PEPTIC ULCER

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In 1936 Selye[1] in describing the findings in animals submitted to physical and toxic stress stated *inter alia:* 'Gastro-intestinal ulcers and other manifestations of shock were actually more severe in adrenalectomised than in intact animals and could be lessened by treatment with cortical extracts. These lesions are not mediated through the adrenal; in fact they are actually combated by an adequate adrenacortical response to stressor agents.'

To those of us who have come to accept peptic ulcer as a stress-induced pathological entity it surely must become a matter of some concern that even after possessing such knowledge for close on 20 years our preventive and therapeutic approach should bear so little relationship to our adopted concept of causation. There must be a reason for this; it may be that we have become too tied down by prejudice to contemplate that past therapy, dietary and medicinal, has been based on erroneous theory and that our ideas urgently need reorientation.

In this field an admirable summary of modern therapeutic measures has been compiled by Berk.[2] In his review he features the vagaries, the limitations and the benefits associated with the exploitation of banthine, methonium salts, sodium carboxymethylcellulose, cortisone, ACTH urogastrone, enterogastrone, protein hydrolysates, anion-exchange resins, gastric mucin, and atropine. Having done so he concludes: 'It is apparent that a specific cure for peptic ulcer is still not at hand.' It is of extreme interest that in this comprehensive review reference to antacid therapy is conspicious by its absence. What the account does reveal is an earnest attempt to give full value to the stress factor and to evolve a therapeutic approach which might adjust the stress as well as the physical and bio-chemical disharmony engendered by such stress or by failure of systemic anti-stress defence.

THE REACTION TO STRESS IN RELATION TO PEPTIC ULCER

In the past we have been led to devote too little attention to the patient as a whole and too much to his ulcer. This being so, it behoves us in the first instance to crystallize in our minds the picture of what constitutes normal reaction to stress, and having done so we are then much better equipped to assess and rectify systemic disharmony indicative of failure of defence against stress.

Normal reaction to stress should be too well known to require lengthy elaboration in such a discussion as this. Cannon[3] has made it common knowledge that adequate reaction by the human economy is represented by an outpouring of adrenaline and a mobilization of sugar into the blood stream. These reactions represent cause and effect, but before the latter eventuates there are numerous hormonal and metabolic activities to be invoked, all of them contributing to the final physiological result and any one, in failure, conditioning the emergence of pathology such as is represented by peptic ulcer.

All digestive stimuli of whatever nature, be they physical or psychological, motor or sensory, visual, olfactory or gustatory, eventually reach the cerebral cortex, whence responses are relayed to the thalamus and hypothalamus. From the latter, impulses are transmitted along the vagus and sympathetic nerves, the latter catering for the outpouring of adrenaline.

In addition to the neurogenic stimuli arising in the autonomic centres in the hypothalamus Hume[4] has adduced evidence that a hypothalamic hormone is formed and that this exerts a stimulatory effect on the anterior pituitary, which in turn by virtue of secreted ACTH sets the suprarenal cortex into active production of its own particular hormones. Hume has also adduced some evidence suggesting that an injection of adrenaline acts on the anterior pituitary in a manner indistinguishable from that of the hypothalamic hormone. If this be so it becomes a matter of interest that a reaction starting in the suprarenal medulla should induce defence response through devious channels at the ultimate level of the suprarenal cortex.

The above findings have been confirmed by Selye[5] and by Ungar,[6, 7] and all investigators are agreed that the ultimate goal to be reached is the prevention of cell-breakdown and of histamine release. In the *British Medical Journal* of 5 March 1947 a sub-leader appraising

research carried out by Ungar in connection with toxic and mechanical injury, summarized as follows:

'Several stages of the argument still need confirmation but it seems probable that normal response to injury is somewhat as follows. The anterior pituitary in response to the stimulus of injury increases its output of ACTH; the adrenal cortex responds with increased activity; the spleen, stimulated by the suprarenal cortical hormones, increases its output of splenin; splenin activates anti-trypsin, which is present in normal serum but which is comparatively inert until combined with splenin; activated anti-trypsin decreases breakdown of protein and thus frustrates the release of histamine; and finally the reduction of circulating vasodilators such as histamine decreases the bleeding time and capillary fragility and permeability which are such constant features of histaminic intoxication.

'It seems not improbable that a new window has been opened through which may be viewed from a fresh angle many problems both of surgery and of general medicine'.

Ungar's research did not stop here. He devised a method of standardized trauma which, when applied to the full, was invariably lethal to the research animal. He was able to show that the lethal effects of such standardized trauma could be neutralized in 95% of cases by giving the animals an injection (*a*) of serum from an animal which had been submitted to a sub-lethal degree of trauma or (*b*) an injection of vitamin C of not less than 100 mg./kg. given within 15 minutes of the infliction of the trauma. He submitted *all* the animals, both those dying and those surviving, to autopsy and macroscopical examination. In all animals which succumbed there were found numerous gastro-intestinal ulcers and haemorrhages and not infrequently actual perforation. In those which survived as the result of administration of serum or vitamin C ulcers were either absent or of minimal degree.

Reverting to the question of histamine: Best[8] has drawn attention to the close integration of this protein derivative into the process of normal digestion. He reminds us that it is recoverable from gastric contents and emphasizes the close analogy of histamine to gastrin as digestive activators. In fact he finds it difficult to differentiate one from the other in that both are inactivated by histaminase and that either pushed to excess is capable of producing hypersecretion of gastric enzymes and eventual haemorrhages and ulceration.

Histamine excess, as is well known, calls up the adrenaline reserves and if these are not freely available histaminic damage becomes inevitable. This may have an important bearing on haemorrhage. With free production of adrenaline as a defence reaction there develops an increased coagulability of the blood; but if defence fails and adrenaline is supplanted by histamine, blood coagulability diminishes and capillary fragility and permeability increase.

The neurological control of digestion is vested in the autonomic nervous system, the vagus being responsible for the intensification of secretion and motility, whereas the sympathetic exercises restraint over these functions.

In the stomach itself there is evidence of sympathetic aberration as recorded by Alvarez,[9] who states: 'Research by Barclay and Bentley has shown that as in the kidney so in the stomach there is in the submucosa a layer of vessels through which blood can be shunted in such a way as to leave areas of the mucus membrane anaemic. This shunt is opened up under stress, and the mechanism like hypermotility and hypersecretion may, therefore, be intimately associated with psychic trauma and could easily explain the formation of peptic ulcers.'

This becomes all the more understandable when viewed in conjunction with the finding of Babkin[10] that *pari passu* with stress-induced accentuation of vagal effects there is thereby produced not only hypersecretion of acid and pepsin but of histamine as well. Nor are these the sole ill-effects of vagal hyperactivity, and as consideration of this involves the question of mobilization of blood sugar, the whole of this subject as it pertains to stress and to the genesis of peptic ulcers will have to be reviewed in some detail.

Mobilization of glucose must depend to a great extent on availability of supplies, and this in turn is subject to the controlling influence of a number of closely integrated functions. It is not sufficient for the purpose that the patient should take liberal quantities of carbohydrate. Control of the storage and utilization of sugar is dependant on adequate production of insulin. Moreover, in the emergency of stress steroidal hormones undertake the role of gluconeogenesis and glycogen storage, the glucose being derived largely from fat and protein. These hormones moreover are powerful insulin antagonists.

McKee *et al.*[11] have recently shown that vitamin C plays a most important part in this hormonal reaction to stress. They found that in normal guinea-pigs, starved for 24 hours, an injection of 3 c.c. of eschatin (suprarenal cortical hormone) given in divided doses produced over a 7-hour period an increase of glycogen storage in these animals amounting to 28 times that found in untreated controls. In similarly treated scorbutic animals, not only was there no increased deposit of liver glycogen but there was an actual decrease. As mobilization of sugar is a prime necessity in adequate defence to stress, vitamin-C quota begins to loom prominently in our thesis.

Thanks to the researches of Giroud[12] and Sayers[13] it is now common knowledge that steroidal hormones generated in the patient as a reaction to stress or administered orally or parenterally as cortisone or ACTH make great demands on vitamin-C storage, and in this respect depletion is particularly accentuated in the suprarenal cortex. Therefore, as peptic ulcer patients have been presumably drawing on these hormonal reserves persistently and continuously, it becomes a reasonable assumption that these patients may in doing so have reduced their storage of vitamin C to vanishing point. This we have known to be so for many years, a conservative estimate being that up to 6,000 mg. will be required to produce saturation of storage in the average case. It might be more than significant that this figure duplicates the dosage employed by Ungar in protecting his guinea pigs from the lethal effects of trauma. Where, moreover, mobilization of sugar is a priority, adequacy of vitamin C becomes indispensable.

From the foregoing it will be apparent that the build-up of sugar and its mobilization as a defence measure are by no means immune from breakdown, and in few conditions is this such a common finding as in peptic ulcer.

In 1945 Abrahamson[14] drew attention to the fact that

peptic-ulcer patients were in a great many instances victims of hypoglycaemia. His findings have been confirmed by Beck,[15] who found 51% of a series of 47 proved cases of peptic ulcer to be hypoglycaemic. Among 40 others with free hydrochloric acid but no ulcers 12·5% had hypoglycaemia. This author emphasizes that control of hypoglycaemia is an important factor in the management of duodenal ulcer. Pock-Steen,[16] in his discussion of the stress-induced leiodystonia syndrome, makes capital of the findings that hypoglycaemia is a prominent feature and peptic ulceration not uncommon. Recently Portis[17] has recorded that in individuals who are victims of severe or prolonged psychological stress, hypoglycaemia is a frequent and significant finding. He attributed the low blood-sugar to hyperinsulinism secondary to right vagal pancreatic stimulation. He would seem to have proved his thesis by being able to adjust blood-sugar and disordered psychology by administration of atropine. It is true that, so far as we know, these patients were not suffering from peptic ulceration, but the stress background was identical in most respects. Gilman confirms the presence of hypoglycaemia in ulcer patients (personal contribution as yet unpublished).

At first sight it may appear to the reader that the relationship of hyperinsulinism and peptic ulcer is being over-emphasized. Let us therefore view the matter from an entirely different angle. How many of us can truthfully declare that he has treated a patient for peptic ulcer who at the same time was suffering from diabetes mellitus? The writer has no recollection of such a happening, and colleagues of long experience agree that such double pathology is a rarity at least. Abrahamson in his series encountered 3 patients with peptic ulcer who had high blood-sugars. He was, however, a careful investigator and submitted these patients to sugar-tolerance tests. The immediate response to the administration of glucose was truly that of a diabetic. This phase was in all 3 cases rapidly followed by a fall of figures to hypoglycaemic levels, indicating the ability of the patients to produce insulin to excess in response to the stimulus of circulating sugar. They were in effect examples of dysinsulinism; and it is recorded that with diet as for excessive production of insulin and antacids ulcers healed rapidly and perfectly with simultaneous adjustment of the blood-sugar to normal levels.

It should never be forgotten that persistent hypoglycaemia is a stressor factor of considerable magnitude. In the researches of Bulato and Carlson[18] it was evident that it stimulated the vagus to redoubled activity in a vicious circle of some gravity.

In view of the foregoing, and accepting that peptic ulceration is the direct or indirect result of stress, the finding in these cases of hyperinsulinism and hypoglycaemia is strong presumptive evidence of failure of hormonal defence, bearing in mind that these hormones are insulin antagonists and are indispensable for gluconeogenesis and glycogen storage such as are characteristic of a normally-constituted defence-reaction to stress.

Sandweiss *et al.*[19] confirmed in a large series of proved cases of peptic ulcer that there was a constant and significant depreciation of the urinary excretion of these hormones, and furthermore that the figures recorded improved as healing took place until ultimately they approximated closely to the average level determined in an equally large number of normal controls. Some indirect confirmation of this finding is contained in the observation of the writer that most ulcer cases exhibit a greatly heightened degree of capillary fragility. Such fragility has been demonstrated by Robson and Duthie[20] to be pathognomonic of suprarenal cortical failure and, as we know, it is also characteristic of histaminic intoxication. It is gratifying to know that this fragility is readily eliminated by administration of cortical hormones.

Critical analysis of the foregoing must lead to certain definite conclusions. They are on the one hand that the hypothalamus is the head ganglion of the autonomic nervous system, and on the other hand that it is the centre through which is inspired the pituitary-adrenal chain defence-reaction to stress. When all factors are working in unison physiological harmony is achieved but, should the chain reaction break down or autonomic-nerve supremacy take control, pathology emerges. Certain schools of thought believe that peptic ulcer arises as the result of autonomic-nerve overactivity, others that ulcers are produced by excess production of adrenal cortical hormones and their maleficent influence on gastric secretion and motility. This article endeavours to show that disharmony of function and associated metabolic distortion are the villains in the piece.

HORMONE, VITAMIN C AND ATROPINE IN THERAPY

If we are right, then, the prerequisites of successful therapy must comprise steroidal hormones, vitamin C, and vagal suppressants. Frequently, and with apparent justification, we are warned against the exploitation of steroidal hormones in ulcer therapy. Such warnings are based on the belief that the action of the hormones in intensifying gastric motility and secretion is the potent factor in promoting disaster. We believe that the intensification of stress by hypoglycaemia plus the severe depreciation in vitamin-C storage are the most important factors in the genesis and perpetuation of the ulcer state. On this basis, when the composite picture of ulcer pathology is unfolded and full value is given to each of a number of diverse features, such warnings if persisted with become an insult to the intelligence.

These hormones should become first choice in ulcer therapy, always provided that in addition (*a*) the patient's storage of vitamin C is brought up to saturation point, (*b*) that steps are taken to neutralize vagal overactivity such as is conditioning hypermotility, hypersecretion, hyperinsulinism and excess release of histamine, and (*c*) that certain adjustments to the waterelectrolyte balance necessitated by hormonal therapy are duly catered for. As these hormones promote potassium excretion and sodium retention, intake of these salts must be closely scrutinized.

As one views the therapeutic problem choice of hormones must lie between (*a*) ACTH, (*b*) cortisone, (*c*) natural adreno-cortical hormones. With each of these, vitamin C on the generous scale advocated by Ungar becomes a *sine qua non*. Moreover, as the vitamin

acts more potently in an acid medium antacids should be used sparingly.

Vagal overactivity must be brought under control, for which purpose atropine would seem to be the agent of choice, combining as it does the 3 virtues of cheapness, of effectiveness, and of confining its activity strictly to the parasympathetic nerves, thereby leaving the sympathetic unhindered in its function of releasing adrenaline for the purpose of mobilization of sugar and inauguration of the hormonal chain defence-reaction. Reactivation of defence will ensure frustration of histamine release and it is certain that in the composite therapy vitamin C will add prestige to its benefactions by promoting healing.

To recapitulate, it is confidently believed that therapy as outlined above will cater for the following desiderata:

1. There will be provided a more effective distribution of essential hormones.
2. Such hormonal augmentation will promote gluconeogenesis and glycogen storage as a defence reaction to stress.
3. Vitamin C will be utilized as a potent factor in the perfection of liver storage of glycogen.
4. Hormones will reduce the inflammatory reaction at the ulcer site, counteract histamine release, and produce local conditions favourable to the healing activity of vitamin C.
5. Reduction of the inflammatory reaction conditions reduction of oedema at the ulcer site, and so may assist relief of pyloric obstruction and pain.
6. Frustration of histamine release will diminish capillary fragility and permeability, increase coagulability of the blood, and thereby minimize tendency to haemorrhage from the ulcer crater. (The inflammatory reaction of course owes its distinctive characteristics to our old friend histamine.)
7. Reduction of histamine release will cater for reduction of excess secretion of acid.
8. Belladonna in the composite therapy will suppress vagal overactivity and thereby subdue hypermotility in the ulcer field, hypersecretion and hyperinsulinism, with its unpleasantand harmfuls tressor factor, hypoglycaemia.
9. The sympathetic contribution to digestive harmony will we hope remain undisturbed, and it is conceivable that the mucosal shunt and patchy mucosal ischaemia may thereby be abolished.

THERAPEUTIC MEASURES AND RESULTS

In 52 of 54 cases so far treated, therapy has comprised (1) 3 c.c. of adreno-cortical hormones mixed with 1,000 mg. of vitamin C given intravenously daily for 3 weeks and thereafter every other day for a further 3 weeks. (2) At the same time oral therapy consisting of 15 gr. of potassium citrate with 10 mm. of tincture of belladonna has been administered thrice daily for the full 6 weeks.

In 2 cases, both of gastric ulcer, ACTH has been used.

Dietary restrictions have been minimal, even in the presence of haemorrhage, but alcohol and tobacco have been strictly rationed.

No patient has been bed-rested or hospitalized except in emergency or at his own request. The majority have remained ambulant and gainfully employed during treatment, and it may be emphasized without fear of contradiction that the psychological uplift engendered by being enabled to continue as wage earners is impressive to a degree.

Over a period of 5 years only 3 patients, none of whom were prepared to submit loyally to the imposed therapeutic discipline, have returned for further treatment.

The most impressive symptomatic reaction to therapy is the rapid and dramatic disappearance of ulcer pain. Unless we ensure that the dosage of vitamin is generous throughout this may engender a feeling of false security and mask the intrusion of a leak or perforation. We can conscientiously affirm that in none of our cases, and in spite of warnings to the contrary, has any complication of this nature been encountered. In fact, in 4 patients active haemorrhage was present when therapy was begun. In each instance bleeding came rapidly under control without recourse to transfusion of blood or other aids to haemostasis.

In 3 instances only has it become necessary to invoke surgical aid. In one case stenosis associated with a juxta-pyloric ulcer precluded the attainment of a successful physiological result, and in the two others posterior ulcers penetrating into the pancreas refused to heal. (Sandweiss recorded 3 of 4 cases treated with cortisone or ACTH as being failures and therefore referred for operation. All 3 cases were examples of ulcers penetrating into the pancreas. Such ulcers are notoriously resistant to all therapy. One hazards the opinion that pancreatic enzymes set free by the ulcer digest the walls of the unprotected ulcer crater.)

CASE REPORTS

It is now proposed to make brief reference to a few of the cases that are illustrative of some of the more intriguing clinical features.

Details of Case 5 are accompanied by serial X-ray pictures illustrating response to therapy consisting of the forbidden ACTH and vitamin C with adopted adjuvants.

Case 1. *Duodenal Ulcer with Haematemesis*

G.G., aged 43, was the first to submit himself to the therapy. In 1948 he had suffered from severe haemorrhage from a duodenal ulcer, necessitating hospitalization and transfusion of blood. He was then treated by strict dietary regime of Lenhartz type and intensive antacid and antispasmodic therapy. Healing was attained and he resumed his profession as an attorney.

In January 1950 he reported to the consulting rooms as the result of a recurrence of ulcer symptoms culminating in a sharp haemorrhage. He refused even to contemplate surgery, influenced understandably by the fact that his father had succumbed to such an operation. He agreed to undertake the role of guinea-pig, to remain at work, and to forbear from the adoption of any dietary restrictions.

He became symptom-free within 5 days except for heart-burn when he drank tea, and full radiological healing was attained in 7 weeks. He has been most cooperative in taking his follow-up ration of vitamin C, has had no necessity to take belladonna, and needless to say is most appreciative of his continued maintenance of digestive health.

Case 2. *Gastric Ulcer*

Mrs. R., the wife of a colleague, had had ulcer symptoms for a long time. Radiological confirmation of an ulcer in the pyloric antrum was obtained in the spring of 1951 and she was hospitalized

and submitted to an intensive course of dietary, antacid and antispasmodic therapy without any abatement of symptoms or evidence of clinical healing.

As the ulcer was gastric and there was a low but not histamine-fast secretion of acid, this, coupled with the site of the ulcer and the age of the patient, inevitably raised the question of possible malignancy. The ulcer was viewed gastroscopically and pronounced simple and not malignant.

As treatment on old-established lines by her medical attendant had failed to promote healing one's suggestion that hormonal and vitamin therapy should be tried was agreed to. In spite of warnings to the contrary (ill-founded in one's opinion) it was decided to administer ACTH in conjunction with vitamin C, the former in dosage of 7½ mg. intra-muscularly 6-hourly and the latter of 1,000 mg. intravenously daily. Oral belladonna and potassium citrate completed the therapeutic attack.

Most gratifyingly the ulcer healed steadily and at the end of 6 weeks healing was completed. To remove all possible doubt the patient was examined radiologically by two separate experts in Durban and one in Johannesburg. All three agreed that evidence of ulcer was negative. There has been no recurrence of ulcer subjectively or objectively.

It is an interesting commentary on this case that ACTH, pronounced dangerous when administered to victims of peptic ulcer because of the probability of induction of haemorrhage or perforation, promoted healing when combined with adequate dosage of vitamin C.

Case 3. *Juxta-pyloric Ulcer with Pyloric Obstruction* (*Spasmodic*)

Mr. A., aged 63, presented himself in March 1952 from Swaziland with a history of epigastric pain over a period of months definitely related to the taking of food and latterly accompanied by persistent vomiting. On occasions the food rejected contained substances taken the day previously. He had obviously lost a lot of weight, and being in the age-group for malignancy one was naturally unhappy about him. These apprehensions were not modified on receiving a radiological report of 6-hour total retention of barium in the stomach, and of apparent complete pyloric stenosis designated as 'due to cicatricial contraction, spasm or new growth but impossible to define'.

It was decided to treat him as a case of simple ulcer with pyloric spasm in the hope of getting relief and a more exact diagnosis. Cortical extract, vitamin C, belladonna and potassium citrate were therefore administered with early and sustained relief. X-ray after 6 days of this therapy disclosed complete relief of pyloric spasm reflected in normal gastric emptying, and definition of a juxta-pyloric duodenal ulcer.

The patient refused to stay in hospital after 3 weeks' therapy, by which time he was symptom-free and X-ray revealed well-advanced healing. He returned to Swaziland with full details for his local doctor to continue therapy, but was apparently not too easy to handle. Six months later he returned with a recurrence of ulcer symptoms but no vomiting. Radiological report was to the effect that there was no pyloric stenosis, the previous ulcer had disappeared, and a fresh active ulcer was present in the posterior wall of the first part of the duodenum.

This time he decided to cooperate for the 5 weeks necessitated by therapy, and when seen 8 months later was adhering to follow-up therapy with meticulous care and a symptom-free result.

Case 4. *Duodenal Ulcer with Hypoglycaemia*

G.A., a clerk in the railway service, had had ulcer symptoms for several months, but was much more concerned with the fact that he had bouts of trembling and sweating several times a day for no obvious reason and attributed to hysteria. Barium X-ray showed an active duodenal ulcer, and resting blood-sugar of 60 mg.%, with figures after taking 50 g. of sugar of 155, 80, 65 and 55 mg.% at half-hourly intervals, confirmed the suspicion of hypoglycaemia.

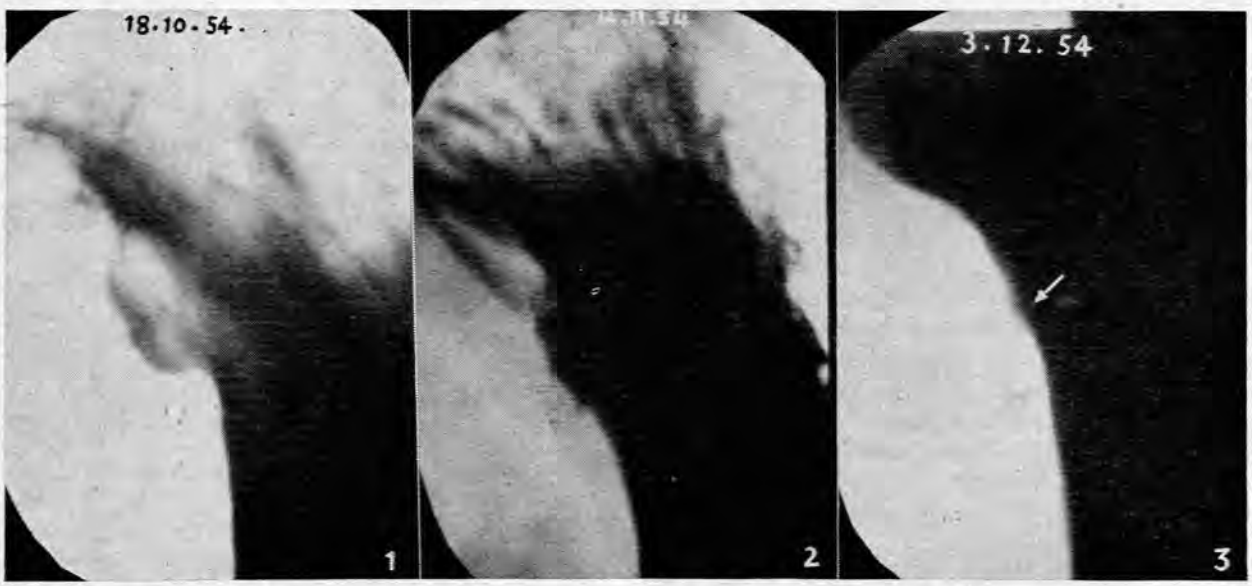
On hormonal, vitamin and belladonna therapy he became symptom-free in 3 days, and achieved complete radiological healing in 3 weeks, at which stage resting blood-sugar was normal. The tolerance curve was not repeated but clinically all symptoms of hypoglycaemia had disappeared.

In view of the constantly reiterated warnings that ACTH and cortisone were absolutely contra-indicated for therapeutic purposes in patients suffering from peptic ulcer, and in view of the success attained with this agent plus vitamin C in Case 2, it was decided to seek a suitable subject and repeat the therapeutic test.

Case 5. *Gastric Ulcer*

E.O.M., aged 57, gave a history of symptoms suggestive of gastric ulcer which had been present for some weeks and were steadily getting worse. X-ray examination on 19 October 1954 (Fig. 1) was reported as follows: 'The crater of a large ulcer was present at a high level on the lesser curvature posteriorly. No direct evidence of any local malignancy was seen but this is impossible to exclude in an ulcer situated at this site.'

He was admitted to a nursing home because of suspected imminence of perforation, and was given 40 units of Acton Prolongatum (slow absorption ACTH) intramuscularly daily and 1,000 mg. of vitamin C intravenously. After 3 days Acton was reduced to 20 units and this was then given every 2nd day. Vitamin continued to be given daily and other therapy comprised 10 mm. of tincture of belladonna *t.i.d.*, 15 gr. of potassium citrate *t.i.d.*, and for the first week an occasional teaspoon of Novasorb. Diet consisted



Case 5. Skiagrams of ulcer. *Fig.* 1. 18 October, *Fig.* 2. 4 November, Fig. 3. 3 December.

of white meats, eggs, cheese, soft vegetables, fruit and milk foods. Three good meals were taken daily and milk or citrus drinks in between.

Another X-ray examination was made on 4 November (Fig. 2) in order to determine as early as possible whether malignancy was involved or not. The ulcer was seen to be reduced to half its original expanse and depth, a most gratifying finding.

Two weeks later the patient was allowed home and he then came in to the consulting rooms regularly for continuance of therapy. On 4 December 1954 further radiological examination was carried out (Fig. 3). The report was as follows: 'The gastric ulcer previously demonstrated at a high level on the lesser curvature posteriorly was still present, but healing appeared almost complete.'

Subsequent progress has been uneventful and the perfect result has been attained. The patient is symptom-free and actively employed, and maintenance therapy consists of 500 mg. of vitamin C by mouth daily in divided doses. Vitamin C remains our sole follow-up insurance against relapse.

ACTH may, in itself, be dangerous to victims of peptic ulceration. Combined with liberal dosage of vitamin C as indicated by Ungar it would at least seem to satisfy the therapeutic requirements of gastric ulcer and may do so for uncomplicated duodenal ulcer. At the same time one's impression is that natural hormones are more effective than ACTH for duodenal ulcers, which is only another indication of the impression one has that these ulcers and the gastric variety are representative of two distinctly different pathologies. What has emerged from this study is that under no circumstances should we capitulate in the face of the ulcer assault. A condition which so consistently reproduces its evolutionary picture should lend itself to solution.

Assuming as correct that the causative background is stress and its multitudinous repercussions, anti-stress agents should supply the therapeutic answer. The first stage towards success is that we must familiarize ourselves with the background, and the disruption and distortion of metabolic harmony which is so characteristic of defence failure. Only by so doing may we position ourselves and organize our curative attack on a scientific basis.

Recently (December 1954) Selye[21] has stated: 'In my opinion research on stress will be most fruitful if it is guided by the theory that we must learn to imitate—and if necessary to correct and complement—the body's own autopharmacological efforts to combat the stress factor in disease.' This is a declaration of therapeutic prophecy which merits our whole-hearted support and approval and embodies principles which it has been one's earnest endeavour to exploit in practical therapy for the past 20 years.

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