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THE PLACE of HISTIDINE in THERAPY.

by

Lieut. William Thomson,
M.B., Ch.B., R.A.M.C.

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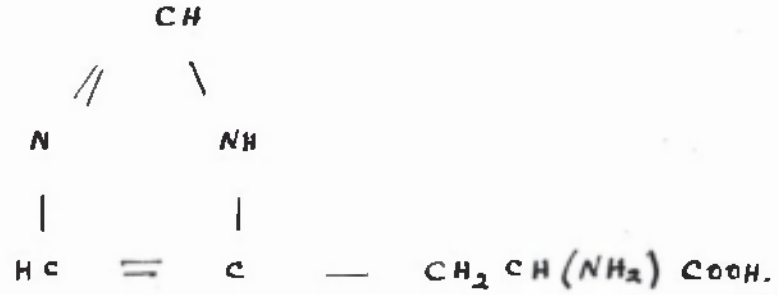
THE PLACE OF HISTIDINE IN THERAPY.

COMPOSITION and PHARMACOLOGY of HISTIDINE.

Histidine is B-iminazolyl-a-amino propionic acid, the decarboxylisation of which produces histamine; it is represented by the formula - .



It was first discovered by Kussel in 1896 among the decomposition products of the protamine of sturgeon testes, but it was not until 1904 that its structure was definitely determined.

Histidine is a constituent of most of the simple proteins. It is found in a great variety of foodstuffs such as beef, eggs, fish and milk. It is found in large quantities in blood, and commercially it is prepared from this source by acid hydrolysis and mercury precipitation. Owing to the presence of the glyoxaline nucleus, histidine cannot be synthesised in the body. In contradistinction to the well known metabolism of the animo acids (oxidation, deamination in the α position), Edlebacher has found that histidine is broken up in the imidazol nucleus by the liver

ferment histidase. Intermediary products are glutamine acid, apparently also arginine and ornithine amino acids which are according to Knebs indispensable for the synthesis of urea in the liver.

Owing to the widespread occurrence of histidine containing proteins in the common foodstuffs, it is difficult to imagine a condition where there is a deficiency in the intestinal contents.

Certain of the amino acids, for example tryptophane and histidine, are recognisable as being essential for the maintenance of normal nutrition. The exact mechanism of the action of histidine is unknown. Eads suggests that there may be some explanation in its essential rôle as a factor necessary to cell integrity and repair, and in the causation of a secretion rich in the protective and acid combining mucin.

Frommel concluded from his experiments on guineapigs that histidine has no harmful action on the heart of warm-blooded animals, and that there need be no fear of heart failure in human subjects after large doses.

In 1933 Weiss and Aron published a paper, reporting the effect of parenteral injections of amino acids in the prevention and healing of experimental peptic ulcer. They made use of the Mann Williamson operation for the production of experimental ulcers in dogs. In this operation the

pylorus is sectioned, and the distal end inverted. Next the jejunum is cut across a few centimetres distal to the ligament of Treitz. The distal end is now anastomosed to the pylorus, and the proximal end anastomosed to the ileum near its termination. The result of this operation is that the gastric contents are expelled from the stomach into the jejunum without becoming mixed with the secretions poured into the duodenum. These secretions - the bile, the pancreatic juice, and the duodenal juice - drain into the ileum.

So the possible protective mechanism of the duodenal mucosa is eliminated by the substitution of jejunal mucosa.

They found that ulcers developed just distal to the pylorus, after one to four weeks. Severe nutritional disturbances occur, the animals have profuse diarrhoea, often with associated melaena. They become anaemic and cachetic, and finally death supervenes from emaciation. The absence of duodenal juice affects the digestion of proteins, and Arom and Weiss contend that the ulcers are caused by the lack of certain amino acids. Some people hold that the ulceration can be explained by the repression of the regurgitation of duodenal contents into the stomach.

The proteins reach the jejunum in the form of polypeptides, but cannot be broken down any further into the amino acids, because the jejunal secretion is deficient in

the necessary pancreatic trypsinogen. Weiss and Aron claim that histidine, cystine, lysine and tryptophane are the four amino acids which cannot be synthesised by the organism.

The operation was carried out on five dogs; two were kept as controls, and the remaining three animals received daily injections of a mixture of histidine and tryptophane. The two control animals lost weight, had melaena and became very anaemic. One of them was killed after three weeks, and post mortem examination revealed the presence of four small ulcers. After five weeks the other control animal died, and autopsy revealed the cause of death to be perforated ulcer. Of the three animals receiving injections all lost weight, became anaemic, but had no melaena. One of them was killed at three weeks, one at 6 weeks, and one at ten weeks after the commencement of the experiment. Post mortem examination of these dogs failed to reveal any evidence of ulceration.

In later experiments Weiss and Aron found that injections of tryptophane or lysine did not prevent ulcers developing, but injections of tryptophane and histidine combined, or histidine alone did. Again the dogs became anaemic and emaciated, but never developed melaena. Post mortem examination did not reveal ulcers.

It was found that as cystine was too difficult to inject it could not be experimented with.

REVIEW of CLINICAL EVIDENCE as to ACTION of HISTIDINE.

Following the experimental work on dogs, Weiss and Aron undertook clinical investigations, first with the administration of histidine and tryptophane, then with tryptophane alone, and then with histidine. They described 8 cases treated with histidine and tryptophane injections. The patients were put on an ample ordinary diet, and during the course of treatment were given 20 injections, one injection of 5 ccs. daily. The immediate results were very promising. They found that the patients tolerated a normal diet almost from the beginning of the treatment; nausea and vomiting stopped, and pain disappeared; in the case of recent ulcers, after two or three injections; in the case of duodenal ulcers, after 6 or 7 injections. Haemorrhage was quickly arrested, and the general condition, including body weight, improved.

The results were not satisfactory in two cases where tryptophane 2% alone was used, but it was found that a 4% solution of histidine was just as effective as a mixture of histidine and tryptophane.

Seven patients were treated with histidine alone. 15-20 injections sufficed to produce complete relief of symptoms in all the cases. Again a normal everyday diet was given and no other therapeutic measures used. They concluded that injections of tryptophane and histidine are

well tolerated, and that absorption is very rapid. Also they concluded that gastric acidity is reduced in ulcer patients treated with histidine, but not influenced in normal patients. That there is a marked beneficial effect on gastric function and that the emptying time of the stomach is accelerated, spasm and hypersecretion disappears. However, they noted that an old indurated ulcer may persist radiologically despite clinical improvement.

Blum was among the early writers to report satisfactory results with amino acid treatment. He found that patients tolerated a normal diet even during the crisis, and that vomiting, nausea, and digestive disturbances show a rapid improvement.

Lenormand reported 18 cases treated with histidine, every one successfully.

Bogendörfer tried histidine in 50 cases. The cases included typical gastric ulcers, diagnosed by X-ray examination as well as cases in which the existence of a gastric or duodenal ulcer was suspected by means of clinical findings. Approximately 30 cases of ulcer, proved by X-ray examination, were in the series. He noted that pain disappeared after a few injections, and that the patient could be put on a normal diet in a very short time.

Weiss reported 91 cases treated over a period of 18 months. In these cases no other medicinal agents were used,

and no special diet was given either during, or after the treatment. In every case he stated there was a gradual but rapid cessation of pain, and occult blood became no longer traceable in the faeces. He expressed the opinion that success was not to be expected in duodenal ulcer complicated by pyloric stenosis, and advised that histidine treatment be postponed when severe gastric haemorrhage was present.

Deloyers administered histidine to 10 patients suffering from gastric and duodenal ulcers. In 7 cases the symptoms rapidly disappeared; in one they were alleviated, and in two patients no effect was noted. He drew attention to the rapid alleviation of pain which sets in between the third and seventh injection. He noticed an increase of weight in most cases, and pointed out that this must not be attributed to a specific action of the medicament, but to the normal routine diet which the treatment permits, and also to an improved state of toleration for the food. He concluded that larostidin therapy possesses no contraindications, offers no risk, and is painless. It allows the patient to pursue his social activities, and does not compel him to submit to a tiresome diet often difficult to carry out.

Hessel describes 24 cases, 18 of duodenal ulcer and four of gastric ulcer. HCl and X-ray examination were carried out before and after treatment in each case. He

found that HCl secretion was not affected when normal or subnormal. In 11 cases of hyperacidity histidine produced no change in 7, but restoration of normal conditions in 4 patients. Gastritis was found to be present in 9 cases and was relieved in 4. Body weight increased in 18 out of 22 patients. X-ray examination after treatment revealed the absence of ulcer in 16 cases, with reduction of size in the other 6.

Bulmer, in 1934, published the first British report on histidine therapy, in 52 cases of peptic ulcer. As far as possible, histidine was the sole treatment, and except in three cases the treatment was ambulatory. No instructions about diet were given, and no medicines were ordered. A number of his patients remained at work and special arrangements were made to enable them to have injections during their leisure hours. In all but one patient, X-ray control was available. Radiography was carried out before treatment, immediately afterwards, and at intervals thereafter. A follow-up in 32 cases was reported.

He did not meet with any local or general reactions to histidine, and reported that in two cases 20 ccs. were given daily without any ill effects. In his summary he reported the immediate results of histidine therapy, expressed in percentages, as being (a) 58% of symptomatic cures with disappearance of the abnormal X-ray findings, (b) 19% of

symptomatic cures with some persistence of some radiological evidence of ulcer. (c) 23% failures.

In the follow-up of 32 cases, 3 relapsed and one of the apparent failures improved. Gastric ulceration seemed to be more amenable to treatment than duodenal ulceration, and cases with a short history seemed to react more favourably than those with a long history. While refraining from drawing final conclusions, he expressed the opinion that the results so far, seemed to be better than those obtained by more orthodox methods, and quicker in achievement, whilst treatment on ambulatory lines had much to commend it.

Volini and McLaughlin published a preliminary report on 21 patients suffering from peptic ulcer, with special reference to the constant finding of a quantitative reduction in fasting and stimulated gastric secretion during and after the treatment. 15 to 36 injections of histidine were given, and the diet was generous, and tended to contain an excessive amount of roughage. It included coffee, tea, candy and nuts. All their patients smoked and were encouraged to do so. The patients were ambulatory in hospital doing the work of orderlies. They found that symptomatic relief was obtained in all the patients very quickly. Subjective changes after 2 to 12 injections were found to correspond with changes in the gastric secretion. There was a decrease in the retention amount, with reduction in the

acid titer and quantity of the fasting and stimulated gastric secretion. Success was met with in every case treated up to the time of the report, but no follow-up was given.

They concluded from their observations, that the parenteral use of histidine produces rapid improvement in patients with gastro-duodenal ulcer upon liberal diets and while ambulatory. Pain, vomiting, hypersecretion and retention quickly improve or disappear. Appetite and weight increase. The fasting and stimulated gastric secretion shows a decrease in amount, and a decrease in the free and total acids. This decrease persists throughout the treatment, but tends to rise in the latter part of the treatment, and when it is discontinued.

Stolz and Weiss. to my mind, made the most important contribution to the literature so far, when they published their experiences in the treatment of 60 cases of gastric and duodenal ulcer, extending over 2 years. 42 of the patients were treated with histidine injections only, the remaining 18 being surgical cases, in which histidine was used prophylactically to prevent a relapse.

Of the 42 cases the majority had tried the whole scale of anti-ulcer treatment, without any marked success. Those with refractory ulcers of long standing had no remissions, such as generally occur in these cases, while in the less severely affected patients, periodic crises recurred at

short intervals, in spite of the therapeutic measures applied. Several of the jejunal ulcer cases had already undergone repeated operations including in 2 cases an extensive gastro-pylorectomy.

21 consecutive daily injections were given at first. Then, if renewal of symptoms occurred, a further course of 21 injections was given. Later they modified this, and after the first series of injections, a new series was given, after a rest of 6 weeks. Experience made them decide that it was not advisable to wait for the return of symptoms, but to give prophylactic treatment at least twice a year, or even three times a year, if it was thought that the ulcerative process was very active.

Histidine was the only therapeutic agent, except in the case of patients in which the ulcer was accompanied by spastic pylorostenosis, when atropine gr.1/100 was given. Diet was very liberal, but tobacco and alcohol were forbidden on principle.

These immediate results can be expressed in the following table. In a 'good' result there was a complete disappearance of all painful symptoms, in a 'fair' result only certain symptoms were relieved.

Type.	No.	Good.	Fair.	Negative.
D.U.	18	15	1	2
G.U.	16	14	1	1
J.U.	8	8	-	-

Only 16 patients were controlled radiologically. In 7 of these patients there was complete disappearance of all radiological signs and all functional disturbances; in 6 there was considerable improvement, and in 3 no apparent change.

In 13 cases gastric acidity was estimated before and after treatment, showing considerable diminution in 10 out of 13 cases.

The general condition of the patients was always improved, appetite increased, and there was a gain in weight of from 2-16 lbs.

Follow-up in 21 cases is reported with the following results:- four patients were clinically cured after 21 injections, 18 months after treatment. Nine cases relapsed immediately after treatment was stopped, but a second series of injections brought about a prolonged remission. Three cases were given short series of injections after 6-8 months without any relapse being waited for.

Two cases were complete failures; so out of the 16 cases only 4 had not relapsed after the initial treatment.

They expressed the opinion in their conclusions that the action of histidine on the gastric mucosa could be compared with that of a hormone or vitamin, and that it seemed to favour cicatrisation of the ulcer. They leave the question open as to whether other therapeutic measure should be adopted also.

Smith reported a series of 12 cases fulfilling the following criteria, (a) History suggestive of gastric ulcer, (b) Exclusion of cases obviously surgical, (c) Unequivocal radiological evidence of ulcer of the lesser curvature.

His patients were allowed to be up and about, and ordinary diet was permitted without restriction. Seven cases were treated in hospital, but allowed up; five cases were treated ambulantly. He reported no case in which there was failure to gain substantially in weight, or in which the function of the gastro-intestinal tract did not improve. In cases where there had been retention due to pyloric spasm, the emptying time improved. Flatulence proved an obstinate symptom and was completely relieved by the administration of histidine tablets containing .2 grm of histidine.

He reported that in his series, striking radiological results were obtained, and in every case the X-ray was normal after treatment. No follow-up was reported, but one patient in the series relapsed after two months, and showed radiological evidence of ulcer. Four injections of histidine were given, and he felt quite well - X-ray examination one week later showed that the stomach was normal! The writer suggests that some means of maintaining the supply of histidine must be considered, and states that further trial and study are indicated.

Winter reported two cases of gastric ulcer and 21 cases

of duodenal ulcer.

The gastric ulcer cases showed very favourable results, occult blood disappeared in the stools, the patients put on weight, and radiologically the ulcer craters became smaller.

In the treatment of his 21 cases of duodenal ulcer, histidine was used exclusively, no other medicaments being used. He reported that the pain of nearly all the patients ceased after a few injections. A vegetable diet was given after the first week, and later on a restricted diet with additional meat. As soon as the pain had subsided, normal diet was allowed. The patients put on weight, occult blood became negative, and after the pain was relieved, they were treated ambulantly. In the cases of duodenal ulcer, X-ray examination after treatment showed little if any change. One recent duodenal ulcer showed radiological evidence of healing. There was only one recurrence during a 6-months follow-up. In this case the patient had undergone two operations previously - one for duodenal ulcer, and eight years later, for jejunal ulcer.

In his case the immediate response to histidine was good, pain disappeared, he put on weight; but occult blood remained weakly positive, and radiologically the ulcer was unchanged. He relapsed four weeks after cessation of treatment.

One patient suffering from duodenal ulcer had pulmonary tuberculosis as a co-existent condition. His temperature varied between 100 and 101, and he showed no response to larostidin. The author concluded from this case that histidine could not be expected to give results in febrile conditions!

Gastric acidity was not influenced to a large extent, in most cases he reported it was reduced after treatment, but an increase was also observed. He decided that the effect of histidine could on no account be compared to that of a non-specific protein, as no elevation of temperature and no influence on the blood picture was ever observed.

Bauke reported the result of research on 46 patients suffering from peptic ulcer, extending over 1½ years. In his opinion the main indication for treatment with histidine, is in the recent florid type of ulcer at its acute form during the crisis, whereas the recurring ulcer is less amenable.

He tried the oral administration of histidine in tablets containing .2 grm. histidine, and found that results were not obtained so quickly as with injections. He found that by simultaneous administration of tablets and injections, it was possible to reduce the time under treatment. There were no secondary effects from the tablets, the injections were painless and did not cause irritation.

X-ray examination revealed a diminution of the ulcer crater in 60% of gastric, and 40% of duodenal ulcers. Long standing ulcers showed no change by X-rays. Relapses were not observed during the 1½ years the cases were under observation, but in chronic cases the subjective freedom from pain was not complete.

His patients were confined to bed for a few days on a strict diet, and he found that the acute and painful ulcer crisis, with vomiting, nausea and gastric disturbance, disappeared in nearly every case after 4-5 injections. Haemorrhages were stopped, and weight increased. The blood picture was not appreciably altered. No histidine was present in the urine, as demonstrated by Ehrlicks diazo reaction, and the secretion of gastric HCl and pepsin was scarcely affected. He concluded that the improvement as measured radiologically is so considerable that larostidin treatment can be described as a decided advance in the non-surgical treatment of peptic ulcer.

Eade issued a preliminary report on 30 duodenal and 5 gastric ulcer cases. Practically all his cases received a minimum dosage of 24 injections and several received as many as 36. Only those cases definitely diagnosed as peptic ulcer, both clinically and radiologically, were selected.

Each patient was given an intradermal test using 1/20 cc of the histidine solution before the treatment was started.

The gastric acidity was determined at various times during the treatment. No special diet or medication was followed, except in some cases where hospitalised patients were given occasional doses of alkalis or told to omit such articles of diet known to cause them trouble. A 6-months follow-up was instituted.

In his description of the cases, he pointed out that 24 of his patients had been on some other form of ulcer treatment before; 26 cases showed gastric hyperacidity before treatment was instituted; 7 gave practically normal acid figures; and in 2 cases there were low acid figures. Two cases had been subjected to previous operative procedures, one with reactivation of the duodenal ulcer, the other diagnosed as marginal ulcer.

The immediate results showed that there were no local or systemic reactions to histidine. The intradermal test was positive in 7 cases out of 27, and was positive in the cases showing the best results. The blood counts were unaffected by the treatment. The gastric acid curve remained generally unaffected except in 5 cases. In these five cases in which a marked hyperacidity was present some reduction was noted but not to normal figures.

There was a disappearance of radiological evidence of ulcer in 6 cases. In 8 cases there was a definite improvement, but in the remaining 21 little or no change was noted.

There was a distinct improvement in both the patients upon whom operations had been performed previously.

6 cases or 17% showed clinical and X-ray evidence of immediate healing.

8 cases or 22% showed evidence of clinical and X-ray improvement.

9 cases showed evidence of amelioration of symptoms, but no X-ray change.

12 cases or 34% were unimproved at the completion of a course of treatment.

Of 6 cases showing clinical and X-ray evidence of cure, three were gastric ulcers, and three were duodenal. The average history of symptoms in these 6 cases was 2½ years - much less than the average of the entire group. Symptomatic relief of distressing complaints was early - after 3 to 4 injections. None of these patients was restricted as to diet or placed on medication. Four showed a positive intradermal reaction, five showed some decline in the acid curve, but not to normal figures. All of these patients presented a disappearance of the characteristic deformities seen at X-ray examination.

In his summary he stated that peptic ulcers, non-obstructive in type, with comparatively short histories, appear to respond best to histidine injections. Gastric ulcers appear to show a more rapid improvement than do duodenal.

Rafsky reported a series of 26 cases, including 24 duodenal, one gastric, and one marginal ulcer. The diet used in those patients treated with histidine varied from a Sippy to a regular diet. With one exception the patients had rest in bed, but 75% were allowed to be up and about to some extent.

Symptomatic relief was obtained in 73% of the patients, during the period of observation, which lasted for 4 months. Marked diminution of acidity almost to the point of anacidity occurred in one quarter of the cases. The patients who did not respond were those with penetrating duodenal ulcer and niche deformity on X-ray examination.

Volini and McLaughlin issued a second report on 73 patients observed over a 6-months period. All their patients had clinically active symptomatology, and were unselected. A clinical diagnosis was substantiated by definite X-ray evidence in all patients. The diet at the beginning of treatment was low in residue, containing approximately 3,000 calories and free from condiments.

When pain was pronounced, then for the first week a bland non-residue diet was employed, but rapidly increased as subjective relief appeared. Smoking was permitted. The number of doses varied from 10 to 60. They found no indication for a repetition of the course. They had no cases of local or focal reaction, nor were they able to

demonstrate any renal injury. 80% of the patients gained weight, although a few who gained were failures. In 10% the weight remained stationary, and in 10% there was a loss ranging from 2-6 lbs.

Immediate results showed that 14 patients were not improved after 24 injections, but after finishing injections, 2 were relieved after one month and one after two months, leaving 11 failures. By the end of six months the failures had increased to 15 or 21% 58 or 79% were classified as being relieved. 27 or 37% showed complete disappearance of the radiological evidence. This included 6 of the 7 gastric ulcer patients. 10 patients or 14% showed radiological evidence of improvement after treatment. 21 patients or 28% showed no change radiologically after treatment.

Their series included 4 patients with previous gastroenterostomies, all of whom were apparently cured.

In their conclusions they stated that the percentage of favourable responses varied inversely with the duration of symptoms, and that radiological evidence of healing was more pronounced in gastric than duodenal types of ulcer.

McNeil Love reported results in 18 cases of peptic ulcer in which the ulcer was confirmed radiologically. His results showed that in 2 cases relief was doubtful, and the ulcer still persisted. In 4 cases there was considerable relief, but the ulcer persisted. In 3 cases the ulcer

was smaller, but symptoms almost entirely disappeared. In 9 cases the patients were free from symptoms, and there was no evidence of ulcer radiologically.

He pointed out that there was no doubt about the results, as the radiological and clinical examinations were conducted in a most exhaustive manner.

Kean treated a large number of cases of peptic ulcer with larostidin over a period of two years, but results were only available in 33 cases. 12-18 months after treatment, 26 of these patients were still symptom-free with ample radiological evidence of healing, and in one case in which laparotomy had to be performed, owing to another condition, direct evidence of healing was observed. He stated that dietetic restrictions are not necessary, with the exception of foods containing pips or seeds, which have an irritant action on the stomach.

In his conclusions he pointed out that histidine is a specific remedy for peptic ulcer, and that consequently results are bound to be disappointing in chronic appendicitis, cholecystitis, gastritis and neurotic dyspepsia. Further, even cases in which ulcer is undoubtedly present will not do well, if complications such as gall bladder disease or chronic appendicitis are associated with the ulcer. He is of the opinion that failure to obtain complete relief of pain within 10 to 14 days should cause the diagnosis to be reviewed.

Kirkby Martin treated a series of 41 selected patients with acute symptoms and radiological signs of active peptic ulcer, with intramuscular injections of histidine. An ulcer crater was demonstrated in 30 of the 41 cases. There were no dietary restrictions, and the patients were kept ambulatory.

30 of his patients were relieved at the conclusion of treatment, and 14 showed radiological evidence of healed ulcer while 12 showed a crater still present. 11 cases showed no change symptomatically or radiologically. After 6-12 months' observation, 13 were still symptom-free, and 26 had one or more relapses.

A control group of 40 selected cases with acute symptoms and radiological signs of active peptic ulcer were treated with the usual ambulatory diet-alkali regime. At the end of a period of 4 weeks - corresponding to the duration of histidine treatment - 31 were symptom-free. After an observation period of 10 months to one year, 16 were symptom-free, but 24 had one or more relapses. He found that histidine showed no constant effect on the HCl secretion, and that in the quantity used it appeared to be harmless. He concluded that the clinical improvement following histidine therapy in acute peptic ulcer appears to be symptomatic and transient.

Sandweiss at the same time reported his observations

on a series of 69 ulcer patients. In the first instance 23 of these patients were treated with histidine, and 46 with the usual diet-alkali regime. Those patients not responding to histidine were put on the diet-alkali regime (7), and those not responding to the diet-alkali regime were put on histidine treatment. So in all 40 patients were treated with histidine and 53 with diet-alkali regime.

It was found that the patients started on histidine were on a diet containing milk, cream, boiled or poached eggs, cereals, creamed soups (custards), vegetables and fruits - 3 feeds a day. After they had become symptom-free they were allowed to increase their diet as they pleased. No alkalis were given.

The immediate results of the 23 patients treated with histidine showed that 13 developed a remission, and 5 became moderately improved; 5 became worse or were not improved.

On the diet alkali regimen 9 became moderately improved and 24 developed a remission.

Of these patients treated with histidine, after the diet alkali regimen had produced no remission, there were 70% of favourable responses.

When the diet alkali regimen was tried after histidine had failed there was also 70% favourable responses.

A follow-up in 20 cases who developed remission in

symptoms after histidine treatment showed that recurrence of symptoms appeared in 85% of the patients within 6 months after the cessation of injections. A similar follow-up in diet alkali treated patients showed that only 31% had a recurrence of symptoms within the same period of time. This spoke unfavourably for the lasting benefit to be obtained from the use of histidine in ulcer therapy as compared with diet alkali.

The writer made the observation that the short duration of remissions and high percentage of recurrence in the histidine group probably resulted from the rapid increase in diet, as 20 of the 22 patients who showed remission after histidine treatment were on practically full diets after the beginning of treatment. The patients on diet alkali regimen were schooled in the essential dietetics of their treatment.

Gastric acidity estimations were made before and after in 17 of the 40 cases treated with histidine: 5 showed no change, 6 an increase, and 6 a decrease. He observed that clinical improvement did not depend on the slight alteration in acidity during treatment.

There was either X-ray or operative check in 24 of the 40 cases treated with histidine. Four were patients suffering from gastric ulcer and the same lesion was present after histidine treatment. In 16 cases of duodenal ulcer, X-ray

examination showed improvement in 8. In the 24 checked none showed disappearance of the ulcer.

16 of the 40 cases developed mild reactions to the histidine - this was only evident in the ambulant cases.

In his conclusions he pointed out that histidine produced remission of symptoms in 55% of patients so treated. When its administration produced remission it did not prolong the symptoms-free interval, nor did it prevent recurrences. 85% of the patients who developed remission returned within 6 months of treatment. He thought that histidine may be used as "extra artillery" in patients not responding to the "diet alkali antispasmodic" regimen and 50% of them may become symptom-free and an additional 20% moderately improved.

Lovell reported 14 cases only two of which failed to react favourably. However, in the one case reported in detail it was seen that alkalis were given and no mention was made of diet. In eleven of his cases the symptoms had disappeared after treatment and X-ray examination showed that the ulcers had healed.

Gardiner reported 12 cases of proved ulcer treated with histidine. Symptomatic relief was obtained in all cases, and he reported an invariable fall in gastric acidity in every case. He expressed the opinion that the action of histidine is probably due to its causing a reduction in

the gastric acidity, and lowering of the gastric motility. A follow-up was instituted in 9 cases. 6 remained symptom-free after 4-6 months whereas 3 had relapsed.

Barry and Florey, working at Oxford in 1936, repeated the experimental work of Aron and Weiss on cats and pigs. They used the operation of experimental Meckel's diverticulum to test the efficacy of histidine in preventing ulcer formation. In this operation the stomach is exposed through a midline incision, and a pouch made from the greater curvature about midway between the cardia and the pylorus. The mucosal and muscle layers are insewn separately, so that the stomach is completely separated from the pouch, and an opening about 1 cm. in diameter left in the pouch. The ileum is now cut about 15 cms. from the ileocaecal junction, and both ends are insewn. The open end of the pouch is anastomosed end-to-side to the distal end of the ileum and the proximal end of the ileum is anastomosed side-to-side to the terminal ileum near the caecum. This operation has the advantage of not interfering with digestion. Chronic peptic ulcers form in the ileal loop immediately below the pouch anastomosis, and as protein metabolism is not interfered with the very appearance of ulcers suggests that histidine deficiency has little to do with their causation. Histidine was administered to both cats and pigs after ulcers had been produced by operation, and as a result of

their experiments they found that histidine was incapable of preventing ulcer formation when caused by the action of unneutralised gastric juice on intestinal mucosa. They reviewed the literature on the clinical use of histidine and concluded that the reports did not prove that it had a specific action on peptic ulcer.

Bulmer issued a second report on a study of 126 cases treated with histidine. 65 cases were of gastric ulcer and 61 duodenal, and 46 and 45 respectively were relieved by treatment. His results are best shown in a table.

	Radiogram Normal.	Radiogram Still abnormal	Radiogram not done after Treatment.	Much Improved.	Failed
IMMEDIATE RESULTS	45	31	16	6	28
Follow up:					
No relapse up to 2 yrs.	12	9	5	-	-
Not traced,	3	5	2	-	-
Much improved,	2	-	-	1	-
Relapsed in 3 months,	8	5	2	-	-
" " 3-6 "	8	10	2	-	-
" 6-12 "	8	1	1	4	-
" 1-2 years,	2	1	-	-	-

It will be noted that after 12 months 45 cases had relapsed, and in that time two had perforated and two had

haematemesis. In his conclusions he observed that the treatment should be reserved for simple uncomplicated cases. and that it is contraindicated in active or recurrent haemorrhage, in deep or callous ulcers, and in cases of pyloric stenosis. He considered that the indications should include cases of stoma ulcer, and those in whom other methods have failed. After-treatment on the lines of simple diet, "feeds", and antacids was also advised.

CLINICAL FEATURES.

The 66 patients comprising this series were drawn mostly from the lower working class population of Liverpool. They included 35 cases of gastric ulcer, 28 of duodenal ulcer and 3 of jejunal ulcer; 63 were males and 3 females.

Age Incidence.

	Under 20	20-30	30-40	40-50	50-60	60-70
Gastric,	4	5	11	10	3	1
Duodenal,	1	10	9	6	1	1
Totals,	5	15	20	16	4	2

Average age in cases of gastric ulcer, 38.4 yrs.
" " " " " duodenal " 34.5 yrs.
Average of the group, 36.4 yrs.

Occupation.

60% were labourers, 20% unemployed, 20% engineers, painters, mill workers, motor drivers, railway workers, barmen, gasfitters.

Symptomatology.

Epigastric pain was complained of in every case with the exception of one. This man's only complaint was "weakness". He was found to have severe melaena due to duodenal ulceration.

In practically every case the pain had a definite relation to food. Patients with gastric ulcer usually had

pain ½-1 hour after food. Duodenal ulcer patients had pain varying from 1 to 4 hours after food. The distinction was by no means marked and there were many variations. A few patients observed that their pains came on with clock-work-like regularity at a fixed time every day.

The pain was variously described as being sharp, severe, dull-aching, gnawing, boring, burning, according to the imaginative and descriptive powers of the patient.

In position the pain was invariably epigastric. About 10% of duodenal ulcer patients had pain situated definitely to the right of the midline, and 15% had pain referred to the back, whereas only 3% of gastric cases had this radiation.

The taking of food relieved the pain in the majority of cases of duodenal ulcer but in only 40% of gastric ulcers. It was noted that in cases of long standing ulceration of the lesser curvature, complaint was made that the pain came on immediately after taking food, and was only relieved by alkalis. Alkalis produced a temporary remission of pain in 95% of the cases.

Belching of wind relieved pain in 30% of gastric ulcer cases and vomiting in another 15%.

In gastric ulcers with a short history, a striking feature was that the nearer the ulcer to the cardiac end, the earlier did the pain come on after meals. This was not true in long standing cases, where it was noticed that pain came

on at increasingly short intervals after food, and was often relieved by vomiting.

Flatulence was a symptom in 60% of gastric ulcer cases, and only 5% of duodenal ulcers.

Vomiting as a symptom occurred in only 20% of gastric ulcer cases. Cases showing definite pyloric obstruction were not included in this series of cases.

Haematemesis as a symptom occurred in 3 cases of gastric ulcer and one of duodenal ulcer.

Melaena in 3 cases of duodenal ulcer was noted, and in one case of jejunal ulcer.

Constipation was equally common in gastric and duodenal ulcers.

Loss of weight was more marked in long standing cases, and appeared to be due to the fact that the patients had been on a restricted diet for a long time, and were often afraid to eat for fear of precipitating an attack of pain.

Periodicity of symptoms was well marked in both types, the period of freedom varying from 2 weeks to years.

75% of the patients had previous treatment of some description, either at home or in hospital.

44% had previous institutional treatment in hospital for the same condition.

31% had previous treatment at home under the care of their own doctor.

Investigation into the personal history of each case showed that 60 smoked tobacco either in the form of cigarettes or tobacco, whilst 40 consumed alcohol in the form of beer or spirits.

Fifty-five patients in the series gave a history of irregular or hurried meals. The nature of their employment did not allow the majority of these patients time to go home for lunch and this was carried in the form of sandwiches and as a rule washed down with a mug of strong tea.

An average day in the life of one of these patients is as follows:

> 7 a.m. Rise from bed and partake of a hurried meal of ham or sausage with tea and bread; then a journey to work usually including a rush to catch a tram or train, or a hurried cycle journey.
>
> 12 noon. Sandwich lunch and tea.
>
> 5-6 pm. A heavy meal of potatoes and meat or "fish and chips" with tea and bread. Those addicted to alcohol usually stopped for a pint of beer on the way home to the evening meal.

Only five patients gave a family history of ulcer.

Psychological Aspects.

In many cases in which special investigation was made for psychological factors as determining the onset of an attack, it was found that mental stress or excitement was related to the onset of symptoms.

One patient, an insurance agent, had been provided with a motor car for his work, which consisted of visiting

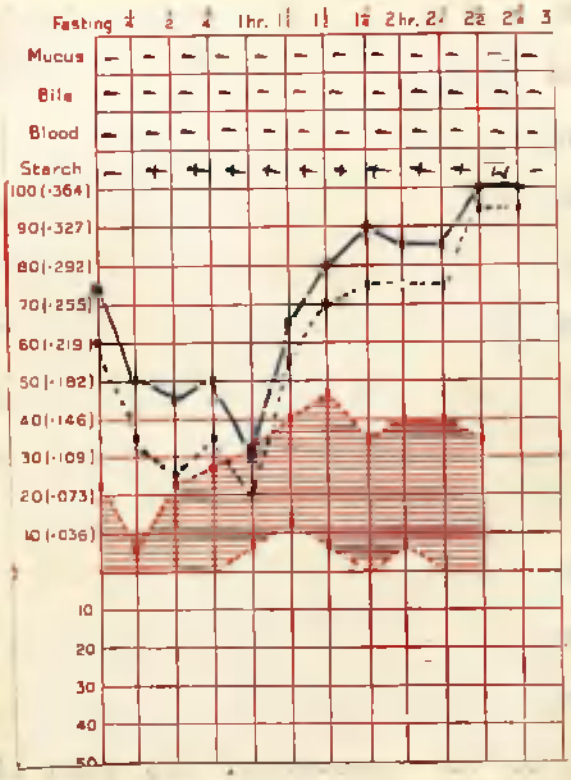
houses to collect premiums. He was very nervous about driving, and stated that he never had had any symptoms until he got the car. He volunteered that "every time I had a 'narrow shave' with my car, then I could be sure that a night of torture was in front of me". Nine months after the conclusion of his treatment he had had only two attacks since discharge and had put on weight. He had given up using a car on my advice and wondered if that or the injections had relieved him.

Another patient, a tramway inspector, stated that he had been subjected to some degree of criticism because the trams on the route that he supervised had been running late and generally not keeping to the timetable. At that time in Liverpool there had been a public outcry against the tramway system in general, and he had been taking it very much to heart. He dated the onset of his gastric symptoms from the time of this trouble. Investigation showed that he had duodenal ulcer. He had the usual course of treatment with histidine and was advised to apply for a change of work. He reported regularly, and although he had a relapse, he was much fitter than he had been before.

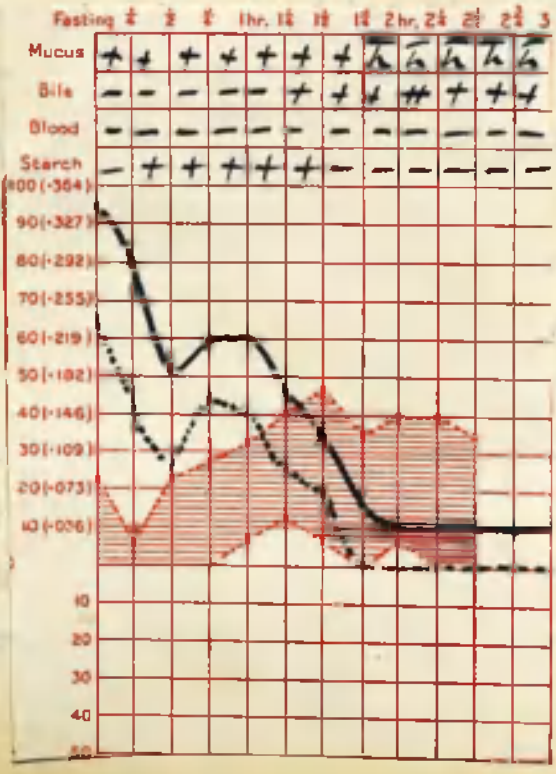
Another patient with a long history of stomach trouble noticed that his pains were much worse once a fortnight and that they always became worse on a Sunday. I found that he was an ardent football 'fan', and always attended

Duodenal

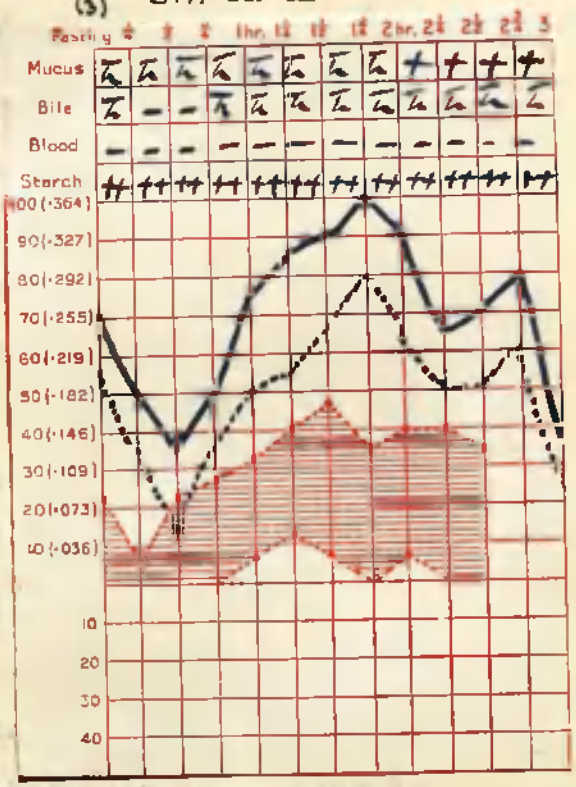
(1) W. H. aet 36.



(2) T. C. aet. 44.



(3) J. H aet 25



the home games once a fortnight on Saturday afternoons. He admitted that he always got very excited at the match and did a fair amount of shouting - however I was not able to establish whether his pains were not so severe if his team won, or vice versa!

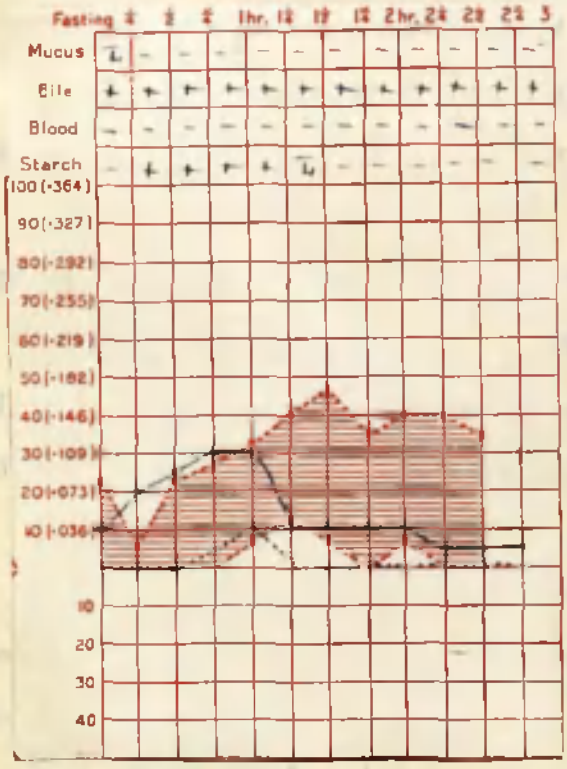
As a class the patients were well built, muscular men, but a striking feature was their anaemic appearance. 24 had evidence of focal sepsis, in that they had carious teeth, 4 had sinusitis, and 15 had dentures having had their teeth extracted previously in the hope that it would alleviate their symptoms. Three cases of duodenal ulcer were suspected of a co-existent gall bladder infection, but a cholecystogram performed in each case showed a normally functioning gall bladder. Three of the gastric ulcer cases and two duodenal ulcer cases had had previous appendicectomies performed for the same symptoms as they presented at the time of investigation. Two of the cases had been operated on in Mill Road Infirmary, and examination of the case records showed that X-ray examination of the gastrointestinal tract had been done, but no ulcer visualised.

Epigastric tenderness to palpation was present in most cases and many of the patients stated, "I can put my finger on the spot, doctor."

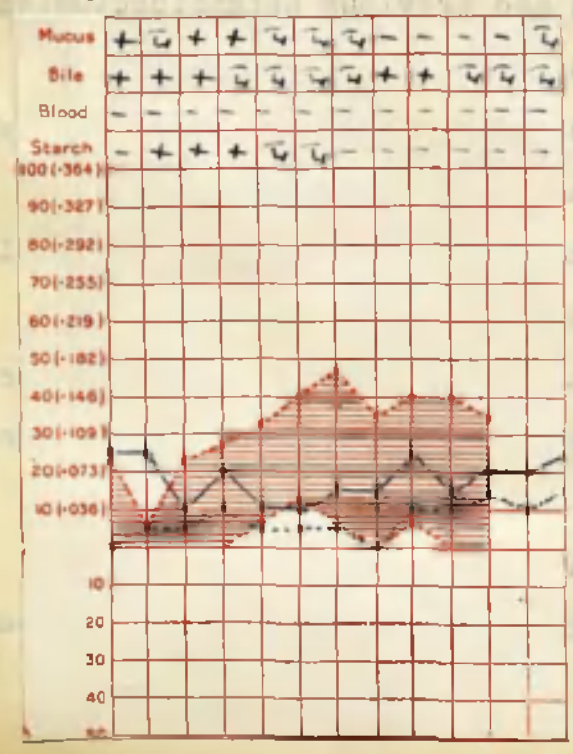
A striking feature of the series as a whole was the comparatively early age at which arteriosclerosis was present.

Jejunal.

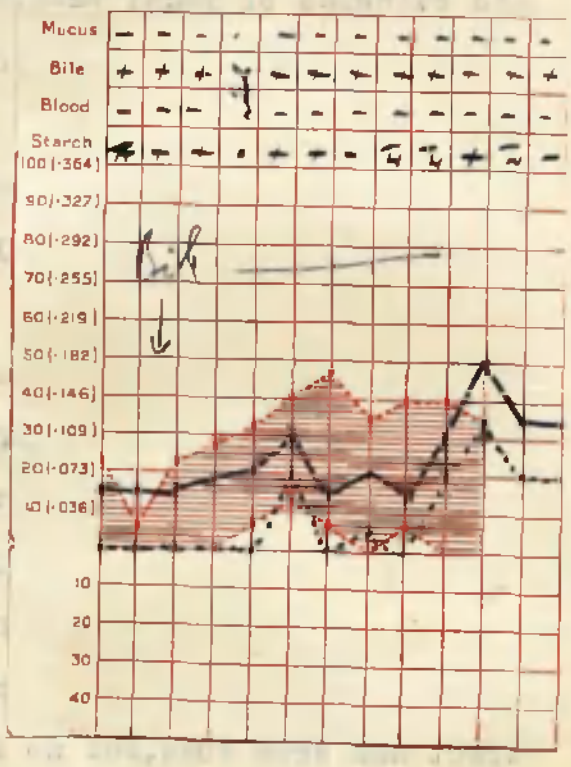
(1) C. M°K. aet. 42.



(2) R. B aet 38.



(3) W. D. aet. 34.



Blood pressures of 150 and 155 accompanied by radial thickening were quite common in men of 35.

Fractional Test Meal.

This was performed as a routine in every case before and after treatment. Typical examples are attached, but in many cases the appearance of the curve was not sufficient to make a diagnosis of either duodenal or peptic ulcer. 29 cases of gastric ulcer showed evidence of hyperchlorhydria (85%). 3 cases (9%) showed normal curves. 2 cases showed achlorhydria.

26 cases of duodenal ulcer showed hyperchlorhydria and two cases showed a normal F.T.M.

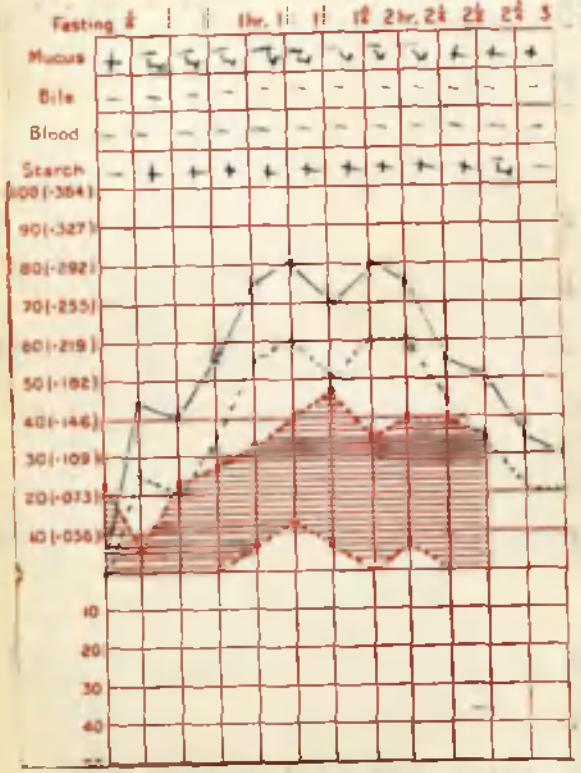
The cases showing achlorhydria were associated with chronic gastritis, and after treatment one showed a normal F.T.M. and the other showed hyperchlorhydria.

The three cases of jejunal ulcer showed interesting F.T.Ms (see opposite). It is generally believed that jejunal ulcer is associated with a high gastric acidity. So the inference is in these cases that the end of the tube was not resting in the stomach but had passed on into the jejunum, or that the lowered acid level is due to the regurgitation of bile.

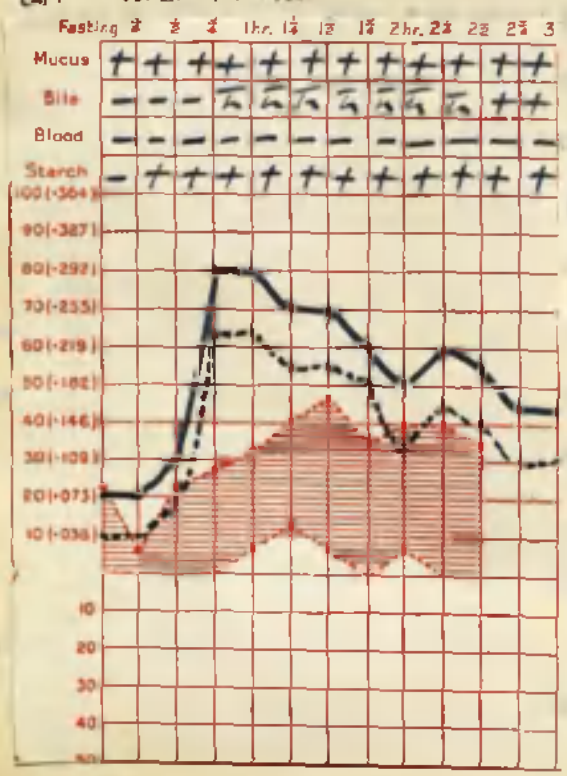
X-ray examination was also carried out as a routine before and after treatment. An ulcer 'niche' was found in 25 cases of gastric ulcer but in only 10 cases of duodenal

Gastric.

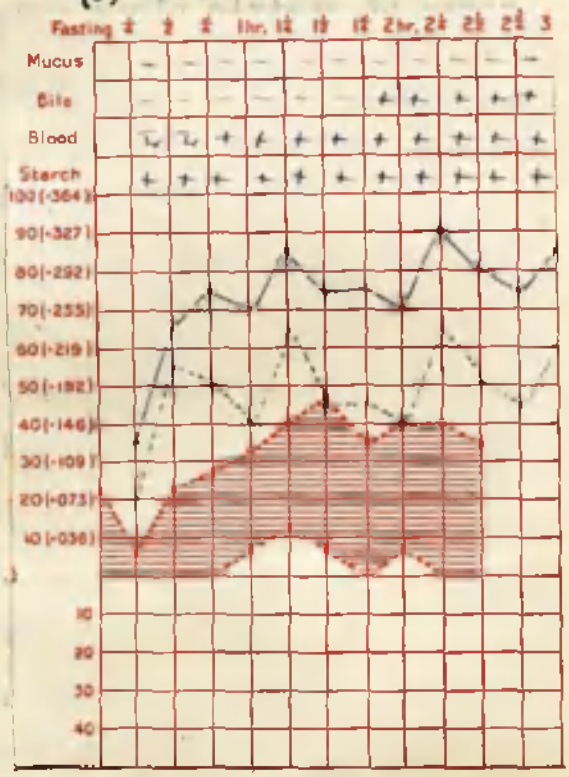
(1). K.W. aet. 37



(2). W.C. aet. 42.



(3.) M.S. aet. 61.



ulcer. Deformity of the duodenal bulb in the other duodenal cases taken in conjunction with the other clinical signs placed the diagnosis beyond doubt. Of the three cases of jejunal ulcer an ulcer niche was demonstrated in two cases and in the third case the radiologist reported that the appearances were "highly suspicious of ulcer". Occult blood tests were positive in 60% of gastric cases and 48% of duodenal cases.

The urea clearance test was performed in every case before treatment, and in 31 cases after treatment.

	Gastric.	Duodenal.
Av. B.U.	56 mgms.%	58 mgms.%
Av. Clearance	48 c.c.%	48 c.c.%

Haematemesis cases: B.U. 61 mgms.%
Av.Cl. 41 c.c.%

Melaena Cases: Av. B.U. 69 mgms.%
Av. Cl. 32 c.c.%

Albuminuria was present in 15 (44%) of gastric cases and in 8 (29%) of duodenal cases.

Blood Count.

This was performed in 58 cases.

Average total Reds,	3,900,000
Average Hb.	66%
Average total Whites,	8,000

Anaemia was present with no evidence of leucocytosis. Considering the blood pictures as a whole, anaemia was the

only constant feature.

The Icteric Index was estimated in 54 cases.

Average in G.U. - 5, and ranged between 3 and 10.
Average in D.U. - 5, and ranged between 3 and 15.

Wassermann Reaction was performed in 66 cases with one positive result in a case of duodenal ulcer.

Urinary indol was tested for and found to be present in 3 cases of gastric ulcer each of which had also albuminuria and severe haemorrhage.

MODE of TREATMENT and MINISTRATION of HISTIDINE.

The patients in the series were those cases suffering from duodenal and gastric ulcer admitted to two male medical wards at Mill Road Infirmary, Liverpool, from December 1935 to March 1936 together with three female patients from the female wards. The total number of medical beds of the two wards was 80, and the admissions to the 80 beds in the period were 721 of which 63 were suffering from duodenal or gastric ulcer, i.e. 8%.

Every potential case of gastric or duodenal ulcer was investigated in the following routine way.

(A) Name. Date.

Occupation.

Present Complaint and History of Complaint.

Symptoms: (1) Pain and relation to taking of food. (2) Whether pain was relieved by food, eructations, vomiting, alkaline powders. (3) Distribution of pain. (4) Whether pain was nocturnal or not. (5) Presence or absence of vomiting. (6) Flatulence. (7) Loss of weight. (8) Haematemesis or melaena. (9) Constipation. (10) Periodicity.

Past History: (a) Other illnesses.
(b) Previous stomach trouble; treatment and effect of treatment.

Personal History: (a) Tobacco. (b) Alcohol. (c) Regular meal times. (d) Well cooked food.

Family History: Ulcer diathesis.

(B) Clinical Examination.

General appearance.
Alimentary system.
Respiratory system.
Weight.
Focal sepsis
Cardiovascular system. B.P.
Central nervous system.

(C) Pathological Examination.

(1) Fractional Test Meal before and after treatment.
(2) Occult blood test daily until 3 consecutive negative specimens were obtained.
(3) Urea Clearance Test.
(4) Wassermann Reaction.
(5) Icterus Index.
(6) Blood Count.
(7) Indoluria.
(8) Microscopic examination of urine.

(D) Radiological examination before and after treatment.

(E) Follow-up Report.

The Urea Clearance Test was repeated after treatment in 38 cases, and the icterus index in 26 cases.

Only those cases showing definite evidence of ulceration both clinically and radiologically were treated with histidine.

Mode of Treatment.

The preparation of histidine used was that known as Larostidin, put up for injection in ampoules containing 5cc. One ampoule was injected daily into alternate buttocks with all aseptic precautions. Every injection was done by the writer personally, and not left to the nursing staff, thus establishing personal control over each patient. Every patient under treatment was examined daily, and a note was made of the progress of his symptoms. The total number of injections given in each case varied from 18 to 50. The average in a case of gastric ulcer was 30, and 27 in a case of duodenal ulcer.

As far as possible every patient was detained in hospital during the course of his treatment, but due to the periodic scarcity of available beds, and for various personal reasons of the patients themselves, a number were treated as out patients. In all 37 patients were in hospital for the whole course of their treatment whilst 29 attended as out patients.

No patient was permitted to be discharged to the out patient group until he was symptom-free. In this group the patients attended each morning for their injection and examination, and special arrangements were made for their readmission on the completion of the course for the purpose of re-investigation.

All the hospital patients with the exception of those who had signs of active bleeding, were encouraged to be up and do light duties in the wards.

Diet.

In consideration of the fact that a number of the patients had previous treatment on diet alkali lines, it was found that they would not tolerate a full diet at the beginning of treatment, and tended themselves to avoid meat, potatoes, fried fish, and fatty foods. The average diet given was the equivalent of Maclean's 3d week (without medicines). The patients' diet was then gradually increased as they became symptom-free.

Patients having melaena or haematemesis were treated rather differently. They had the usual routine treatment of the condition, and in addition daily injections of histidine were given right from the day of admission to hospital.

Smoking was absolutely prohibited, and these patients attending the out patient clinic were warned to cooperate under penalty of their treatment being discontinued.

After the course of treatment each patient reported once a month to the Continuation Clinic, and if he had relapsed he was put on to the usual diet alkali regime, or in a few cases given a further course of injections.

RESULTS, SUCCESSES, FAILURES, MISHAPS.

(1) TABLE I. shows the results 6-9 months after the commencement of treatment with Larostidin.

	Gastric.	Duodenal.	Anastomotic.	Total
No. of cases	35	28	3	66
Immediate relief,	26	22	3	51
No relief,	8	6	0	14
Died during treatment,	1	0	0	1
Well after 6-9 months,	6	6	2	14
Relapsed within 6 months,	18	15	1	34
Untraced,	2	1	0	3

Immediate relief indicates freedom from symptoms after the course of injections.

(2) TABLE II shows the results as seen by radiological examination after treatment.

	Gastric.	Duodenal.	Anastomotic.	Total.
Radiological cure,	5	0	0	5
Radiological improvement,	8	1	1	10
No change radiologically,	21	27	2	50

Tables IV, V and VI indicate the follow-up of the three groups in Table II.

TABLE IV.

	Gastric.	Duodenal.	Anastomotic.
Radiological cure,	5	0	0
Relapsed,	3	0	0
Well,	0	0	0
Untraced,	2	0	0

In this group the average age of the patients was 28 and the average duration of symptoms 2.1 years. Critical examination of the X-ray films in this group revealed no evidence of ulceration.

TABLE V.	Gastric.	Duodenal.	Anastomotic.
Radiological improvement,	8	1	1
Relapsed,	4	1	0
Untraced,	0	0	0
Well,	4	0	1

The average age in this group was 40 and the average duration of symptoms 5.0 years.

TABLE VI.	Gastric.	Duodenal.	Anastomotic.
Radiologically unchanged,	21	27	2
Relapsed or No relief,	19	20	1
Untraced,	0	1	0
Well,	2	6	1

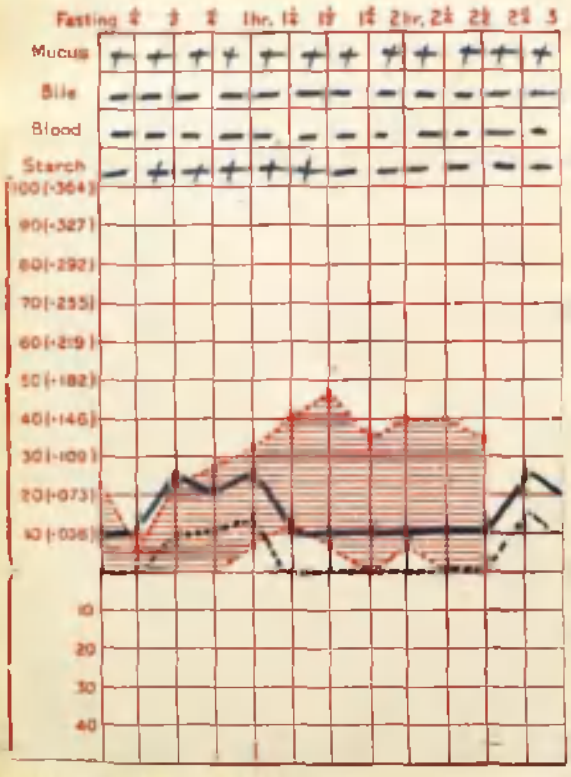
TABLE VII. Gastric Acidity. This table shows the results of the F.T.M. in all the cases before and after treatment. It will be noted that 29 gastric and 26 duodenal cases showed evidence of hyperchlorhydria.

	GASTRIC		DUODENAL		TOTAL	
	Before	After	Before	After	Before	After
High normal,	29	20	26	26	55	46
Normal,	3	14	2	2	5	16
Achlorhydria,	2	0	0	0	2	0

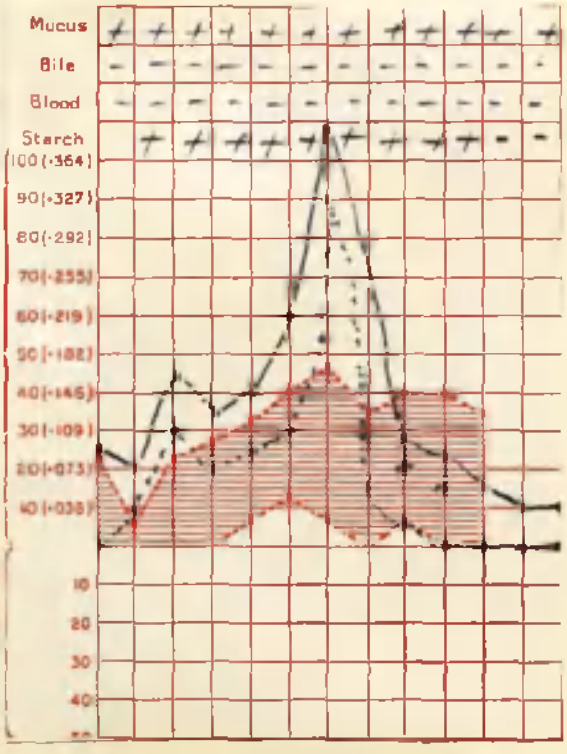
TABLE VIII shows the changes in gastric acidity. It will be noted that the acid curve became normal in only 11 cases after treatment.

(1). E. B. aet. 49.

Before.

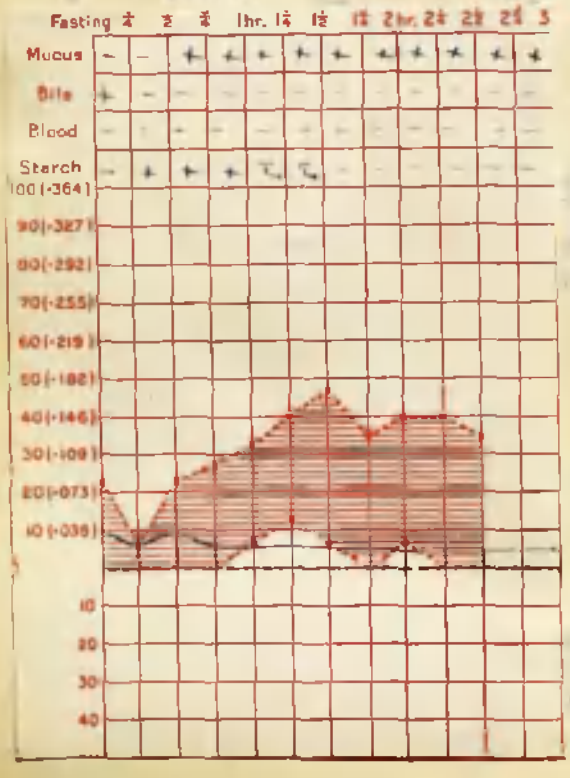


After.

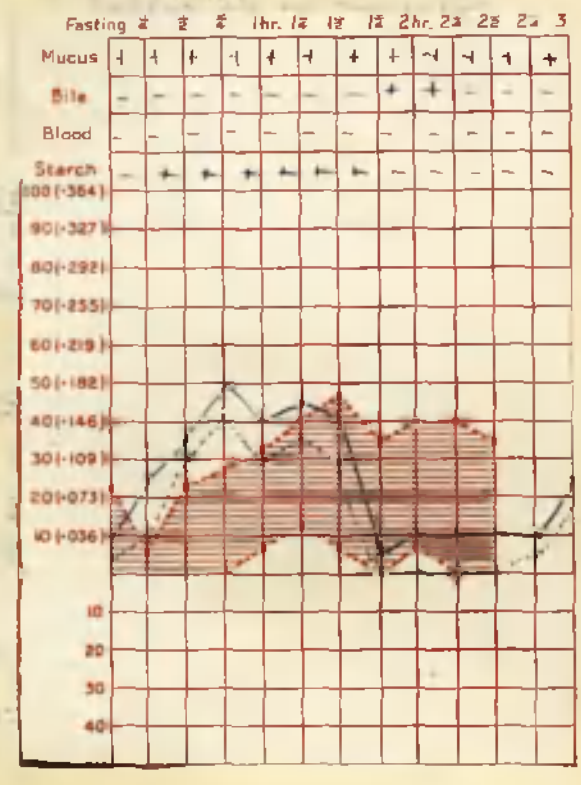


(2). T. E. aet. 54.

Before.



After.



	Gastric.	Duodenal.
High Normal to Normal,	11	1
No change,	21	27
Achlorhydria to Normal,	1	0
Achlorhydria to Hyperchlorhydria,	1	0

Three cases with definite X-ray evidence of gastric ulcer had normal acid curves, and treatment did not have any effect on the acidity. Two cases with indisputable evidence of gastric ulcer had achlorhydria or low acid curves. One became normal after treatment and the other showed a typical acid curve of gastric ulcer. (Vide attached F.T.Ms.). Both of these cases had in addition, evidence of chronic gastritis.

UREA CLEARANCE and BLOOD UREA.

(A) Gastric Ulcer Cases.

Blood urea was estimated in 20 patients after treatment and urea clearance test in 18.

The average clearance after treatment was found to be 54 (48)cc./, and the average blood urea 49 (56) mgms.% .

(B) Duodenal Ulcer Cases.

Blood urea and urea clearance tests were estimated in 13 cases after treatment: Average Clearance, 55 (48)cc./ Average Blood Urea, 52 (58)mgms%.

This would indicate that there is a slight improvement in kidney function after treatment, and that histidine does not have any toxic effects on the kidneys.

Weight.

44 patients gained weight, the average gain being 5 lbs. in gastric ulcer cases and 3 lbs. in duodenal ulcer cases. 8 patients lost weight and in 10 the weight remained unchanged.

CASE HISTORIES of SUCCESSFUL PATIENTS.

(1) J.F., aet.19, machinist. Admitted on 26/10/35 complaining of vomiting blood.

History. 17 days before admission he had slight attacks of epigastric pain after meals but paid little attention to them. 5 days later he noticed that his stools were very dark in colour. Despite the fact that he felt very weak he continued at work until 3 days before admission, when he had an attack of haematemesis, vomiting up about ½ pint of blood. He was confined to bed and treated by his panel doctor with glucose drinks and injections of morphia. On the day of admission he vomited about ½ pint of dark-coloured blood.

Past History. No previous stomach trouble.

Family History. No ulcer diathesis.

Examination. Well nourished, anaemic patient. Physical examination negative, with no abdominal tenderness or rigidity. Stools tarry in colour.

Treatment. Nothing by mouth for first 24 hours, thereafter small quantities of milk daily until the 5th day when he was put on 2nd week Maclean's diet. Daily injections of Larostidin were commenced on the day after admission. The patient had no further haematemesis and by the 7th day was fit for special examination.

F.T.M. Hyperchlorhydria. Blood Urea, 85 mgms.%. Urea Clearance, 29.4 cc. W.R., negative. Icterus Index, 3. Blood: Reds 3,560,000; Leucocytes, 7000; Hb., 60%. X-ray report: appearances suspicious of juxta-pyloric ulcer.

By the 15th day the occult blood test was negative and he was put on light diet and by the 21st day up and about the ward. He was discharged on 23/11/35 on normal diet, and having gained 6 lbs. in weight.

Special examination repeated showed that there was some slight hyperchlorhydria in the gastric contents, and the X-ray appearances were unchanged. This patient reported regularly, and 9 months after discharge was free from any symptoms.

(2) J.C., aet.49. Labourer. Admitted on 27/12/35.

Complaint. Epigastric pain ½ hour p.c.

History. The patient was well until one month before admission when he began to have attacks of pain situated in the epigastrium coming on about half an hour p.c. At this time the pain was not relieved by food, but was relieved to some extent by alkalis. For two weeks before admission he had "sour mouthfuls" and loss of weight. Constipation troubled him greatly.

Past History. No previous stomach trouble or illness of note.

Personal History. Moderate smoker and took an occasional glass of beer.

Family History. No family history of stomach trouble.

On Examination. Patient was a sallow, sparely built man and physical examination of the abdomen revealed some epigastric tenderness to palpation.
Special examination gave the following results: F.T.M. showed slight hyperchlorhydria. Occult Blood, positive. Blood Urea, 45. Urea Clearance 48. W.R., negative. Icterus Index, 3.

Blood Count: Red blood cells, 3,700,000.
Leucocytes, 10,000
Hb. 65

X-ray showed an ulcer on the posterior wall of the stomach.

Treatment. The patient was now put on a light diet and given daily injections of Larostidin. He had no pain after 8 injections. 25 injections were given, and he was discharged on 22/1/36 eating a normal diet, and having gained 2 lbs. in weight.

Tests for occult blood became negative after the 4th injection. Special examination was repeated at the conclusion of the course:
F.T.M., fairly normal acid curve. Occult blood, negative. Barium meal examination showed that the stomach emptied rapidly, and that the ulcer crater was smaller than before. The patient reported regularly, and remained symptom-free after 9 months.

(3) A.B., aet.50. Labourer. Admitted 2/3/36.

Complaint. Epigastric pain coming on ½ hour p.c., and of one year's duration.

History. One year before admission the patient began to have attacks of epigastric pain coming on after meals. These pains became more frequent and during the three months prior to admission followed every meal. Regularly the pain awakened him during the night.

Past History. No previous stomach trouble.

Personal History. Smoked 20 cigarettes per day and drunk about one pint of beer.

Family History. No family history of ulcer.

On Examination. Patient an anaemic individual. Clinical examination of the abdomen revealed some tenderness on deep palpation in the epigastrium.

Special Examination: (1) FAECES: Occult blood test weakly positive. (2) F.T.M. showed rising curve and some delay in emptying. (3) BLOOD UREA, 52; CLEARANCE, 60. cc. (4) W.R., negative. (5) ICTERUS INDEX, 3. (6) BARIUM MEAL showed a small pyloric ulcer.

Treatment. Treatment was commenced and the patient put on light diet with daily injections of Larostidin. After the 5th injection he became symptom-free and was transferred to the out-patient department to attend daily for injections of Larostidin. 25 daily injections were given and at the end of the course the patient had no pain and was symptom-free. He gained 2 lbs. in weight and on the third day after treatment was commenced the occult blood test was negative.

Special examination repeated showed that the occult blood test was negative. F.T.M. showed hyperchlorhydria with slight delay in emptying, but apparently improved stomach tone. Blood urea, 30. Clearance, 70. Icterus 3.

X-ray appearance of the ulcer was unchanged. The patient was symptom-free 9 months after the conclusion of his treatment.

(4) J.F., aet.19. motor driver. Admitted 6/11/35.

Complaint. Abdominal pain one hour after meals, relieved by eating.

History. The patient had no stomach trouble until one year before admission. At that time he had epigastric pain coming on after meals and vomiting. The attack only lasted three days and was relieved by alkalis. He had no further stomach trouble until 6 months later when he began to have epigastric pains after meals. This time alkalis only gave temporary relief, and the pains became more severe. He vomited at times, lost weight and felt unable to work. In addition he complained of constipation.

Past History. Nothing of note.

Personal History. Smokes 20 cigarettes daily.

Family History. Father had gastric ulcer.

On Examination. Well coloured, nervous type of individual.

Clinical Examination revealed some epigastric tenderness to palpation, otherwise N.A.D.

Special examination: OCCULT BLOOD, positive. BLOOD UREA, 35 mgms.%. CLEARANCE, 62 mgms.% Icterus Index 3. F.T.M. showed hyperchlorhydria plus slight delay in emptying.

X-ray examination showed a pyloric ulcer.

Treatment. Light diet and daily injections of Larostidin were commenced and pain was relieved after the 6th injection and occult blood test was negative after the 4th. In all 30 injections were given, and at the end of the course he was taking a full diet and had gained 3 lbs. in weight.

Special examination repeated showed that the Blood Urea was 25 mgm.%. Clearance 82 mgms.%. Icterus 3. F.T.M. Hyperchlorhydria plus slight delay.

Fluid Meal:- Some dmininution in size of ulcer.

This patient remained symptom-free 9 months after treatment.

(5) J.P., aet.40. Jobber. Admitted 3/2/36.
Discharged 19/2/36.

Complaint. Epigastric pain ½ hour p.c.

History. Three years ago the patient began to have attacks of epigastric pain with occasional vomiting coming on after meals. For a time his symptoms were completely relieved by alkalis. He noted that he remained symptom-free for periods of about 3 months, then pain after meals with vomiting returned. During the 6 months previous to admission the pain came on constantly after every meal and temporary relief was got by taking Maclean's powder. He had no previous institutional treatment.

Past History. No stomach trouble or illness of note.

Personal History. Smokes 20 cigarettes a day and has an occasional glass of beer.

On Examination. Well nourished patient with an anxious expression. Examination of the abdomen revealed marked tenderness to palpation in the epigastrium.

Special Examination. OCCULT BLOOD, positive. BLOOD UREA, 20. mgm. CLEARANCE, 93 c.c. ICTERUS INDEX, 3. F.T.M., hyperchlorhydria with slight delay in emptying.

Barium meal examination showed a pyloric ulcer.

Blood Count:	Red blood cells,	4,500,000
	Leucocytes,	8,000
	Hb.	80

Treatment. The patient was put on second week Maclean's diet and daily injections of Larostidin given. He became symptom-free after the third injection, and the occult blood test became negative after the fourth. In all 26 injections were given, and he had gained 5 lbs. in weight at the end of the course of treatment.

Special examination repeated showed that the B.U. was 26 mgm.%. Clearance, 78 c.c. Icterus Index, 3. F.T.M., showed a climbing curve of ulcer. Barium meal showed some diminution in the size of the ulcer.

The patient was fit and well 9 months after and had had no recurrence of symptoms.

(6) A.M., aet. 50. Unemployed. Admitted 3/2/36.
Discharged 18/3/36.

Complaint. "Nagging" upper abdominal pains after meals, and weakness.

History. 20 years ago the patient had an attack of abdominal pain and vomiting after meals, lasting for about 4 weeks. This attack was relieved and eventually cured by alkalis. He had no further stomach trouble until 2½ years before admission, when he had another similar attack. His doctor made a provisional diagnosis of gastric ulcer at that time and his symptoms disappeared entirely after a week's rest in bed and diet alkali regime. He remained well until 3 weeks before admission, when he had attacks of epigastric pain coming on about ½ hour p.c., and relieved by food. One day he vomited a fair amount of blood and noticed that his stool was dark in colour thereafter. Between these three attacks of stomach trouble he was quite well and could eat anything.

Personal History. Moderate smoker and drinker. No family history of gastric ulcer.

On Examination. Anaemic patient. ABDOMEN: some epigastric tenderness to deep palpation, otherwise N.A.D. CHEST: chronic bronchitis.

Treatment. On admission the patient was put on a first week Maclean diet and Larostidin commenced. After 7 days' treatment he was considered fit for special examination with the following results: F.T.M., rising curve plus slight delay in emptying. BLOOD UREA, 38 mgms.%. UREA CLEARANCE, 65 c.c. . . OCCULT BLOOD, positive. ICTERUS INDEX, 3.

Barium meal showed an ulcer of the lesser curvature. After 14 injections the patient had no abdominal pains and was put on third week Maclean's diet. The occult blood test became negative after 12 injections, but again became positive after the 14th, and remained so until after the 21st, by which time he was having a fourth week Maclean's diet. He was discharged to the out-patient department after the 25th injection. In all, 36 injections were given, and at the end of the course the patient was symptom-free, and had gained 12 lbs. in weight.

Special examination repeated showed that the F.T.M. was within normal limits, Blood Urea, 60 mgms.%, Clearance, 47 c.c. . . Occult Blood, negative. Icterus Index, 3. Barium meal showed that the ulcer crater was markedly diminished in size. The patient reported regularly and 9 months after treatment remained free from all symptoms.

DUODENAL ULCER CASES.

(1) F.M., aet.35. Printer. Admitted 8/1/36.
Discharged 27/1/37.

Complaint. Abdominal pain.

History. Two weeks before admission the patient had felt some abdominal pain which was relieved by alkaline powder. At this time he had only three attacks of pain occurring on successive days and although he had no further symptoms he continued taking the alkaline powder after meals. On the night of his admission to hospital two hours after eating a hearty meal, he was seized with a severe epigastric pain which "doubled him up". Half an hour after the onset of the pain he vomited and this gave him temporary relief.

Past History. Negative - patient had never had any previous gastric trouble.

Family History. No family history of ulcer.

On admission to hospital there was marked rigidity of the upper abdomen and tenderness to palpation. The rigidity was confined to the epigastrium and the liver dullness was normal. No sign of peritoneal irritation was detected. He was admitted to a surgical ward with a provisional diagnosis of perforated ulcer and the surgeon decided that he should be kept under observation.

On examination next day his rigidity in the upper abdomen had disappeared, but tenderness to palpation persisted. Investigations were commenced in four days' time with the following results: F.T.M., rising curve with hyperchlorhydria. OCCULT BLOOD, positive. BLOOD UREA, 75 mgms.%. UREA CLEARANCE, 34 c.c. . . ICTERUS INDEX 8.

Barium meal examination revealed the presence of a duodenal ulcer.

Treatment. The patient was not put on light diet and daily injections of Larostidin. He complained of slight epigastric pain after meals but after the 6th injection he was symptom-free. The occult blood test became negative after the third injection. He was discharged to the outpatient department and in all 25 injections were given. On completion of the course he was partaking of a normal diet, was symptom-free, and had gained 5 lbs. in weight. Special examination repeated gave the following results: F.T.M., hyperchlorhydria. Occult blood, negative. Blood Urea, 57 mgms.%. Clearance, 32 mgms.%. Barium meal,

ulcer appearance unchanged. He reported regularly every month and 8 months after his discharge he was symptom-free and had no recurrence of symptoms.

(2) A.G., aet.28. Electrician. Admitted 14/2/36. Discharged 3/3/36.

Complaint. Upper abdominal pain two hours after meals.

History. The patient was well until 18 months before admission, when he had an attack of dyspepsia. At that time he had epigastric pain, coming on at various times after meals, and relieved by alkaline powders. The whole attack lasted two weeks and was apparently cured by intensive alkaline therapy. He remained well until 6 months before admission when his pain returned. The pain was now different in character. It came on regularly 2 hours after meals. It wakened him during the night at times, and on occasion radiated to his back. He suffered continually until the time of his admission, and during the 6 months alkaline powders gave him temporary relief from pain during the day, whilst he slept at night with a glass of milk at his bedside.

Personal History. Heavy smoker.

Family History. No ulcer diathesis.

On Examination. The patient was a well coloured, well nourished patient of a nervous, worrying type.
Abdomen: Examination revealed slight rigidity and tenderness on palpation in the epigastrium.
Special examination gave the following results: F.T.M., hyperchlorhydria. BLOOD UREA, 60 mgms.%. CLEARANCE, 43 c.c. . ICTERUS INDEX, 5. OCCULT BLOOD, positive.
Barium meal - ulcer of first part of the duodenum.

Treatment was commenced with light diet and daily injections of Larostidin. The patient became symptom-free after 5, and occult blood test became negative after 4 injections. He was transferred to the out-patient department. In all, 25 injections were given and at the end of the course he was symptom-free, eating a normal diet and had gained 4 lbs. in weight.
Investigation repeated: F.T.M., hyperchlorhydria. Blood Urea, 54 mgms.%. Clearance, 43 c.c. . Occult Blood, negative. Barium meal - ulcer present as before with no change apparent in size. The patient reported regularly and 8 months afterwards was symptom-free.

(3) A.B., aet.43. Coalman. Admitted 24/2/36. Discharged 10/3/36.

Complaint. Abdominal pain 1-2 hours after meals.

History. Patient had stomach trouble 'off and on' for 20 years. The pain came on at various intervals from 1-2 hours after meals and were relieved by alkalis. He had remissions of about 6-18 months at a time when he was completely free from pain. During the 6 months previous to admission the pain was more severe than ever before. At times he had severe attacks of pain and vomiting. The pain was relieved by alkalis, vomiting, and sometimes by belching of wind but returned again in a short time.

At times the pain radiated to his back and for the past three weeks he had been wakened during the night with the pain.

Personal History. Heavy smoker and moderate drinker.

Family History. No family history of ulcer.

On Examination. Well nourished patient of a nervous disposition. Abdomen: some rigidity to palpation in the epigastrium. Chest: chronic bronchitis. Heart: sounds pure. B.P., 145/80.

Special examination: F.T.M., hyperchlorhydria. OCCULT BLOOD, weak positive. BLOOD UREA, 56 mgms.%. UREA CLEARANCE, 51 c.c. . W.R., negative. ICTERUS INDEX, 3.

Barium meal revealed duodenal ulcer.

Treatment with light diet and Larostidin was commenced and 25 injections were given. The Occult Blood test became negative the second day after admission. After 3 injections he became symptom-free. On completion of the course he had gained 5 lbs. in weight and was eating a normal diet.

Special examination repeated: F.T.M., hyperchlorhydria. Barium meal, appearance of ulcer unchanged since previous examination.

Eight months after the completion of his course of treatment he remained symptom-free.

(4) C.T., aet.26. Jobber. Admitted 21/2/36.
Discharged 10/3/36.

Complaint. Epigastric pain coming on one hour after meals.

History. One month before admission the patient began to have pain after meals. At first the pain only came on occasionally, but later became constant and followed every meal. At times he was awakened in the night by severe boring epigastric pain. He obtained a certain amount of relief by taking alkaline powders, but had become depressed and felt that he was unable to work. He noticed that latterly the pain seemed to shoot through to his back.

Family History. Father had gastric ulcer.

Personal History. Moderate smoker and drinker.

On Examination. A thin, under nourished, anxious looking individual. Chest: some prolongation of expiration was heard over both lung areas with occasional rhonchi. X-ray examination of the chest showed heavy lung markings and repeated examination of the sputum revealed no tubercle bacilli. Abdomen: epigastric tenderness maximal over a point 2" above the umbilicus. Special examination: F.T.M., hyperchlorhydria with slight delay. BLOOD UREA, 60 mgms.%. CLEARANCE, 40 c.c. . OCCULT BLOOD TEST, weak positive.

X-ray examination revealed deformity and imperfect filling of the duodenal bulb with flecks of barium persisting at 4 hours.

Treatment with Larostidin and light diet was commenced and after 4 injections he became symptom-free and was discharged to the out-patient department.

The Occult Blood test became negative after two days in bed. In all 25 injections were given and the patient gained 3 lbs. in weight on completion of the treatment.

Special examination repeated gave the following results: F.T.M., hyperchlorhydria. X-ray examination: no change since previous examination.

9 months afterwards the patient was still symptom-free.

(5) J.A., aet.29. Butcher. Admitted 25/4/35.
Discharged 7/12/35.

Complaint. Abdominal pain 1½ hours p.c.

History. The patient was well until 12 months before admission when he began to have vague gnawing pains in the upper abdomen, mainly at night time. He paid no attention to them but 6 months later they became more frequent and more severe, occurring about 1½ hours after every meal. He noticed that temporary relief from the pain could be got by belching wind, and at other times by taking alkaline powders. During the three months previous to admission the pains were very severe at times and on occasion they shot through to his back.

Personal History. Heavy smoker and drinker.

Family History. No family history of ulcer.

Examination. Tenderness to palpation in the epigastrium.

Special Examination. F.T.M., hyperchlorhydria. Barium meal showed duodenal ulcer. BLOOD UREA, 52 mgms.%. CLEARANCE, 64 c.c.. . ICTERUS INDEX, 5.

Treatment with light diet and daily injections of histidine was commenced and he became symptom-free after 5 injections and was discharged to the out-patient department.

In all, 25 injections were given and the patient had gained 2 lbs. at the end of his course.

Special investigations repeated showed: F.T.M., hyperchlorhydria. Barium meal, ulcer appearance as before.

Eight months after treatment was finished he reported fit and well and had had no recurrence of symptoms.

(6) John G., aet.37. Carter. Admitted 8/1/36.
Discharged 22/1/36.

Complaint. Abdominal pain, epigastric in situation, occurring two hours after meals.

History. Three years before admission the patient had an attack of "indigestion" which took the form of pain after meals accompanied by belching of wind and vomiting. The attack lasted for two weeks and was cured by alkaline powders. He had no further stomach trouble until one year before admission when he had an attack of severe epigastric pain coming on after meals. He rested in bed for one week and took large doses of alkaline powder with the result that his symptoms disappeared for 3 months. During his next attack, nine months before admission, the pains returned with increased frequency and severity accompanied by occasional vomiting, and often radiation into his back. On this occasion he was admitted to hospital and treated with diet alkali regime and had no further trouble until three weeks before admission when the same symptoms returned.

Personal History. Confirmed alcoholic and heavy smoker.

Family History. Mother had gastric ulcer.

On Examination. Sparely built man with an anxious expression. Abdomen: palpation revealed slight epigastric tenderness to palpation.
Special examination: F.T.M., hyperchlorhydria. OCCULT BLOOD, positive. BLOOD UREA, 54 mgms.%. CLEARANCE, 63 c.c. . W.R., negative. Barium meal examination showed ulcer on first part of the duodenum.

Treatment with light diet and daily injections of histidine was commenced and the occult blood test became negative after 8 injections. After the 12th injection he became symptom-free and was discharged to the out-patient department. A course of 30 injections was given and at the end he had gained 2 lbs. in weight.

Special examination showed that the radiological appearance of the ulcer was unchanged. Blood Urea, 60 mgms.%. F.T.M., hyperchlorhydria.

Nine months later he was still symptom-free,

JEJUNAL ULCER CASES.

(1) J.B., aet.38. Unemployed. Admitted 3/12/36.
Discharged 17/1/36.

Complaint. Vomiting of blood.

History. Ten years ago he was operated on for perforated duodenal ulcer and after the operation remained well for 2 years when he had an attack of haematemesis. At this time he had 6 weeks' hospital treatment and remained free from severe symptoms for 3 years, when he had a further haematemesis and had a further course of hospital treatment. Two days before admission whilst at work he felt weak, had an attack of nausea, and then vomited about half a pint of blood. On the evening that he was admitted to hospital he had a further attack. From the date of his first attack of haematemesis until his present admission, he had fairly frequent attacks of indigestion and pain after meals, and stated that he had swallowed pounds of alkaline powder during that period.

Personal History. Heavy drinker and moderate smoker.

Family History. No family history of ulcer.

On Examination. Markedly anaemic and dehydrated on admission. Abdomen: tenderness at a point 1" above the umbilicus.

Blood count: Reds, 3,000,000
Leucocytes, 9,000
Hb. 55%

Treatment. He was given the routine treatment for haematemesis cases and in addition daily injections of histidine. It was noted that his occult blood test became negative after 10 injections. X-ray examination showed the presence of jejunal ulcer.

F.T.M., hydrochlorhydria. Blood Urea, 40 mgms.%. Clearance, 52 c.c.. Icterus Index, 3. 35 injections were given and at the end of the course he had gained 5 lbs. in weight and was eating a normal diet.

Special examination repeated showed that the jejunal ulcer persisted and 9 months later he was still free from all symptoms.

(2) W.D., aet.34. Plasterer. Admitted 4/1/36.
Discharged 26/1/36.

Complaint. Severe epigastric pain and weakness.

History. Ten years' history of stomach trouble. During that period he had attacks of epigastric pain after meals, nausea and vomiting. The attacks would often last for three weeks at a time, and were ultimately relieved by intensive alkali therapy. Two years before admission the pains were very severe and frequent, and at times shot through to his back and awakened him at night, and in addition he had attacks of vomiting. He was operated on and posterior gastro enterostomy performed. He remained well until one week before admission when he had an attack of epigastric pain coming on 2 hours after food. He noted that this pain also came on when he was hungry. Alkalis produced a temporary relief from pain.

Family History. No family history of ulcer.

Personal History. Moderate drinker and smoker.

On Examination. Well nourished patient. Abdomen: generalised epigastric tenderness to palpation.
Special examination: OCCULT BLOOD, positive. F.T.M., hyperchlorhydria. X-ray examination - stomal ulcer together with an ulcer on the middle third of the lesser curvature. BLOOD UREA, 42 mgms.%. UREA CLEARANCE, 51 c.c. ICTERUS INDEX, 5.

Owing to this patient having tarry stools on admission he was treated as a case of haematemesis, with daily injections of histidine. The occult blood test became negative after 12 injections at which time the above investigations were carried out. 36 injections were given and at the end of the course he had gained 5 lbs. in weight.

Special examination repeated: F.T.M., hypochlorhydria as before. X-ray - this showed that the lesser curvature ulcer had disappeared but that the stomal ulcer persisted. Blood Urea, 44 mgms.%. Clearance 41 c.c.

Consideration of (a) the age of the patients as a group, and (b) the duration of symptoms in relation to the successes.

(a) Age. TABLE IX.

	Under 20	20-30	30-40	40-50	50-60	60-70
Gastric ulcers,	4	5	12	10	3	1
'Cures',	2	0	1	3	0	0
Duodenal ulcers,	1	10	9	6	1	1
'Cures'	0	3	2	1	0	0
Anastomotic ulcers,	0	0	2	1	0	0
'Cures',	0	0	2	0	0	0

It will be seen that of the 9 cases of gastric ulcer occurring in patients under 30 years of age, only 2 were symptom-free after 9 months, and of the 22 between 30 and 55 only 4 were in a similar happy state after 9 months.

Similarly in the case of duodenal ulcer of 11 cases under 30 years only 3 were improved and a like number of the 15 occurring between 30 and 50 years of age.

(b) Duration of Symptoms. TABLE X.

	Up to 1	1-5	5-10	10-15	15-20 years.
Gastric ulcers,	11	15	3	2	3
'Cures'	3	2	0	0	1
Duodenal ulcers,	7	14	6	0	1
'Cures'	2	3	0	0	1

Of the 11 cases of gastric ulcer with a history of less than one year, only 3 were successfully treated, and of the 7 cases of duodenal ulcer with a history of less than one year, only two were 'cured'.

FAILURES.

Three of the failures are of special interest:

(1) M.S., female, aet 61. Admitted 11/11/35.

This patient was admitted complaining of epigastric pain coming on after meals, and of vomiting.

History. Her history was typical of peptic ulcer and extended over 20 years.

The F.T.M. showed well marked hyperchlorhydria and X-ray examination revealed a large penetrating ulcer on the lesser curvature of the stomach with no evidence of malignancy.

Treatment. She was treated with daily injections of histidine and put on a Maclean's diet (third week). After 25 injections her condition was not improved, and the pain was just as severe and frequent as previously.

X-ray examination when repeated showed that the ulcer crater remained the same size with no evidence of improvement.

On 25/12/35 partial gastrectomy was performed. At the operation a large lesser curvature ulcer firmly adherent to the pancreas was found.

She made an uneventful recovery from her operation and reported every month after her discharge, and six months after the operation she was symptom-free and had gained 1 stone in weight.

F.T.M. was repeated with the result shown on opposite page. A portion of the ulcer was removed at the operation and sent for microscopic examination. The pathologist reported that the section showed no evidence of healing.

(2) E.F., aet.52. Housewife. Admitted 30/10/35.

This patient gave a history suggestive of peptic ulcer extending over 20 years. The F.T.M. showed a fairly normal acid curve.

X-ray examination revealed a penetrating ulcer on the middle third of the lesser curvature.

Treatment. She was put on light diet and daily injections of histidine. After the 5th injection her symptoms were rather relieved and at her own request, for family reasons, she was transferred to the out-patient department. 30 daily injections were given and at the completion of the course she stated that her pains were no better.

Special investigation repeated showed that the acid curve was unchanged and that the X-ray appearance of the ulcer was unaltered. The patient was now re-admitted to hospital and put on the usual diet alkali regime for 5 weeks, and at the end of that time she was completely free from symptoms. On this occasion the x-ray of the stomach showed that the ulcer crater had diminished in size.

She relapsed on 7/2/36 and was readmitted and partial gastrectomy performed. She made an uneventful recovery from the operation, and 6 months later was still symptom-free and had gained 9 lbs. in weight.

A portion of the ulcer was examined microscopically, and the section showed no evidence of healing.

(3) F.R., aet.44. Labourer. Admitted 6/1/36.
Discharged 13/2/36.

This patient gave a history of stomach trouble of 4 years' duration.

Special examination showed the presence of a pyloric ulcer with hyperchlorhydria.

He was treated with histidine and put on a light diet. After 12 injections he became symptom-free and was discharged to the out-patient department. After 30 injections he had gained 5 lbs. in weight and was eating a normal diet.

Special examination repeated showed that the X-ray appearance of the ulcer was unchanged, whilst the hyperchlorhydria persisted. He remained symptom-free until 8/6/36 when he became seized with an acute epigastric pain and was admitted to hospital, where operation revealed the presence of a perforated pyloric ulcer.

MISHAP.

H.W., aet.46. Labourer. Admitted 20/11/35.
Died, 19/12/35.

Complaint. Epigastric pain coming on after meals with occasional vomiting.

History. Two years previous to admission the patient began to have attacks of epigastric pain coming on after meals, and relieved by alkalis. These attacks continued periodically until his admission. He noted that he would be free from pain for often as long as four months at a time. Two weeks before admission he noted that the pain was constant after every meal, and epigastric in situation. By this time alkalis gave him very little relief and he had frequent attacks of vomiting which seemed to relieve his pain to some extent.

Past History. Tape worm disease in India in 1922.

Personal History. Smokes 20 cigarettes a day and drinks a fair quantity of alcohol.

On Examination. A sallow, well built type of individual. Physical examination showed epigastric tenderness to deep palpation, otherwise nothing of note.

Special examination: URINE, contained a few hyaline casts and albumen. F.T.M., fairly normal acid curve with evidence of gastritis. BLOOD UREA, 84 mgms.%. CLEARANCE, 27.4 c.c.

Blood count:	Red blood cells,	3,700,000
	Whites,	6,000
	Hb.	70%
	C.I.,	.9

DIFFERENTIAL polymorphs 60%. Small mononuclears, 34%. Large mononuclears, 4%. Eosinophils, 1%. Mast cells, .3%. OCCULT BLOOD, positive. Barium meal - pyloric ulcer with no delay in emptying of the stomach.

Treatment. Routine treatment with light diet and daily injections of histidine into alternate buttocks was commenced. After 5 injections he became symptom-free, Occult blood test became negative, and he was allowed up.

On 9/12/36 after the 12th injection, he complained of pain in the region of the right buttock. No tenderness was felt on palpation, but nevertheless, injections on the right side were discontinued.

On 11/12/36 he still complained of pain in the right buttock and examination showed that some swelling of the right buttock was present. Palpation was accompanied by marked tenderness.

On 12/12/36. Pyrexia of 100.5, tongue furred, otherwise as above.

On 13/12/36. An area of red skin about the size of a five-shilling-piece was seen over the middle of the right gluteus maximus.

On 14/12/36. Definite signs of an abscess in the right gluteus present.

On 15/12/36. Abscess incised by the hospital surgeon. Clear, odourless watery pus escaped and it was noted that the muscle in the depths of the incision was a slaty colour.

On 16/12/36. The patient felt more comfortable but examination of the area revealed discoloured skin around the incision.

On 17/12/36. The area of discoloration now covered the whole of the right buttock and the patient was markedly toxic. Red, painful patches were present over his back and these gradually became discoloured, and eventually black in colour. Anti gas-gangrene serum, and polyvalent anti-streptococcal serum were administered.

On 18/12/36. The whole of the right buttock and the back as far up as the scapulae was now completely discoloured. Large areas of black skin were sloughing off. Death took place on 19.12.36.

Post Mortem Findings. All the right gluteal muscles were found to be quite necrotic and dark slaty-grey in colour. No pus was found but an abundant odourless watery fluid.

Examination of the lungs showed nothing of note. The heart muscle was very friable and of poor consistency. Spleen and liver not enlarged. The kidneys showed the appearance of advanced parenchymatous nephritis.

Stomach: An ulcer was present at the pyloric end, and was removed for section. Microscopic examination of the ulcer edge showed no signs of healing. Bacteriological examination of the watery discharge revealed abundant B.coli and no other organisms.

GENERAL COMMENTARY on the SERIES.

The series represents all types of peptic ulceration, is well balanced and compared favourably with other series reported, including as it does 35 cases of gastric ulcer, 28 of duodenal ulcer and three of jejunal ulcer. The patients belong to a class of people to whom the value of this form of treatment would be inestimable, were it only successful. One was fortunate in having the facilities for having 37 of the patients in hospital during the whole course of their treatment, thus affording ample opportunity for the detailed study of the progress of each case.

In the treatment no alkalis were prescribed, and as far as possible each patient was put on as liberal a diet as he would tolerate, with the exception of the 8 cases with severe haemorrhage who had the routine treatment for that condition, together with daily injections of histidine.

It was found that in those who responded to the treatment and gained a remission, an average of 7 injections sufficed to render them symptom-free, the smallest number being 3, and the greatest 19. This rapid alleviation of pain has been frequently commented on by other observers, but generally they noted that it occurred after a smaller number of injections.

The fact that 51 out of 66 patients were free from

symptoms immediately after treatment is in accordance with the findings of others, but 34 relapses within 6 months is a higher rate than any others have found, with the exception of Kirkby Martin. Failures were encountered soon after the series was begun, and were interspersed with the successes throughout. In these 14 failures there was absolutely no response to the treatment, and despite intensive psychotherapy not one would admit to any improvement. Two of these failures (as reported above) were operated on, whilst the remaining 12 obtained a complete remission of symptoms on a rigid Maclean's regime. These unsuccessful cases were by no means all callous ulcers of long duration, as several had quite short histories, and there was no apparent reason why they did not respond to treatment. As can be seen in Table I, 8 of the failures were gastric ulcers and 6 duodenal ulcers, so it would seem that gastric and duodenal ulcers are equally liable to resist treatment.

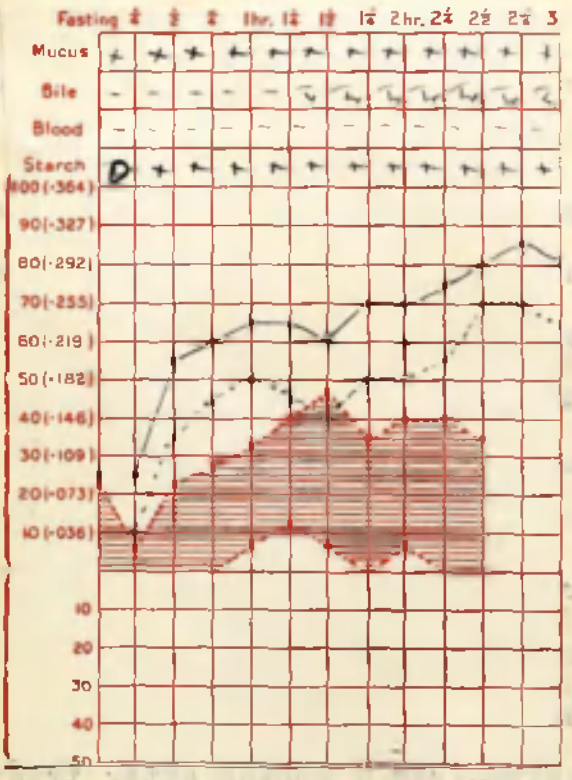
The X-ray appearances after treatment were most striking, and the figures quite sensational. Only 5 cases of gastric ulcer showed evidence of cure, whereas not one case of duodenal ulcer had a normal X-ray. 8 cases of gastric ulcer and 1 of duodenal ulcer showed evidence of improvement, and the radiological appearances in 50 cases were unaltered. Sandweiss reported that in 24 cases X-rayed after treatment with histidine, not one showed evidence of cure.

This report of his has been criticised on the grounds that his series had a preponderance of duodenal ulcer cases, but it would seem to correspond with the duodenal ulcer cases in this series. The figures of only 5 gastric ulcer cases showing radiological cure,and only 8 showing improvement are much lower than any published. In a series of 126 cases (65 gastric ulcers and 61 duodenal ulcers) Bulmer reports that there were 45 normal radiograms after treatment. It is noticeable that of the 6 gastric ulcer cases in this series, remaining symptom-free 9 months after treatment, not one had a normal X-ray after treatment,and only two showed evidence of improvement. None of the 6 cases of duodenal ulcer remaining symptom-free 9 months after treatment had a normal X-ray at the conclusion of the course of histidine and of the two cases of jejunal ulcer, only one showed X-ray evidence of improvement. The six cases of gastric ulcer remaining symptom-free after 9 months include three cases of pyloric ulcer, two lesser curvature ulcers, and one posterior wall ulcer.

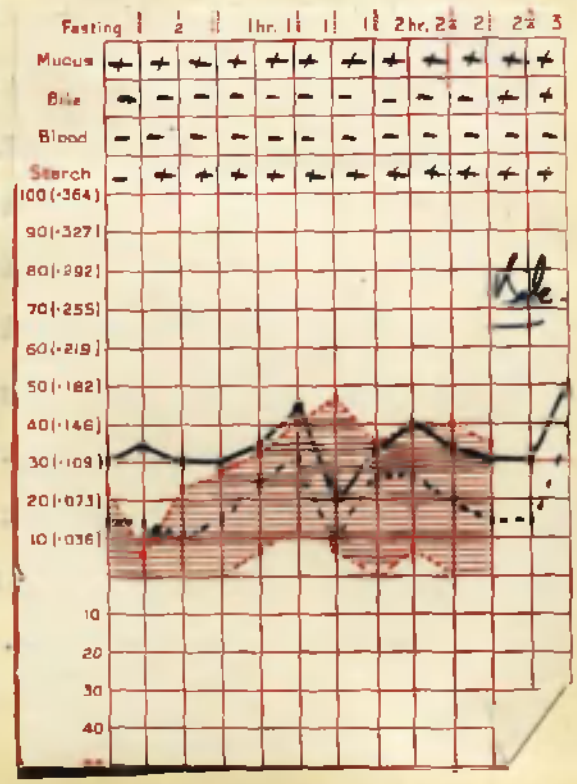
" Weiss and Aron, Volini and McLaughlin, Gardner and others found that the gastric acidity was invariably diminished after histidine treatment whilst Bauke, Martin,and Sandweiss have shown that it was unaltered. In the present series a fractional test meal was done on each patient before and after treatment. 55 showed hyperchlorhydria

A.M. aet. 50.

Before.



After.



before treatment whilst 46 showed hyperchlorhydria after treatment. In only 12 cases was there evidence that the acid curve had been lowered after treatment.

At this point it is worth noting that of the 12 cases of gastric and duodenal ulcer remaining symptom-free after 9 months, only one case had a normal F.T.M. after treatment (vide opposite) whilst in another case the acid curve had been appreciably lowered. Again in only one case was the freedom from symptoms after 9 months accompanied by a normal acid curve and radiological evidence of improvement.

The following figures would indicate that there is no evidence that histidine has any toxic effect on the human kidney, as seen by blood urea estimations and the urea clearance test:-

	Aver.B.U. Before	Aver.B.U. After	Aver.Urea.Cl. Before	Aver.Urea.Cl. After.
Gastric, (20 cases)	56mgms.%.	49mgms.%.	48 cc.	54 cc.
Duodenal, (13 cases)	58mgms.%.	52mgms.%.	48 cc.	55 cc.

It is interesting to note that 23 cases (15 gastric and 8 duodenal) had albuminuria before treatment and of that number 3 remained symptom-free 9 months after treatment with persistent albuminuria. In the series, examination of the urine revealed the presence of indol bodies in three cases, each associated with albuminuria and severe haemorrhage.

Only one case in the series had a positive Wassermann reaction and although he was amongst the 'relapses' it was almost certain that his symptoms were due to duodenal ulcer and not related to his specific condition.

Sandweiss reported that 16 patients in his series developed mild general reactions after injections of histidine. In the present series the author administered a total of 1719 injections of histidine personally, and in no case was any reaction noted.

In common with other writers a striking increase in weight was noted in the majority of the patients under treatment. 44 patients gained weight, the average gain being 5 lbs. in the case of gastric ulcer patients, and 3 lbs. in the case of duodenal ulcer patients. Deloyers rightly points out that this increase in weight is probably due to the normal routine diet that the treatment permits. I am in agreement with this, but would add that in this series another contributory factor is that the majority of the patients came from poor homes.

The icteric index estimated in 54 cases before treatment ranged between 3 and 10 in gastric ulcer cases and 3 and 15 in duodenal ulcer cases with an average of 5 in each case, and showed no change in the 26 cases in which it was estimated after treatment.

As indicated before, each patient reported once a month after treatment and was subjected to a close examination. If the patient relapsed then he was put on a diet alkali regime. In a few cases after the first relapse a second series of injections was given but this proved so unsuccessful that it was discontinued.

Table IX shows that a "success" bears no relation to the age of the patient but that most successes occur in the age group containing the most patients. Likewise Table X shows that the "successes" bear no relation to the duration of symptoms, but that the largest number of successes tends to occur in the groups containing the largest number of cases. This shows that histidine treatment is not necessarily successful in either a young patient or a patient with a short history of ulceration.

The histological examinations carried out on the specimens obtained from the two "failures" operated on, and on the fatal case, would seem to show that histidine has no specific healing effect on ulcers. This is supported by consideration of the patient who perforated shortly after the cessation of treatment.

In view of the original experimental work done by Aron, and the common belief that jejunal ulcers are specially suitable for histidine therapy, it is of interest to note that

one such case in this series was treated with an immediate relief of symptoms, but relapsed within 4 months.

Weiss, Bulmer and others have expressed the view that histidine is contraindicated in severe haemorrhage. Eight cases with severe haemorrhage in this series had daily injections of histidine right from the day of admission. All were included in the "immediate successes", five relapsed within 6 months, whilst three remained symptom-free after 9 months. Thus it would seem that there is no special contraindication for the use of histidine in cases with severe haemorrhage.

The lesson to be learned from the fatal case is that repeated intramuscular injection of a foreign liquid is not without danger.

REVIEW of the PLACE of HISTIDINE in TREATMENT.

Soon after the early results of Aron and Weiss were published, the histidine treatment of peptic ulcer attracted the attention of doctor and patient alike. They thought that at last a wonderful new method of treating peptic ulceration had been discovered, a sure method that would abolish irksome dieting and hospitalisation forever. The results of early observers were very encouraging and old-established methods of treatment were cast aside, and soon, thanks to intensive advertising, practically every patient with gastric symptoms was demanding that he should have this new treatment. Many reports of success appeared in the medical press, but few showed any evidence of proper radiological control with adequate follow-up. Later some writers began to report a few unsuccessful cases, and doubts began to be expressed as to the efficacy of the treatment. Distinguished surgeons and physicians held and expressed divergent views on its value. The American observers, Martin and Sandweiss, dropped the first bombshell when they published the results of their investigations in April 1936. Barry and Florey repeated the original experimental work of Aron and Weiss and found that the theoretical basis of the treatment could not be substantiated. At the present time histidine has more or less fallen into disrepute, but

many members of the medical profession still imagine that it exerts some wonderful healing power on peptic ulcers. Authorities like Hurst and Ryle do not consider that its value has been proved, and have long since ceased to employ it.

Five different views are expressed as to the action of histidine:

> (a) that it exerts a protedtive action on the gastric mucous membrane and a deficiency causes ulceration;
>
> (b) that it is a factor necessary to cell integrity and repair, and stimulates a protective secretion rich in mucin;
>
> (c) that it acts by causing a lowering of the gastric acidity.
>
> (d) that it acts as a form of protein shock.
>
> (e) that histidine by itself has no action at all but that rest, regular hours, change, well cooked food in moderate quantities, limitation of smoking and drinking and most important, a daily injection coupled with the assurance that "this injection will certainly cure your ulcer", causes a remission of symptoms.

Barry and Florey have by their experiments proved conclusively that histidine is incapable of preventing ulcer formation when this is caused by the action of unneutralised gastric juice on intestinal mucosa. Besides, owing to the widespread occurrence of histidine containing proteins in the common foodstuffs, it is difficult to imagine a condition where there is any deficiency. The X-ray findings in the present series after treatment, together

with the fact that histological sections of three ulcers recently treated with histidine showed no evidence of healing, would suggest that it has no specific healing power. Careful examination of the fractional test meals after treatment showed no evidence that the secretion of mucous had been stimulated. The view that the action of histidine is due to a reduction in gastric acidity is disproved by the fact that in this series although 51 cases were symptom-free immediately after treatment, 46 had hyperchlorhydria after treatment. Then again of the 12 cases of gastric and duodenal ulcer remaining symptom-free after 9 months only one had a normal acid curve after treatment. As regards protein shock, no reactions were noted after the injections nor was there any rise in temperature or increase in pulse rate.

An examination of the "successes" shows that of the 12 gastric and duodenal ulcer cases only one had a normal acid curve and another a fairly normal acid curve after treatment. No case showed radiological evidence of cure whilst only four cases (all gastric ulcers) showed evidence of improvement. In one of the jejunal ulcer cases (W.D.) it was noted that a lesser curvature ulcer present before treatment, was not visualised after treatment. Thus it is apparent that it is not necessary for the acid curve to be

normal nor for the ulcer to disappear to secure a remission of symptoms. Sandweiss treated 20 patients with injections of sterile water and obtained results comparable with those obtained with histidine.

The results obtained in this series of cases show that histidine has no specific curative effect on peptic ulcers, and should have no place in their treatment, but that rest, regular hours, change, liberal diet without special medicines, limitation of tobacco and alcohol, and a daily injection given along with a personal assurance that cure is inevitable will produce a remission of symptoms in a large number of cases.

If 66 cases are taken and treated in this way then a remission of symptoms may be expected in 77%, but of that 77%, 67% will relapse within 6 months.

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