absence of free acid. Palmer and Pickering brush aside reports of pain associated with achlorhydria as being unreliable or untrue. Had more frequent samples of the gastric juice been taken, had the end of the tube been in the right place, had the patient been given histamine, then at some time free acid would have been found. However that may be Hardt (1918 and 1922) noted pain when there was no free acid but when there were contractions. It is true that he does not mention whether his patients had duodenal or gastric ulcers, nor did he state where his recording balloon was situated. Ryle (1925) and Kinsella (1928 and 1948) have reported cases of gastric and duodenal ulcer who have had pain relieved by food and alkali but who have had achlorhydria. (I have myself had a patient with a duodenal ulcer who complained of spasms of pain at a time when his gastric juice contained no free acid). Alvarez notes that Winkelstein had a case of a syphilitic girl /

girl who had hunger pain relieved by food. There was no acid in the stomach and on removal the stomach was found to have gummatous lesions in the submucous layer, but no sign of any ulceration. It is well known that many people who have the typical pain of peptic ulcer have no demonstrable ulcer radiologically or even at operation. thus it would appear that "ulcer" pain can occur in the absence of an ulcer and in the absence of acid. As Alvarez remarks, "When one examines a man with hunger pain relieved by alkalies and finds an achlorhydria which persists during the eating of several Ewald meals, one should not throw out this record as meaningless and to be forgotten simply because with the help of histamine one can secure a few drops of acid. Knowledge is not obtained by rejecting embarassing data".

Clearly there are difficulties in the way of explaining peptic ulcer pain entirely on the basis of acid irritation.

Do the various motility theories fit the facts more satisfactorily?

THE MOTILITY THEORY

It was in 1892 that Ewald noted that the surface of an ulcer was distorted and the nerves irritated by the contractions accompanying digestion. In 1911, Hurst, having failed to produce pain when he poured acid into the stomachs of patients with an ulcer, propounded the theory that tension was the only true cause of visceral pain. Tension, he thought, was produced in the muscle fibres of the prepyloric region when strong peristaltic waves passing towards the pylorus actually cut off the small portion of stomach between the contraction and the pylorus from the rest of the stomach. The pressure in this part rose until it was sufficient to force the chyme into the duodenum. If for any reason the pylorus failed to relax the /

the pressure would rise still further and the tension on the muscle fibres would be even greater. Pain would be produced by the development of such tension. Hurst believed that acid played a part by stimulating peristalsis and by inhibiting relaxation of the pylorus. This effect was increased in the presence of an ulcer since the reflexes were more easily stimulated through bared nerve endings in the ulcer base.

The experimental basis for the motility theory was laid by Cannon and Washburn who by means of the balloon-kymograph technique demonstrated that hunger pains in normal people coincided with vigorous peristaltic contractions in the stomach (1912).

Ginsburg, Tumpowsky and Hamburger (1916) investigating 10 patients with peptic ulcer and using a similar balloon method of recording found that spasms of pain were associated with peristaltic contractions. Carlson (1917) made similar observations on a student with a peptic ulcer but he pointed out that the contractions were no more vigorous than the hunger contractions occurring in a normal person. He thought that the pain must be due to an increased sensitivity of the nerve endings. Hardt (1918 and 1922), by inducing his patients to swallow two tubes, one of which carried a balloon, was able to study both the motility of the stomach and the acidity of its contents. He demonstrated the occurrence of pain during contractions when there was no free acid present. Palmer himself, although wedded to the acid theory, found on 19 occasions pain associated with intense motor activity but in 198 other experiments pain was not attended by any unusual activity. The latter finding was supported by Ortmayer who failed to relate ulcer pain to contractions.

Patterson and Sandweiss (1942) made some interesting observations on 4 patients with a duodenal ulcer. They made simultaneous recordings of gastric and duodenal motility and showed after 21 studies that ulcer distress occurred only when the duodenum was active. The stomach /

stomach might or might not be active at the same time. When the patients had severe epigastric ulcer pain for 15 to 18 minutes or longer there was definite abnormality in the activity of the duodenum which passed into a state of increased tonus simulating a state of incomplete tetanus. They made the interesting observation that alkali introduced into the patient's stomach through a tube relieved the distress but had no effect on motility. These workers were not the first to suggest that there might be disordered duodenal motility - particularly in patients with a duodenal ulcer. Wilson (1928) as a result of radiological studies found in 13 of 16 cases of duodenal ulcer that filling of the duodenal cap by pressure on the abdominal wall was followed by relief of pain. In 10 of these 13, there was a high free acid in the gastric contents at the time of the experiment. The relief of symptoms was extremely shortlived - lasting in some only for a minute or so. However, Wilson thought as a result of these studies that pain was due to overaction and contraction of the caput of the duodenum. Relief of pain was due to relaxation of the muscle of the caput.

PAIN DUE TO INFLAMMATION

Kinsella has for many years championed the theory that ulcer pain is caused directly by the inflammation around the ulcer. Ivy also believed that the continuous pain of ulceration is due to congestion oedema and inflammatory reaction around the ulcer. In 1953 Kinsella strengthened his case by examining microscopically sections taken from 22 gastric ulcers. He searched for nerves in the four Askanazy layers of inflammatory tissue in the ulcer base and found that degeneration of nerves began in the fibrous layer and was complete in the granulation layer. The more superficial leucofibrinous and eosinophil-necrotic layers contained only a few ghostly remains of nerves, and moreover these two layers were shown to be impermeable /

impermeable to the acid of the gastric juice. Kinsella based this statement on the observation that leucocytes in the leucofibrinous layer showed no signs of digestion by the gastric juice nor did some meat fibres which happened to be embedded in the layers of one of the ulcers. The edges of the ulcers contained numerous healthy nerves but these were generally drawn away from the edge by the retracting muscular coat under cover of the intact but thickened submucosa. The nerves of the edge were inaccessible to gastric acid. How then could acid cause pain by irritating nerve endings in the ulcer if the nerve endings were quite inaccessible? On the other hand pain could be caused by the direct action of inflammation on the nerves in the edge of the ulcer. Kinsella went on to attempt to explain the relief of pain with food alkali and vomiting on a haemodynamic basis. He listed as being important Bernoulli's principle - which states that in a fluid in motion there is an increase of pressure when the velocity decreases, and a decrease of pressure when the velocity increases - and the principle of the branched tube. According to this second principle if the flow through one limb of a tube is increased, e.g. because of increased function requiring increased blood supply, the flow through the other limb diminishes. After a meal gastric secretion and therefore gastric blood flow increase, and Kinsella seems to think that the stomach as a whole is supplied by one limb of the tube, as it were, while the ulcer area is supplied by the other limb of the tube. Since the stomach as a whole is getting more blood at this time than usual the ulcer area will get less, with diminution in congestion and pain. He says that alkalies act in the same way by increasing secretion and blood flow. No evidence is produced in support of these statements. Another aspect of relief of pain after food is, he says, the relaxation of postural tone which follows the ingestion of food. The grip on the inflamed parts is relaxed. Later Kinsella attributes relief /

relief after vomiting to the fact that the stomach is able to rest. Filling and emptying the stomach would therefore seem to be equally effective methods of relaxing the stomach. Alkali (Carman, 1921) is also said to relax the stomach and duodenum. Acid conversely may produce gastric and duodenal spasm. In short Kinsella believes that inflammation is the primary cause of pain, while gastric or duodenal contractions increase pain by squeezing inflamed tissues. Acid he thinks produces pain by stimulating spasm. His more detailed haemodynamic hypotheses are on rather unsure ground.

The experiences of Tom, Wolf and Wolff's subject, support the theory that pain is largely due to oedema and increased tension. Normally the mucosa of his gastric fistula was insensitive to painful stimuli such as pinching or pricking but on several occasions the mucosa became grossly engorged and oedematous. For instance there was once "complete herniation of the stomach lining following an injury in a football game". The membrane became cyanotic and oedematous and remained so for 3-4 hours. The pain was intense and the mucosa was markedly tender to the slightest digital pressure. Again, when the mucosa of the stoma became red and oedematous following the use of a coarse rubber tube for feeding, contact of the mucosa with the rubber tube was painful (Wolf and Wolff, 1943).

It is well known that pain can be produced by injecting normal saline into the layers of the bowel wall exposed at a colostomy. Dragstedt and Palmer (1932) reported that a patient with a duodenal ulcer who had a laparotomy performed under local anaesthesia experienced pain when the ulcer area was pinched. Traction on the ulcer scar also produced pain, and, to complete the picture, while the traction was maintained, 20 ml. of a 5% solution of $NaHCO_3$ was injected into the duodenum with immediate relief of pain.

PAIN STUDIES

I have carried out pain studies on 26 patients all with symptoms of peptic ulceration. Fourteen of these had a duodenal ulcer, three had an ulcer deformity of the duodenal cap without a demonstrable ulcer crater, six had a gastric ulcer and one had prepyloric scarring. Of the remaining two patients, both of whom had symptoms typical of duodenal ulceration, one had a negative barium meal and the other discharged himself from hospital before a barium meal had been carried out.

A balloon-kymograph technique was used, and studies were made both of gastric and duodenal motility and of gastric acidity. The apparatus consisted of a radio-opaque Miller Abbott tube, a Ryle's tube, a water manometer with an ink writing float recorder and an electrically driven kymograph with a continuous paper attachment. This last device allowed one to take continuous records for hours on end. A latex rubber condom was tied to the end of the Miller Abbott tube in such a way that the distal part of the condom projected beyond the end of the tube and contained 6 ml. of mercury while the proximal portion of the condom was tied over the tube to form a balloon which could be inflated with air through the appropriate lumen of the tube. The balloon was 2" long and held 40 cc. of air without distension. The weight of the mercury helped to carry the end of the tube towards and through the pylorus into the duodenum when it was desired to record duodenal motility. Several holes were made in the wall of the suction half of the tube just proximal to the balloon. The Ryle's tube was tied to the Miller Abbott tube so that when the former lay in the duodenum the tip of the latter would be in the lower part of the body or antrum of the stomach. Thus fluid could be introduced into or aspirated from both stomach and duodenum while duodenal motility was being recorded. When gastric motility was being recorded, the Ryle's tube was usually dispensed with.

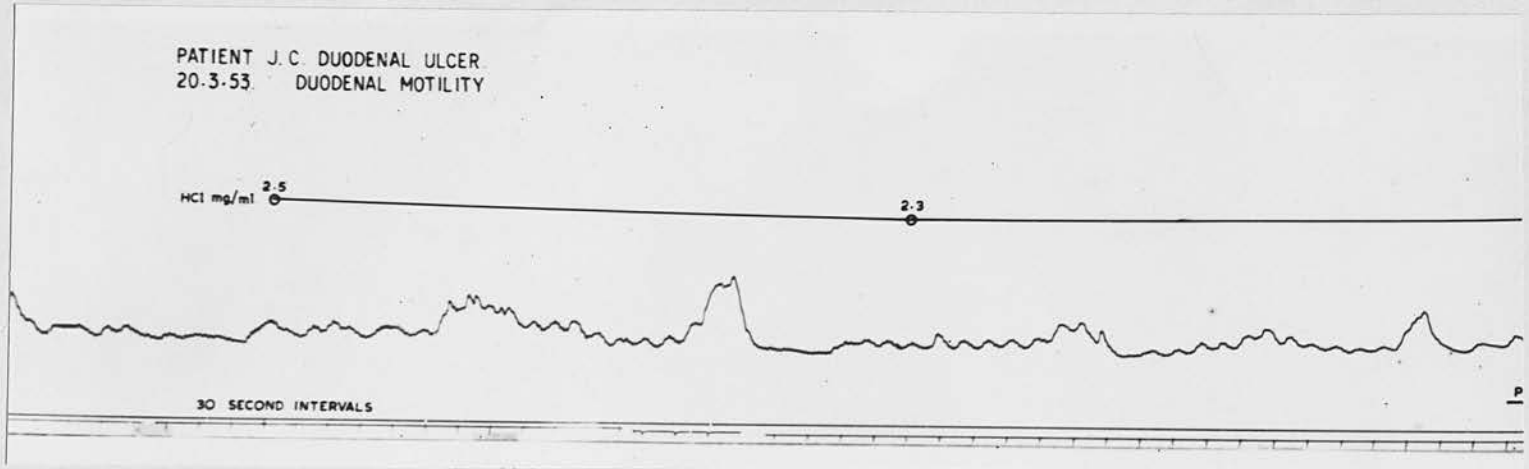
It /

It is well known that duodenal intubation is frequently attended with some difficulty. The technique used in these studies was as follows: The soft palate and oropharynx were sprayed with 2 ml. 2% xylocaine hydrochloride. After a few minutes, when the anaesthetic had taken effect, the patient swallowed the tubes and then lay on his right side for 45 - 60 minutes to allow the weight of the mercury to carry the end of the Miller Abbott tube towards the pylorus. At the end of an hour the patient was screened and in 50 - 60 per cent. of cases the end of the tube had by then passed through into the duodenum. The balloon was inflated and could be seen as a translucency on the screen. Its position in the first or second part of the duodenum was thus checked. The Miller Abbott tube was then connected to the water manometer and the balloon inflated with air - 20 c.c. for duodenal records and 40 c.c. for gastric records. During the period of the record the patient lay comfortably on his back and read a book. He made a signal at the onset or disappearance of pain.

Spontaneous Pain.

Pain which was identical with their usual "ulcer" pain occurred spontaneously in the course of motility and secretion studies on 16 patients. Of these 16 patients 12 had a lesion of the duodenum either proved by X-Ray - ulcer (9), ulcer deformity of the cap (2) - or assumed from the history (1); and 4 had a gastric ulcer. Ten of the 12 patients with a duodenal lesion experienced pain while duodenal motility was being recorded and 2 felt it while gastric motility was being recorded.

The records obtained from patients with a duodenal lesion are equally confusing whether the motility was recorded from the duodenum or the stomach. There was certainly no constant relationship between either motility or acid and pain. In only 2 of the 12 patients did pain come in spasms which coincided with powerful peristaltic /



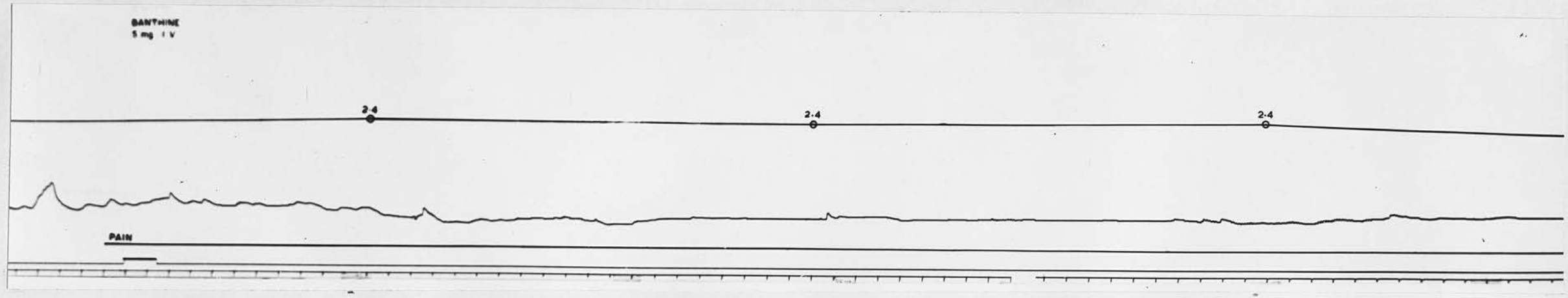


Fig. I.

J.C. Duodenal Ulcer. Record of duodenal motility showing pain in the absence of contractions following Banthine.

peristaltic contractions. The pain in the other ten was steady and boring.

The following details from the records will illustrate the varying relationship between motility and secretion and pain.

J.M. Duodenal cap deformity.
Duodenal motility recorded.

At the beginning of the record, during quite minor motor activity, there was continuous pain which lasted for 25 minutes and stopped 6 minutes after the onset of vigorous peristaltic waves. The peristalsis continued during the subsequent pain free period. Later pain occurred when motility was limited by Banthine to insignificant tonus changes and a few minute contractions. The free acidity had fallen (from 1.65 mg. HCl/ml. of gastric juice to 0.9 mg.) but was tending to rise again (to 1.0 mg.) when the first attack of pain stopped. A second attack of pain began when the acidity had fallen still further (to 0.65 mg.). On the other hand, the end of a third attack of pain coincided with a fall in acidity.

J.C. Duodenal Ulcer.
Duodenal motility recorded. (See Fig. I)

There was a long continuous spell of pain in this case which lasted for 90 minutes. At times during this period motility was completely absent following an intravenous injection of Banthine. The free acidity was high during the pain period, but it had been equally high, or higher, for 30 minutes before the onset of the pain. Twenty-six minutes elapsed after the neutralisation of the stomach contents with sodium bicarbonate before the pain disappeared.

J.L. Duodenal Ulcer.
Duodenal motility recorded.

Nine spasms of pain lasting 1 minute or less were seen to coincide with peristaltic contractions. These spasms were superimposed on a constant dull ache. Other spasms of similar duration did not coincide with particular contractions. One spell of steady pain which had lasted for 13 minutes was relieved within $2\frac{1}{2}$ minutes by the injection into the stomach of sodium bicarbonate. The injection /

injection and the relief of pain coincided with the onset of duodenal spasm which lasted for 6½ minutes without causing further discomfort. Previous duodenal spasm had been associated with hunger pain which was not as severe as pain which he had at other times during the record and which was of a different quality. The free acidity reached its lowest level during this particular pain period. The bout of steady pain which occurred at the beginning of the record stopped while the acidity remained constant at its highest level during the recording.

A.S. Duodenal cap deformity.
Duodenal motility recorded.

Pain occurred in two spells of 13 minutes and 24 minutes respectively. During the first spell the free acidity rose from about 2.5 mg.HCl/ml. gastric juice to 2.75 mg. and it was still rising when the pain stopped. It then remained between 2.7 and 2.8 mg. during the subsequent pain free interval. Motility was extremely brisk before the two attacks of pain, but during the attacks it consisted of minimal tonus changes. It is true that the pain free period coincided with the period of least motor activity of all, extreme duodenal depression having been induced by an intravenous injection of homatropine methyl bromide. It might be argued that the stomach was equally depressed and consequently was not pumping acid into the duodenum. Why then was there no pain when duodenal activity was extremely brisk and free acidity was 2.5 mg. HCl/ml? Was it because the stomach was again inactive, or had the acid not had long enough to act on the ulcer area in the duodenum - assuming for the moment that acid has something to do with pain?

J.H. Duodenal Ulcer.
Duodenal motility recorded.

In this record there was a long period (2 hours and 10 minutes) of very brisk peristaltic activity, and one spell of duodenal spasm, without any pain whatsoever. During this time the free acid reached the /

the high level of 3.55 mg. Pain then occurred during motor activity which was certainly no greater than before and when the acidity was no higher than 2.3 mg. The pain finally disappeared 12 minutes after sodium bicarbonate had been injected into the stomach. This injection was followed immediately by duodenal spasm.

J.D. Duodenal Ulcer.
Duodenal motility recorded.

An attack of steady pain lasting 12 minutes was felt during a period of marked activity and raised tone. The tone had decreased slightly 5 minutes before the pain stopped but when the tone increased again during the succeeding 15 minutes and the activity was even more marked than before, there were only two brief attacks of pain lasting less than 1 minute each, which did not coincide with any particularly marked contraction. Antral acidity fell gradually during the 27 minutes just described from 1.3 mg. to 0.95 mg. The fall in acidity might have been held to be sufficient to explain the absence of steady pain during the second half of the period but the recurrence of two spasms of pain unaccompanied by any outstanding contraction is left unexplained.

H.S. Duodenal Ulcer.
Duodenal motility recorded.

There were two bouts of pain in this record, one lasting 6 minutes and the other 23 minutes. The first attack was accompanied by moderate peristaltic activity. There was then a pain free interval of 15½ minutes during which duodenal spasm was recorded. Pain then returned and while there were 5 peristaltic contractions and constant tonus changes during the painful period, neither tone nor contractions were as strong as they had been during the pain free period. The acidity changes were perhaps suggestive in this case. Free acid wss in excess of 1 mg. during the first pain period but it fell to 0.95 mg. when the pain disappeared. It rose again to 1.85 mg. and four minutes after this level was recorded pain started again. The acidity fell once more and when it reached 1.05 mg. the pain stopped.

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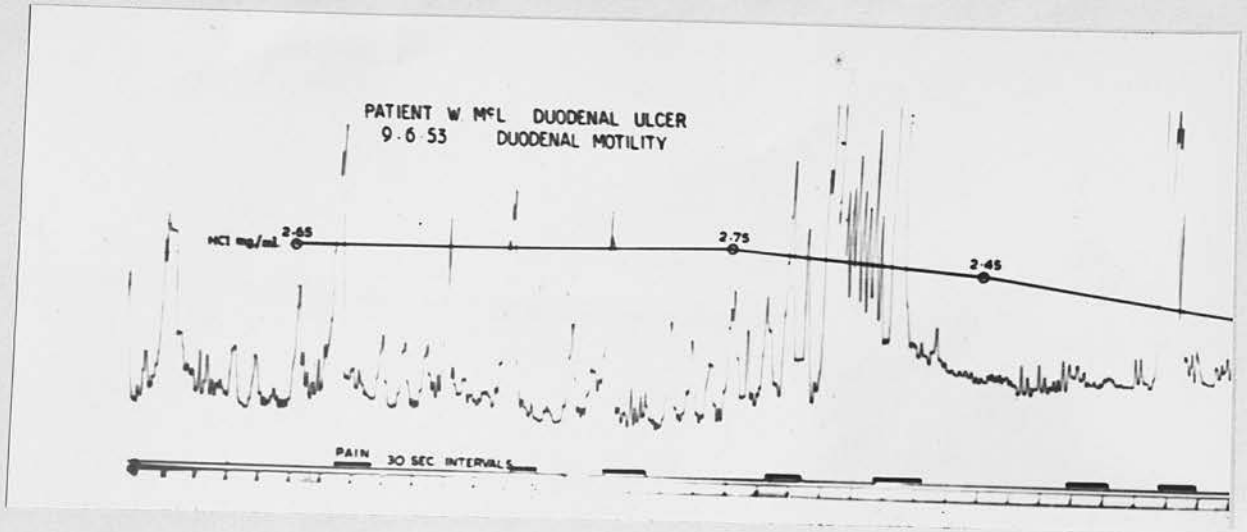

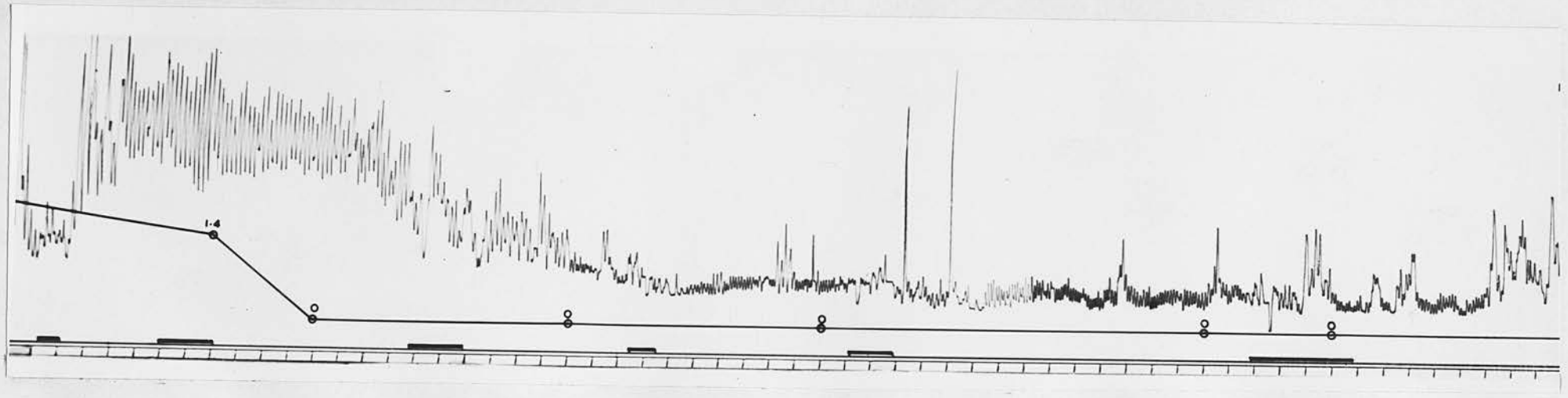

Fig. II.

W. McL. Duodenal Ulcer. Record of duodenal motility showing spasmodic pain during period of achlorhydria.

Unfortunately for the theory, eight minutes later the acidity was found to be 2 mg. without any recurrence of pain. Was this because motility had been almost eliminated by Banthine?

W.M. Duodenal Ulcer.
Duodenal motility recorded. (See Fig. II)

In this record there were six spasms of pain lasting less than 1 minute which coincided with powerful peristaltic contractions. There was also an attack of pain lasting $6\frac{1}{2}$ minutes which was steady and continuous and during which there were nine peristaltic contractions which did not produce any spasmodic increases in the severity of the pain. Also, during an episode of duodenal spasm lasting 6 minutes, pain occurred only during the second minute. Other spasms of pain lasting 1 minute or less were noted when activity was quite minimal and moreover when there was no free acid in the stomach. Five such attacks of pain occurred during a period of achlorhydria lasting 38 minutes.

The findings were similar in another record obtained from the same patient several days later.

B.D. Duodenal Ulcer.
Gastric motility recorded.

There was moderate motor activity throughout the record - tonus changes and small peristaltic waves. There seemed to be no correlation between the motility and the attacks of pain. It was possible to relate the onset of pain to the peak of free acid (3.2 mg.) which preceded it by a few minutes. Cessation of pain coincided with a fall in free acidity to 2.3 mg. On the other hand there was a spasm of pain later when the acidity was only 1.9 mg. It is possible that this spasm was caused by a duodenal contraction.

W.B. Duodenal Ulcer.
Gastric motility recorded.

It was impossible to correlate pain with acidity in this case. Pain was felt during a period when the free acid concentration was rising (1.8 mg. to 2.25 mg.), but the pain then stopped while the acidity /

acidity remained at 2.25 mg. or above for the next 24 minutes. There were tonus changes in the stomach during the painful period, but the maximal activity developed in the five minutes immediately following the cessation of the pain.

J.W. Gastric Ulcer.
Gastric motility recorded.

There was a spontaneous attack of constant pain which lasted for 21 minutes in the early part of this record. During the first 11½ minutes of the attack there were five peristaltic waves of varying size in addition to tonus changes. With the abolition of peristaltic waves with Banthine the pain became much less severe but did not entirely disappear until 8 minutes after the injection. During this latter period of 8 or 9 minutes motility was almost absent. When the pain did disappear the level of free acid in the stomach remained high.

E.F. Gastric Ulcer.
Gastric motility recorded.

There was perhaps some correlation between pain and acidity in this record, though the level of acidity (0.5 mg, HCl/ml.) apparently required to produce pain was not very high. When the free acid concentration dropped to zero pain became slight while motility was unaltered. The pain did not disappear completely until 15 minutes after the onset of achlorhydria, but it returned when the acid level once more approached 0.5 mg.

Pain was most severe when the acid concentration was highest (0.6 mg.) and the motility minimal.

Artificially induced Pain.

A further series of studies was made on the production of "ulcer" pain by injecting hydrochloric acid into the stomach or duodenum of patients with peptic ulceration. Twenty-one patients were used in this part of the investigation, six with a gastric ulcer, thirteen with ulceration or deformity of the duodenum and two with a history suggestive of duodenal ulceration.

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The practice was to inject 100 ml. of 0.5% HCl into the stomach of each patient in the first instance. The injection was given slowly over the course of 3-5 minutes. This dose was given to all of the patients except two who were given 80 ml. Thirteen of the 21 patients developed epigastric pain after this single injection - 4 of the 6 patients with gastric ulcers and 9 of the 15 with duodenal lesions. Another three patients developed pain when the injection was repeated. Of the total 21 patients only 4 failed to develop pain after the injection of acid into the stomach. One of the four had not had spontaneous pain in the preceding 24 hours and was consequently, according to Palmer, in a pain insensitive phase. All the other patients were in a pain sensitive phase. It is interesting to note that in two patients an initial injection of 100 ml. 0.5% HCl produced pain but a second injection, 12 minutes later in one and 18 minutes later in the other, did not.

The pain was generally of the usual ulcer type but it varied considerably in severity as compared with the patient's spontaneous pain. Occasionally the pain was burning in character and unlike the patient's own pain.

The average interval between the injection of acid into the stomach and the onset of pain was 6 minutes (1-11) in cases of gastric ulcer and 5 minutes (1-17) in cases of duodenal ulcer.

In five patients with duodenal ulceration or scarring 0.5% HCl was injected directly into the duodenum, the volume of acid ranging from 30 to 100 ml. Pain was produced in all 5 cases though in one only when an initial injection of 40 ml. was followed by a second injection of 60 ml. In another patient when acid was later injected into the stomach no pain resulted, although a duodenal injection produced pain within $1\frac{1}{2}$ minutes. The time intervening between the injection of acid and the onset of pain when the acid was injected into the stomach was compared with the delay when the injection was made direct /

direct into the duodenum in two patients. In both, the interval was much shorter when the acid was injected into the duodenum. In one case the time intervening between the injection and the onset of pain was 2 minutes when the acid was injected into the duodenum and 7 minutes when it was injected into the stomach. In the other case the duodenal injection was followed by immediate pain, whereas 5½ minutes elapsed before pain occurred after an injection of acid into the stomach.

In view of the suggestion that HCl caused pain by increasing gastro-duodenal tone and spasm (Kinsella, 1948), the frequency of such increased motor activity was noted. Hydrochloric acid was injected into the stomach on 31 occasions. On 16 of these occasions there was a definite increase in tone with or without an increase in the strength and number of contractions. On the other hand 11 injections were made without causing the least change in tone and another 4 were followed by a very doubtful or minimal increase in motor activity. Of 6 injections made directly into the duodenum 4 produced a marked increase in motor activity. One injection caused pain without increasing duodenal tone or activity and there was a similar lack of correlation between the incidence of increased motor activity and the presence or absence of pain when the acid was injected into the stomach.

The effect of a 9% solution of sodium bicarbonate on motility when injected into the stomach or duodenum was also investigated. The volume of the injection varied from 30-60 ml. Eighteen injections were made into the stomach and 9 of these were followed by an increase in motor activity. This increase amounted to duodenal spasm lasting 6-7 minutes in two cases. Two of the six injections made into the duodenum were followed by increased tone and movement. Pain was relieved in one case in spite of the development of duodenal spasm immediately following the injection.

These /

These observations are at variance with the view that alkalies relieve pain by relaxing the postural tone of the stomach and duodenum (Carman, 1921).

There was no doubt that pain could be produced by the injection of 0.5% HCl and it was frequently elicited in the absence of motor activity, the gut having been put at rest with Banthine. Pain so induced could be relieved by the injection of sodium bicarbonate, whether or not this provoked increased motor activity.

Discussion.

From these varied observations on pain, spontaneous and induced, it is obvious that neither motor activity nor irritation by acid can be the sole cause of the pain of peptic ulcer. It is true that spasms of pain were observed which coincided with peristaltic waves of the duodenum in a patient with a duodenal ulcer deformity. It is also true that another patient was free of pain when motility was reduced to a minimum and at a time when the acid level remained high. On the other hand some patients had pain which was quite unrelated to motility. This pain would stop for 10 minutes or more and then resume while contractions continued uninterrupted. Even duodenal spasm could occur in patients with duodenal ulceration without causing pain. It could hardly be argued that the ulcer was insensitive since a matter of a few minutes before or after the patient was in pain. During one episode of duodenal spasm a patient had pain for a minute but the pain then disappeared while the spasm continued for another few minutes.

It has been suggested that acid causes pain by causing spasm (Hurst, 1911, Kinsella, 1948) but 35% of the injections of 0.5% HCl failed to produce any increase in tone or movement and the majority of these injections were followed by pain. The converse of this argument - that alkaline powders act by relaxing tone - is difficult to /

to sustain since 50% of 18 injections of sodium bicarbonate were followed by increased tone or movement, usually with relief of pain. In one case the injection was followed by duodenal spasm, relief of pain and spasm coinciding.

The case for the acid theory of pain is not much better. Certainly in some of the experiments there was a relationship between increasing acid concentration and the onset of pain and also between decreasing acidity and relief of pain. Other experiments, however, showed no such relationship. Pain often disappeared when the acidity remained constant or even increased. Indeed pain was sometimes intermittent when no change could be detected in either acidity or motility. Relief of pain with sodium bicarbonate was usually possible but there was sometimes a delay of 30 minutes before relief was obtained. Palmer also encountered long delays between the giving of alkali and the relief of pain. He found similar delay between the injection of acid and the onset of pain. If one has to allow for such long latent periods it makes interpretation of spontaneous pain rather difficult because the acid level in the stomach is constantly varying. Pickering took samples of gastric juice half hourly but during this period there could have been considerable variations in acidity. One has seen the acid concentration rise from 2.3 mg. HCl/ml. of gastric juice to 3.35 mg. and fall again to 2 mg. within the space of half an hour. The pain sensitivity of the ulcer may not be sufficiently great to follow such changes quickly. If pain takes some time to develop and reach its acme it is difficult to explain why it may disappear for a short time and then return while the acidity remains constant. Pain can occur in the absence of free acid as was shown in one case when there were several spasms of pain during a spell of achlorhydria lasting 38 minutes.

Motility and acid may each cause pain but they obviously do not account for all the facts. It is possible that Kinsella may be right /

right in ascribing the intermittency of the pain to alterations in blood flow through an ulcer area which is sensitive because of inflammation and oedema. Much, however, remains to be done to prove this theory.

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